Tetrahedron: *Asymmetry* xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

An efficient and practical enantiospecific synthesis of methyl chromanone- and chroman-2-carboxylates

Dong Woon Kim [a], Md. Maqusood Alam [b], Young Hun Lee [b], M. Naseer A. Khan [b], Yong Zhang [a], Yong Sup Lee [a,b,*]

[a] Department of Pharmacy, College of Pharmacy, Kyung Hee University, Seoul 130-701, Republic of Korea
[b] Department of Life and Nanopharmaceutical Science, Kyung Hee University, Seoul 130-701, Republic of Korea

ARTICLE INFO

Article history:
Received 27 May 2015
Accepted 1 July 2015
Available online xxxx

ABSTRACT

Chromanone-2-carboxylates and chroman-2-carboxylates are useful building blocks for the synthesis of a variety of bioactive compounds, such as repinotan, fidarestat, and nebivolol. An efficient and practical enantiospecific synthesis of chromanone-2-carboxylates and chroman-2-carboxylates has been accomplished using intramolecular Mitsunobu etherification of methyl (*S*)-2-hydroxy-4-oxo-4-(2′-hydroxy)phenylbutanoates derived from L-malic acid.

1. Introduction

Chromans are the common skeleton of many natural products, such as epigallocathechin gallate and vitamin E, and are also found in the structures of various pharmaceuticals. Chiral chromanone-2-carboxylates **1** and chroman-2-carboxylates **2** are used as key intermediates in the synthesis of a variety of bioactive compounds (Fig. 1). Fidarestat, an aldose reductase inhibitor, is a compound that has shown promise in the treatment of complications associated with diabetes such as neuropathy and retinopathy.[1] Fidarestat has been synthesized from chiral 6-fluoro-chromanone-2-carboxylic acid.[2] Chiral chroman-2-carboxylic acids, which can be easily obtained from the corresponding chromanone-2-carboxylic acids after hydrogenation, have also been used for the synthesis of pharmaceuticals and several drug candidates. Repinotan, a potent 5-HT_{1A} receptor agonist, is being developed by Bayer as a potential treatment for ischemic strokes and traumatic brain injuries.[3] Recently, new compounds containing the chroman ring have also been characterized as potent 5-HT_{1A} receptor agonists that exhibit in vitro and in vivo neuroprotective properties, where the absolute configuration significantly influences the receptor binding affinities.[4] The racemic forms of chroman-2-carboxylic acids have also been used as starting compounds in the synthesis of diverse anticancer,[5] antibacterial,[6] antiinflammatory,[7] and antioxidant[8] compounds including nebivolol.[9] Nebivolol is a third-generation β1-selective adrenergic receptor blocker that is used as an anti-hypertensive drug.[10] It is a racemic mixture, the D-nebivolol [(*S*,*R*,*R*,*R*)-nebivolol] of which shows a beta receptor affinity more than 1000 times higher than that of L-nebivolol. This emphasizes the importance of the stereogenic center with regard to the biological activity.[11]

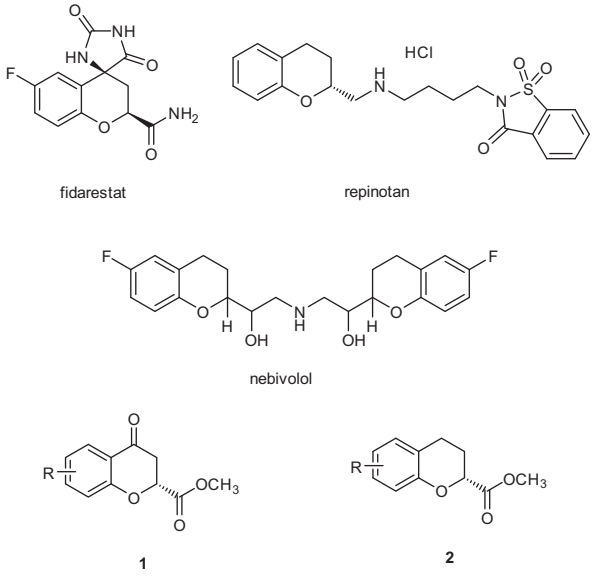


Figure 1. Structures of chiral chroman ring containing bioactive compounds, and their key intermediates **1** and **2**.

