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N-METHYLPSEUDOEPHEDRINE-MEDIATED ASYMMETRIC SYNTHESES OF *O*-CARBOXYALKYLATED FLAVONES

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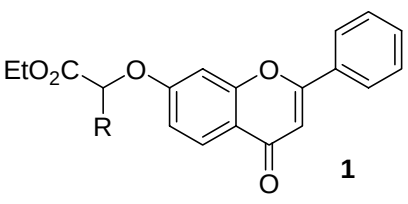
Abstract – *N*-Methylpseudoephedrine-mediated dynamic resolution of α-bromoacetates for stereoselective preparation of *O*-carboxyalkylated flavone has been developed. Substitutions with hydroxyflavone and Cs_2CO_3 in MeCN and following ethanolysis provided *O*-carboxyalkylated flavones **3-10** up to 60% overall yield and 98:2 er. In addition, we have described the regioselective alkylations of chrysin to provide 7-*O*-carboxyalkylated chrysins **11-13** with high enantioselectivities.

INTRODUCTION

Flavones are plant products with many biological and pharmacological activities.[1] A number of synthetically modified flavones have recently been prepared to improve their efficiency as potential therapeutic agents.[2] Among them *O*-carboxyalkylated flavone (**1**) have attracted high interest not only for their interesting bioactivities, but also as valuable intermediates for further synthetic elaboration of flavone derivatives.[3] Introduction of chiral *O*-carboxyalkyl group might provide flavones with high stereoselectivities for their biological targets and improved therapeutic indices. Even *O*-carboxyalkylation of flavone is relatively simple and some of them are commercially available, to our knowledge, there is no report on the asymmetric syntheses of those compounds. In continuation of our investigations on stereoselective modification of bioactive flavonoids and their activity studies,[4] we report herein first example of asymmetric syntheses of 7- or 6- *O*-carboxyalkylated flavones.

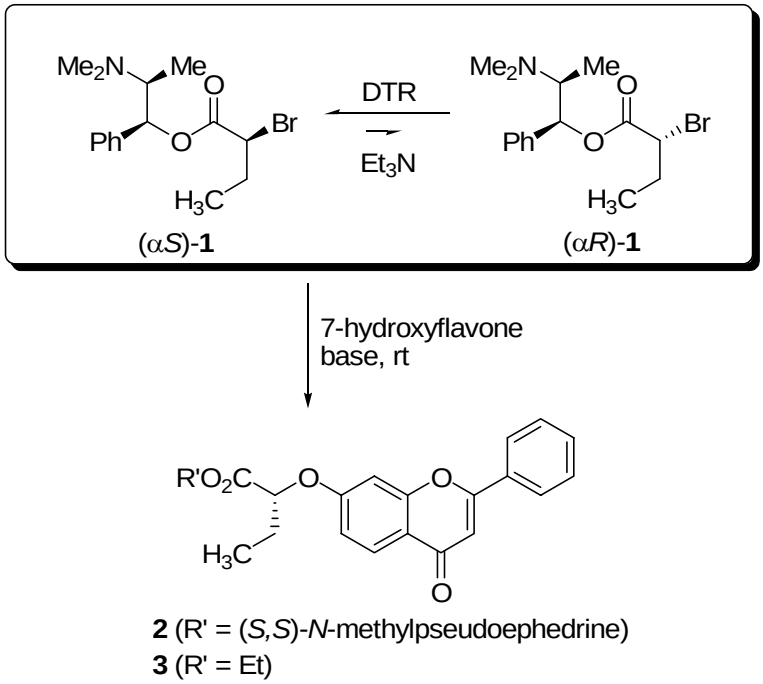


1

efloxate (R = H)
vasodilator

RESULTS AND DISCUSSION

N-Methylpseudoephedrine mediated asymmetric nucleophilic substitution of α-bromoacetates has recently been developed in our laboratory for stereoselective preparation of α-heteroatom substituted carboxylic acids.[5,6] We reported that the primary pathway of the asymmetric induction is a dynamic thermodynamic resolution (DTR) in which the product ratio is determined by the ratio of two epimeric α-bromoacetates that is established before the substitution.[7] The successful results on dynamic resolution of *N*-methylpseudoephedrine α-bromoacetates prompt us to extend the methodology to asymmetric syntheses of *O*-carboxyalkylated flavones.



Scheme 1.

As shown in Scheme 1, initial studies were carried out with two diastereomeric mixture of (*S,S*)-*N*-methylpseudoephedrine α-bromo-α-ethylacetates (α*RS*)-**1** and 7-hydroxyflavone. Treatment of (α*RS*)-**1** (56:44 dr) with 7-hydroxyflavone and potassium carbonate (K_2CO_3) in DMF for 18 h provided *N*-methylpseudoephedrine α-flavonoxybutanoate **2** and following removal of chiral auxiliary gave ethyl α-flavonoxybutanoate **3** with 57:43 er. (Table 1, entry 1) In contrast, when **1** was allowed to equilibrate before the addition of nucleophile, the epimerization with Et_3N gave the thermodynamically equilibrated mixture (89:11 dr) of **1** and the following substitution provided (*R*)-**3** with 82:18 er after alcoholysis.[8] (entry 2) The dependency of product ratios on the dr of α-bromoacetate implied that the epimerization of **1** is not fast with respect to the rate of substitution. The use of Na_2CO_3, Rb_2CO_3 or Cs_2CO_3 as a base in DMF did not improve the stereoselectivity as shown in entries 3-5. Also, the longer substitutions for

48 h under the same condition produced **3** with lower ers ranging from 70:30 to 60:40 ratios. The lower ers of **3** compared to thermodynamic ratio (89:11 dr) of α-bromo acetate **1** might imply that the substitution (S_N2) in DMF is attended by some epimerization of **2** although in most cases the amount is not great for 18 h reaction. In an effort to reduce the risk of the epimerization of **2** during the substitution, we examined the less polar solvent, MeCN with Cs_2CO_3 as a base. To our delight, the slow substitution for 72 h and following alcoholysis furnished 7-*O*-carboxyalkylated flavone **3** in 41% overall yield with 94:6 er. (entry 6) Slower reaction in MeCN compared to the reaction in DMF could provide α-bromoacetate **1** more time for epimerization of **1** before the substitution and the improved er. Significant enhancement of product ratio compared to thermodynamic ratio (89:11 dr) of **1** suggest an additional asymmetric induction by kinetic resolution.[5a] In order to increase the solubility of Cs_2CO_3 in MeCN and the rate of the substitution, we used tetrabutylammonium bromide (TBAB) as a phase transfer catalyst. However, the TBAB promoted reaction produced *O*-carboxyalkylated flavone **3** with lower er of 85:15. (entry 7)

Table 1.

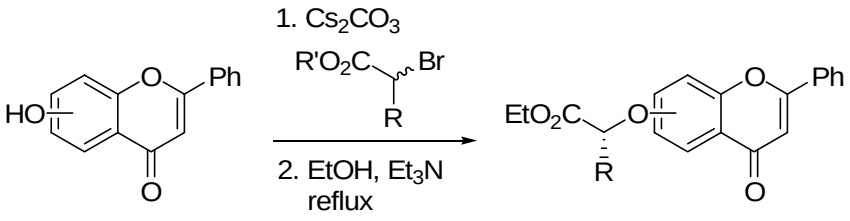
Entry	Substitution Conditions[a]	Overall Yield (%) of **3**	Er (*R:S*)[b]
1	K_2CO_3, DMF	62	57:43
2	K_2CO_3, DMF	47	82:18
3	Na_2CO_3, DMF	50	80:20
4	Rb_2CO_3, DMF	43	79:21
5	Cs_2CO_3, DMF	51	83:17
6	Cs_2CO_3, MeCN	41	94:6
7	Cs_2CO_3, TBAB, MeCN	40	85:15

(a) The epimerization (with Et_3N in MeCN for 20 h) was carried out before the substitution in all cases, except for entry 1. (b) The ers were determined by CSP-HPLC (Chiralpak AD-H).