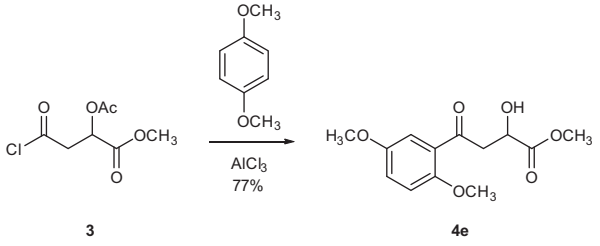
* Corresponding author. Tel.: +82 2 961 0370; fax: +82 2 966 3885.
E-mail address: kyslee@khu.ac.kr (Y.S. Lee).

http://dx.doi.org/10.1016/j.tetasy.2015.07.006
0957-4166/

Accordingly, the development of general and efficient synthetic methods for chromanone- or chroman-2-carboxylates is in high demand for the synthesis of existing or potential pharmaceuticals. The synthesis of these compounds in enantiomerically pure form is of enormous practical importance in the synthesis of chiral drugs for both economic and environmental reasons.

Due to the pivotal role of the chroman ring on the biological activity of several bioactive compounds, various synthetic approaches toward chromanone- and chroman-2-carboxylic acids have been investigated. The racemic form of chroman-2-carboxylates **2** was synthesized by the condensation of 2-hydroxyacetophenone with diethyl oxalate to form ethyl 4-oxochromene-2-carboxylate followed by hydrogenation of 4-carbonyl oxygen and double bond.[7,12] Although interest in the asymmetric synthesis of chroman-2-carboxylates has increased, almost all of the synthetic routes rely upon kinetic resolution of racemic chromanone or chroman derivatives by converting them into diastereomeric mixtures by using homochiral amines as resolving agents[13] or enzymatic resolutions.[4,14] However, these resolution processes have some drawbacks such as a loss of at least 50% of the yield since the undesired enantiomer is discarded. The asymmetric synthesis of enantiomerically pure chroman-2-carboxylic acids using D-mannitol as a chiral pool starting material has been accomplished, but this process gives the chroman intermediate as a mixture of two diastereomers.[15] Although other enantioselective approaches utilizing Sharpless asymmetric epoxidation[16] or chiral catalysts[17] have recently appeared, there is still further room for improvement regarding the number of synthetic steps, the high cost of the complex structured chiral ligands or the use of expensive starting materials to indicate that the practical synthesis of chiral chroman-2-carboxylic acid is highly desirable. Herein we report a general and efficient process for the synthesis of diverse chromanone-2-carboxylates **1** and chroman-2-carboxylates **2** in enantiomerically pure forms.

In an effort to develop enalapril analogs as new ACE inhibitors, we recently reported the convenient synthesis of methyl 2-hydroxy-4-oxo-4-phenylbutanoates possessing a 2-methoxy-substituent on the phenyl ring (e.g., **4e**) from methyl 2-acetoxy-4-halo-4-oxo-butanoate **3** (Scheme 1).[18] We envisioned that compound **4e** could be utilized for the synthesis of chromanone-2-carboxylates **1** through Mitsunobu etherification with cyclization to form a chroman ring if the methoxy group at the *ortho*-position of the phenyl ring was selectively demethylated. The chromanone-2-carboxylates **1** obtained could be easily transformed into the corresponding chroman-2-carboxylates **2** through hydrogenation. This procedure could also be applied to the synthesis of **1** in enantiomerically pure form, since enantiomerically pure methyl (*S*)-2-acetoxy-4-halo-4-oxo-butanoate **3** can be easily obtained in quantitative yield from L-malic acid.[19] It should be noted that malic acid is a versatile chiral pool method for the enantiospecific synthesis of diverse chiral compounds. We considered that if the synthetic method for some chiral compounds from malic acid was to be established, it might guarantee the synthesis of both enantiomers of these compounds because D-malic acid is also commercially available. Accordingly, methyl (*S*)-2-acetoxy-4-halo-4-oxo-butanoate **3**, which can be derived from L-malic acid, was chosen as a chiral synthon for the synthesis of chromanone-2-carboxylates **1** and chroman-2-carboxylates **2** in enantiomerically pure forms.