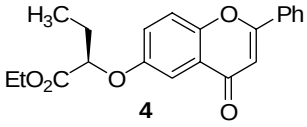
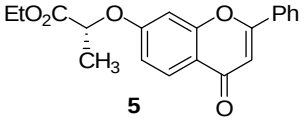
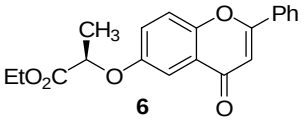
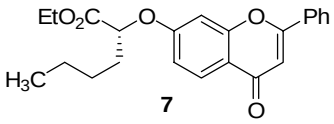
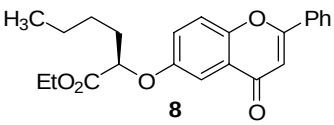
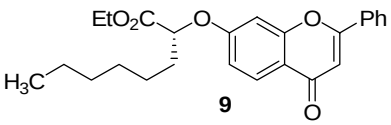
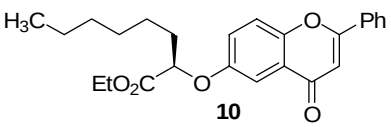
Next, we examined the scope of the epimerization-substitution protocol in MeCN with various α-bromoesters and hydroxyflavone nucleophiles as shown in Table 2. Treatment of thermodynamically equilibrated mixture **1** (89:11 dr) with 6-hydroxyflavone for 72 h at room temperature gave 6-*O*-carboxyalkylated flavone **4** in 60% overall yield with 97:3 er. (Table 2, entry 1) When the equilibrated mixture of α-bromo-α-methylacetate was treated with the hydroxyflavones, the reactions afforded *O*-carboxyalkylated flavones **5** and **6** with 95:5 er and 96:4 er, respectively. (entries 2 and 3) This methodology is also efficient for the asymmetric preparation of 7-*O*-carboxypentylated flavone **7**

with 96:4 er. (entry 4) As with 6-hydroxyflavone nucleophile, the reaction in MeCN took place to afford 6-*O*-carboxypentylated flavone **8** in 60% overall yield with 98:2 er. (entry 5) In addition, reaction of α-bromo-α-hexylacetate with the hydroxyflavones under the same condition provided *O*-carboxyalkylated flavones **9** and **10** with 95:5 er and 94:6 er, respectively. (entries 6 and 7).

Table 2.

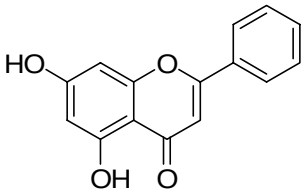


(R' = (*S,S*)-*N*-methylpseudoephedrine)

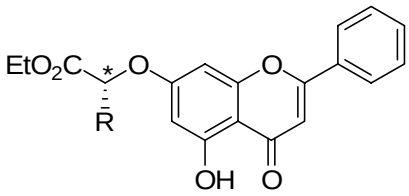
Entry[a]	Nucleophile	R	Product	Overall Yield[b] (%)	Er (*R:S*)[c]
1	6-hydroxy-flavone	Et	 **4**	60	97:3
2	7-hydroxy-flavone	Me	 **5**	34	95:5
3	6-hydroxy-flavone	Me	 **6**	40	96:4
4	7-hydroxy-flavone	*n*-Bu	 **7**	58	96:4
5	6-hydroxy-flavone	*n*-Bu	 **8**	60	98:2
6	7-hydroxy-flavone	*n*-Hex	 **9**	36	95:5
7	6-hydroxy-flavone	*n*-Hex	 **10**	32	94:6

(a) The epimerization (with Et_3N in MeCN for 20 h) was carried out before the substitution in all cases. (b) Overall isolated yield after two-step process (c) The ers were determined by CSP-HPLC (Chiralpak AD-H).

Encouraged by the observation of high stereoselectivities in the reactions with 7- and 6-hydroxyflavones, we examined the nuclephilic substitutions of α-bromoacetates with chrysin nucleophile which have two hydroxyl groups at 7 and 5 positions. It is thought that the nucleophilicity of the phenolic hydroxyl group at 7 position is much higher than that at 5 position in chrysin.[2] Actually, the *O*-carboxyalkylation of chrysin using 1.5 equiv of α-bromoacetates gave only 7-mono-*O*-alkylated flavones, not the di-*O*-alkylated flavones. The reaction of (*S*,*S*)-*N*-methylpseudoephedrine α-bromo-α-ethylacetate with chrysin and Cs_2CO_3 in MeCN and subsequent ethanolysis afforded 7-*O*-carboxyalkylated chrysin **11** with 98:2 er in 59% overall yield. As with α-bromo-α-butylacetate, the reaction successfully took place to afford 7-*O*-carboxyalkylated chrysin **12** in 59% yield with 98:2 er. When α-bromo-α-hexylacetate was treated with chrysin and Cs_2CO_3 for 72 h, 7-*O*-carboxyalkylated chrysin **13** was obtained in 36% overall yield with 96:4 er.



chrysin



11 (R = Et) 98:2 er
12 (R = *n*-Bu) 98:2 er
13 (R = *n*-Hex) 96:4 er

In summary, we have developed *N*-methylpseudoephedrine mediated asymmetric syntheses of *O*-carboxyalkylated flavones via nucleophilic substitution of α-bromo-α-alkylacetates. To the best of our knowledge, there is no previous report of asymmetric synthetic strategy for *O*-carboxyalkylated flavones. Simple two-step process with mild condition suggests the applications of this methodology to the asymmetric syntheses of various flavonoid derivatives. Further studies to extend the scope of the methodology as well as to improve the overall yields are underway.

EXPERIMENTAL

General procedure for the asymmetric preparation of *O*-carboxyalkylated flavones 3-13: To a solution of *N*-methylpseudoephedrine α-bromoacetate (1.5 equiv) in CH_3CN (0.1 M) at rt was added Et_3N (1.0 equiv).[5] The resulting reaction mixture was stirred at room temperature for 20 h, and then a hydroxyflavone nucleophile (1.0 equiv) and Cs_2CO_3 (1.0 equiv) were added. After the resulting reaction mixture was stirred at rt for 72 h, the mixture was quenched with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with EtOAc twice and the combined extracts were washed with brine.

The solvent was removed under reduced pressure and the crude mixture and Et_3N (0.2 equiv) in EtOH were refluxed for 8 h. The solvent was evaporated and the crude material was purified by column chromatography.