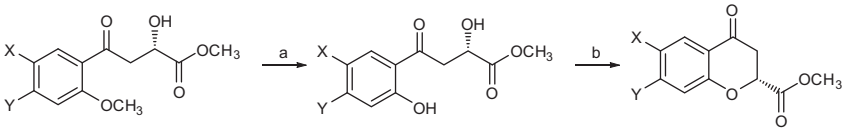
3 4e

Scheme 1. Reported procedure for methyl 2-hydroxy-4-oxo-4-phenylbutanoate.[18]

2. Results and discussion

The chromanone-2-carboxylates **1** were synthesized in a straightforward manner, as shown in Scheme 2. Methyl (*S*)-2-hydroxy-4-oxo-4-(2′-methoxy)phenylbutanoates **4a**–**4e**[18] derived from L-malic acid were used as starting materials. To assess whether racemization occurs at the stereogenic center during the reaction sequence, racemic **4a**–**4e** were subjected to the same reaction procedure independently, to compare their HPLC chromatograms with those of chiral compounds. Demethylation of 2′-methoxy group in **4a**–**4e** was carried out in the presence of an excess of aluminum halide in CH_2Cl_2 to give 2′-hydroxy compounds **5a**–**5c** in good yields. Compounds **5d** and **5e**, which have an additional methoxy group at the phenyl ring, were also obtained in acceptable yields. Finally, compounds **5a**–**5e** were transformed into chromanone-2-carboxylates **1a**–**1e** through internal cyclization under Mitsunobu reaction conditions. Compound **1a**, a key intermediate for the synthesis of fidarestat,[2] could be synthesized by this method from L-malic acid in a 36% overall yield. Enantiomeric purities of **5a**–**5e** and **1a**–**1e** were determined to be greater than 99% when both racemic and enantiomerically pure forms of these compounds were analyzed by HPLC using a chiral column, which indicated that no racemization occurred during the reaction sequences.

Next, to extend the utility of this procedure, the transformations of chromanone-2-carboxylates **1a**–**1e** into other versatile key intermediates, chroman-2-carboxylic acids **6a**–**6f**, were investigated (Scheme 3). The C-4 carbonyl group of **1a** and **1d** could be reduced by catalytic hydrogenation using 5% Pd/C in methanol to provide chroman-2-carboxylates **2a** and **2d** in 85% and 88% yields, respectively. Under these conditions, 6-chloro-chromanone-2-carboxylate **1b** gave a dehalogenated product **2f** in 80% yield, while

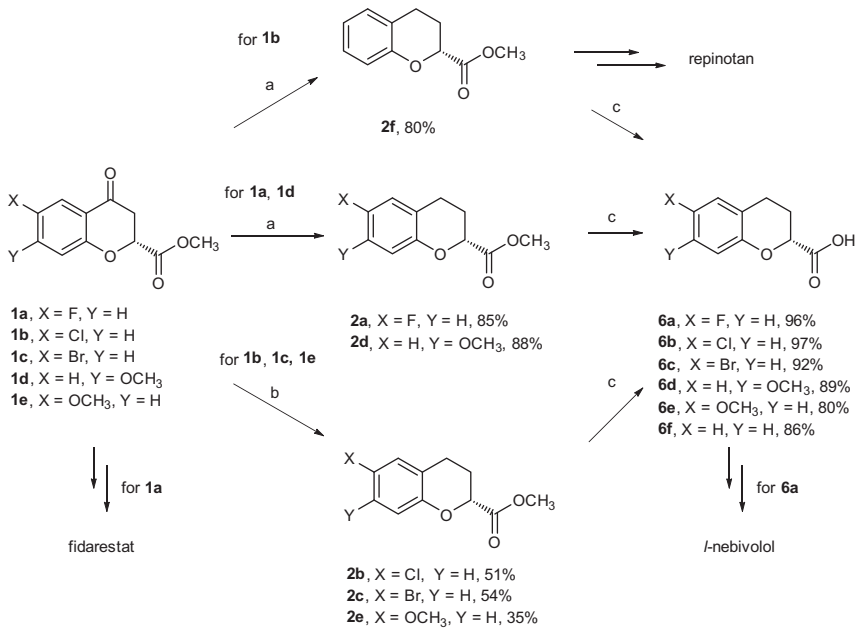


4a, X = F, Y = H
4b, X= Cl, Y = H
4c, X = Br, Y = H
4d, X = H, Y = OCH_3
4e, X = OCH_3, Y = H

5a, X = F, Y = H, 84%
5b, X= Cl, Y = H, 88%
5c, X = Br, Y = H, 77%
5d, X = H, Y = OCH_3, 55%
5e, X = OCH_3, Y = H, 51%

1a, X = F, Y = H, 60%
1b, X= Cl, Y = H, 80%
1c, X = Br, Y = H, 55%
1d, X = H, Y = OCH_3, 74%
1e, X = OCH_3, Y = H, 56%

Scheme 2. Synthesis of (*R*)-chromanone-2-carboxylates **1a**–**1e**. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, rt; (b) Ph_3P, DEAD, THF, 0 °C.