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]butanoate (3) A colorless oil was obtained in 41% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.14 (d, *J* = 8.8 Hz, 1H), 7.89 (m, 2H), 7.51 (m, 3H), 7.00 (d, *J* = 9.1 Hz, 1H), 6.93 (s, 1H), 6.76 (s, 1H), 4.70 (t, *J* = 6.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.07 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.2, 171.1, 163.6, 162.8, 158.2, 132.2, 131.9, 129.4, 127.8, 126.6, 118.9, 115.0, 108.0, 102.4, 78.4, 62.0, 26.4, 14.6, 10.0; Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.42; H, 5.73. Chiral HPLC: 94:6 er, t_R (*R*)-major enantiomer, 47.7 min; t_R (*S*)-minor enantiomer, 23.5 min; (Chiralpak AD-H column; 20% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-6-yl)oxy]butanoate (4) A colorless oil was obtained in 60% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.83 (m, 2H), 7.51-7.33 (m, 6H), 6.72 (s, 1H), 4.72 (t, *J* = 6.0 Hz, 1H), 4.24 (m, 2H), 2.03 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.3, 171.2, 163.6, 155.6, 151.6, 132.3, 131.8, 129.5, 126.4, 124.8, 124.5, 120.3, 107.5, 107.2, 79.1, 61.6, 26.4, 14.5, 9.9; Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.32; H, 5.66. Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 37.4 min; t_R (*S*)-minor enantiomer, 49.1 min; (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]ethanoate (5) A pale yellow solid was obtained in 34% overall yield. mp 143-145°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.14 (d, *J* = 8.9 Hz, 1H), 7.88 (m, 2H), 7.51 (m, 3H), 6.98 (dd, *J* = 8.9 and 2.3 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.75 (s, 1H), 4.89 (t, *J* = 6.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.70 (d, *J* = 6.8 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.1, 171.6, 163.6, 162.5, 158.1, 132.2, 131.9, 129.4, 127.7, 126.6, 118.9, 115.0, 108.0, 102.4, 73.4, 62.1, 18.8, 14.5; Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 70.79; H, 5.36. Chiral HPLC: 95:5 er, t_R (*R*)-major enantiomer, 38.1 min; t_R (*S*)-minor enantiomer, 49.7 min; (Chiralpak AD-H column; 20% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-6-yl)oxy]ethanoate (6) A pale yellow oil was obtained in 40% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.92 (m, 1H), 7.52 (m, 5H), 7.37 (dd, *J* = 9.2 and 3.0 Hz, 1H), 6.79 (s, 1H), 4.92 (q, *J* = 6.8 Hz, 1H), 4.25 (m, 2H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.4, 171.9, 163.6, 155.4, 151.5, 132.3, 131.9, 129.4, 126.7, 124.9, 120.2, 107.3, 107.2, 73.3, 61.9, 18.8, 14.6; Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 70.81; H, 5.46. Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 50.9 min; t_R (*S*)-minor enantiomer, 28.3 min; (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]hexanoate (7) A colorless oil was obtained in 58% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.14 (d, *J* = 8.8 Hz, 1H), 7.88 (m, 2H), 7.51 (m, 3H), 7.00 (dd, *J* = 8.9 and 2.3 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.76 (s, 1H), 4.74 (t, *J* = 5.6 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 2.00 (m, 2H), 1.52 (m, 2H), 1.41 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.2, 171.3, 163.6, 162.8, 158.2, 132.2, 131.9, 129.4, 127.8, 126.6, 118.9, 115.0, 108.0, 102.3, 77.4, 62.0, 32.7, 27.7, 22.7, 14.6, 14.3; Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.64; H, 6.41. Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 38.6 min; t_R (*S*)-minor enantiomer, 18.2 min; (Chiralpak AD-H column; 20% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-6-yl)oxy]hexanoate (8) A pale yellow oil was obtained in 60% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.92 (m, 2H), 7.53 (m, 5H), 7.38 (m, 1H), 6.79 (s, 1H), 4.78 (t, *J* = 6.0 Hz, 1H), 4.24 (m, 2H), 2.00 (m, 2H), 1.51 (m, 2H), 1.41 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.4, 171.6, 163.6, 155.7, 151.8, 132.3, 131.9, 129.4, 126.6, 124.9, 124.8, 120.1, 107.3, 107.2, 77.3, 61.8, 32.7, 27.7, 22.7, 14.6, 14.3; Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.70; H, 6.35. Chiral HPLC: 98:2 er, t_R (*R*)-major enantiomer, 18.0 min; t_R (*S*)-minor enantiomer, 24.7 min; (Chiralpak AD-H column; 20% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]octanoate (9) A colorless oil was obtained in 36% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.14 (d, *J* = 8.8 Hz, 1H), 7.89 (m, 2H), 7.52 (m, 3H), 6.99 (dd, *J* = 9.0 and 2.2 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.76 (s, 1H), 4.74 (t, *J* = 5.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.01 (m, 2H), 1.53 (m, 2H), 1.31 (m, 9H), 0.90 (t, *J* = 6.5 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.1, 171.3, 163.5, 162.8, 158.2, 132.2, 131.9, 129.4, 127.8, 126.6, 118.9, 115.0, 108.0, 102.3, 77.4, 62.0, 33.0, 32.0, 29.2, 25.5, 22.9, 14.6, 14.4; Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.35; H, 7.01. Chiral HPLC: 95:5 er, t_R (*R*)-major enantiomer, 56.9 min; t_R (*S*)-minor enantiomer, 20.2 min; (Chiralpak AD-H column; 20% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(4-oxo-2-phenyl-4*H*-chromem-6-yl)oxy]octanoate (10) A colorless oil was obtained in 32% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.91 (m, 2H), 7.52 (m, 5H), 7.00 (m, 1H), 6.79 (s, 1H), 4.78 (t, *J* = 6.1 Hz, 1H), 4.25 (m, 2H), 2.00 (m, 2H), 1.53 (m, 2H), 1.33 (m, 9H), 0.89 (t, *J* = 6.7 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 178.4, 171.6, 163.6, 155.8, 151.8, 132.3, 131.9, 129.4, 126.7, 124.9, 124.8, 120.1, 107.3, 107.2, 77.3, 61.8, 33.1, 32.0, 29.3, 25.5, 22.9, 14.6, 14.4; Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.52; H, 6.96. Chiral HPLC: 94:6 er, t_R (*R*)-major enantiomer, 15.2 min; t_R (*S*)-minor enantiomer, 20.5 min; (Chiralpak AD-H column; 20% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(5-hydroxy-4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]butanoate (11) A pale yellow solid was obtained in 59% overall yield. mp 134-137°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.73 (s, 1H), 7.87 (m, 2H), 7.53 (m, 3H), 6.67 (s, 1H), 6.50 (s, 1H), 6.34 (s, 1H), 4.65 (t, *J* = 6.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H),

2.03 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 182.9, 171.0, 164.5, 164.3, 162.7, 158.1, 132.3, 131.7, 129.5, 126.7, 106.6, 106.3, 99.3, 94.2, 78.2, 61.9, 26.4, 14.6, 10.0; Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.18; H, 5.57. Chiral HPLC: 98:2 er, t_R (*R*)-major enantiomer, 27.8 min; t_R (*S*)-minor enantiomer, 25.5 min; (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(5-hydroxy-4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]hexanoate (12) A pale yellow solid was obtained in 59% overall yield. mp 131-132°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.74 (s, 1H), 7.88 (m, 2H), 7.53 (m, 3H), 6.66 (s, 1H), 6.49 (s, 1H), 6.34 (s, 1H), 4.70 (t, *J* = 6.9 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.99 (m, 2H), 1.50 (m, 2H), 1.41 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 182.9, 171.2, 164.5, 164.2, 162.7, 158.1, 132.3, 131.7, 129.5, 126.7, 106.5, 106.3, 99.2, 94.1, 77.2, 62.0, 32.7, 27.7, 22.7, 14.6, 14.3; Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.65; H, 6.03. Chiral HPLC: 98:2 er, t_R (*R*)-major enantiomer, 37.0 min; t_R (*S*)-minor enantiomer, 35.5 min; (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min).

Ethyl 2-[(5-hydroxy-4-oxo-2-phenyl-4*H*-chromem-7-yl)oxy]octanoate (13) A pale yellow solid was obtained in 36% overall yield. mp 100-102°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.72 (s, 1H), 7.86 (m, 2H), 7.53 (m, 3H), 6.65 (s, 1H), 6.48 (s, 1H), 6.33 (s, 1H), 4.69 (t, *J* = 5.6 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.99 (m, 2H), 1.51 (m, 2H), 1.30 (m, 2H), 0.89 (t, *J* = 6.5 Hz, 3H)**;** ^{13}C NMR ($CDCl_3$, 100 MHz) 182.9, 171.2, 164.5, 164.3, 162.7, 158.1, 132.3, 131.7, 129.5, 126.7, 106.5, 106.3, 99.3, 94.1, 77.2, 61.9, 33.0, 32.0, 29.2, 25.5, 22.9, 14.6, 14.4; Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.71; H, 6.70. Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 22.7 min; t_R (*S*)-minor enantiomer, 21.4 min; (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min).

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6. Both (*S*,*S*)- and (*R*,*R*)-*N*-methylpseudoephedrine are commercially available and also can be easily prepared by *N*-methylation of pseudoephedrine with formaldehyde and formic acid.
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8. In references 5a-c, we have established that (*R*)-products were provided in the substitution of (*S*,*S*)-*N*-methylpseudoephedrine α-bromoacetates with various nucleophiles. We confirmed that the absolute configuration of (*R*)-**5** by comparison of CSP-HPLC retention time with authentic product prepared from commercially available (*S*)-α-bromopropionic acid. The absolute configurations of *O*-carboxyalkylated flavones **3**-**4** and **6**-**13** are provisionally assigned by analogy.