Scheme 3. Synthesis of (*R*)-methyl chroman-2-carboxylates **2a**–**2f** and (*R*)-chroman-2-carboxylic acids **6a**–**6f**. Reagents and conditions: (a) 5% Pd/C, H_2, cat. HCl, MeOH, rt; (b) Et_3SiH, TFA, 55 °C; (c) LiOH, THF, MeOH, H_2O, rt.

the fluoro-substituent survived. This result indicates that the chloro-substituent can be used as a protecting group in the synthesis of unsubstituted chroman-2-carboxylate. Compound **2f** has been used as a key intermediate for the synthesis of several neuroprotective agents including repinotan.[3,4] In contrast to 7-methoxy compound **1d**, 6-methoxy compound **1e** remained unreactive under catalytic hydrogenation conditions even when 10% Pd/C was used as a catalyst under a pressure of 45 psi of hydrogen atmosphere. Fortunately, 6-chloro, 6-bromo, and 6-methoxy-substituted chroman-2-carboxylates **2b**, **2c,** and **2e** could be produced in 35–54% yields by reduction with triethylsilane in trifluoroacetic acid. The obtained chroman-2-carboxylates **2a**–**2f** were readily transformed into chroman-2-carboxylic acids **6a**–**6f** in good yields by the hydrolysis of the methyl ester group using LiOH in aqueous THF and MeOH. The enantiomeric purities of **2a**–**2f** and **6a**–**6f** were greater than 99% when determined by chiral HPLC, thus indicating that every reaction had proceeded without racemization. Compounds **2a** and **6a** can be used as key intermediates for the synthesis of the antihypertensive drug L-nebivolol.[9]

3. Conclusion

We have developed a practical and efficient method for the synthesis of chiral chromanone-2-carboxylates **1** and chroman-2-carboxylates **2**, which are key intermediates for the synthesis of fidarestat, repinotan and nebivolol, from methyl (*S*)-2-acetoxy-4-halo-4-oxo-butanoate **3**. The key step features the intramolecular Mitsunobu etherification of (*S*)-2-hydroxy-4-oxo-4-(2′-hydroxy)phenylbutanoates **5a**–**5e** to construct a chiral chroman ring. This method is also amenable to the synthesis of both enantiomers of diverse chroman ring-containing bioactive compounds[3–8] since enantiomerically pure (*S*)- or (*R*)-acetoxy-4-halo-4-oxo-butanoate is readily available from the chiral pool, L- and D-malic acids.

4. Experimental

4.1. General

All the solvents were purified under dry conditions. NMR spectra of all new compounds were recorded on Bruker AC 400 spectrometer operating at 400 MHz for ^1H and Bruker AMX-500 spectrometer operating at 125 MHz for ^{13}C in $CDCl_3$. Chemical shifts and coupling constants are presented in parts per million δ relative to tetramethylsilane and Hertz, respectively. High resolution mass spectra (HRMS) were recorded on a Jeol accuTOF (JMS-T100TD) equipped with a DART (direct analysis in real time) ion source from Ionsense (Tokyo, Japan) in positive modes. Every racemic compound was also synthesized independently and from these compounds, the retention times (t_R) for the (*R*)- and (*S*)-isomers were observed by chiral HPLC with UV detection at 230 nm using a Shimadzu HPLC equipped with a Diacel Chiralpak IA column (25 cm × 0.46 cm ID) or a Diacel Chiralcel ODH column (25 cm × 0.46 cm ID). The enantiomeric excess was checked by comparing HPLC chromatograms of racemic and enantio-enriched compounds. Optical rotation values were measured on a Perkin–Elmer Polarimeter 341 instrument. Analytical thin layer chromatography (TLC) was carried out using precoated silica gel (E. Merck Kiesegel $60F_{254}$, layer thickness 0.25 mm) and flash column chromatography was performed using Merck Kiesegel 60 Art 9385 (230–400 mesh).

4.2. Experimental details

4.2.1. General procedure for the synthesis of 5a–e

To a solution of **4a**–**e** (1.0 equiv) in anhydrous CH_2Cl_2, anhydrous $AlCl_3$ (8.4 equiv) was added in one portion at 0 °C. The reaction mixture was stirred vigorously under rt and then poured onto a mixture of crushed ice and concentrated aqueous HCl. The mixture was extracted with CH_2Cl_2 twice and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude product as a slightly yellow oil. The crude product was purified by flash column chromatography (*n*-hexane/ethyl acetate = 4:1) to afford **5a**–**e**.

4.2.2. Methyl (*S*)-4-(5-fluoro-2-hydroxyphenyl)-2-hydroxy-4-oxo-butanoate 5a

Compound **5a** (317 mg) was obtained according to Section 4.2.1 from **4a** (400 mg, 1.56 mmol). Yield 84%. ^1H NMR: δ 11.66 (s, 1H),

7.39 (dd, $^3J_{H-F}$ = 8.8, ^4J = 3.0, 1H), 7.25 (ddd, ^3J = 9.1, $^3J_{H-F}$ = 7.7, ^4J = 3.0, 1H), 6.97 (dd, ^3J = 9.1, $^4J_{H-F}$ = 4.6, 1H), 4.69 (dd, J = 6.0, 4.0, 1H), 3.85 (s, 3H), 3.55 (dd, J = 17.6, 4.0, 1H), 3.44 (dd, J = 17.6, 6.0, 1H), 1.60 (br s, 1H); ^{13}C NMR: δ 202.1 (d, $^4J_{C-F}$ = 2.7), 173.9, 158.8 (d, $^4J_{C-F}$ = 1.4), 154.9 (d, $^1J_{C-F}$ = 237.8), 124.7 (d, $^2J_{C-F}$ = 23.5), 120.1 (d, $^3J_{C-F}$ = 7.3), 118.7 (d, $^3J_{C-F}$ = 6.2), 114.8 (d, $^2J_{C-F}$ = 23.2), 66.6, 52.9, 41.9; $[\alpha]_D^{20}$ = +13.8 (c 2.0, $CHCl_3$); ee >99%, Chiralpak IA column, n-hexane/ethanol = 60:40, flow rate = 1.0 mL/min, t_R = 8.95 (S) and 11.11 min (R); HRMS calcd for $C_{11}H_{12}FO_5^+$ $[M+H]^+$, 243.0663. Found 243.0658.

4.2.3. Methyl (*S*)-4-(5-chloro-2-hydroxyphenyl)-2-hydroxy-4-oxo-butanoate 5b

Compound **5b** (334 mg) was obtained according to Section 4.2.1 from **4b** (400 mg, 1.47 mmol). Yield 88%. ^{1}H NMR: δ 11.8 (s, 1H), 7.69 (d, J = 2.4, 1H), 7.43 (dd, J = 8.8, 2.4, 1H), 6.96 (d, J = 8.8, 1H), 4.67 (dd, J = 6.0, 4.0, 1H), 3.83 (s, 3H), 3.56 (dd, J = 17.6, 4.0, 1H), 3.46 (dd, J = 17.6, 6.0, 1H), 1.61 (br s, 1H); ^{13}C NMR: δ 202.1, 174.0, 161.0, 136.8, 129.1, 123.8, 120.3, 119.8, 66.5, 52.9, 41.9; $[\alpha]_D^{20}$ = +16.8 (c 1.0, $CHCl_3$); ee >99%, Chiralpak IA column, n-hexane/ethanol = 60:40, flow rate = 1.0 mL/min, t_R = 7.88 (S) and 9.66 min (R). HRMS calcd for $C_{11}H_{12}ClO_5^+$ $[M+H]^+$, 259.0369. Found 259.0386.

4.2.4. Methyl (*S*)-4-(5-bromo-2-hydroxyphenyl)-2-hydroxy-4-oxo-butanoate 5c

Compound **5c** (298 mg) was obtained according to Section 4.2.1 from **4c** (400 mg, 1.26 mmol). Yield 77%. ^{1}H NMR: δ 11.82 (s, 1H), 7.83 (d, J = 2.4, 1H), 7.56 (dd, J = 8.8, 2.4, 1H), 6.91 (d, J = 8.8, 1H), 4.67 (dd, J = 6.0, 4.0, 1H), 3.83 (s, 3H), 3.55 (dd, J = 17.6, 4.0, 1H), 3.45 (dd, J = 17.6, 6.0, 1H), 1.57 (br s, 1H); ^{13}C NMR: δ 202.0, 173.9, 161.4, 139.5, 132.1, 120.4, 110.7, 66.5, 52.9, 41.9; $[\alpha]_D^{20}$ = +15.4 (c 1.0, $CHCl_3$); ee >99%, Chiralpak IA column, n-hexane/ethanol = 60:40, flow rate = 1.0 mL/min, t_R = 7.73 (S) and 9.13 min (R). HRMS calcd for $C_{11}H_{12}BrO_5^+$ $[M+H]^+$, 302.9863. Found 302.9874.

4.2.5. Methyl (*S*)-4-(2-hydroxy-4-methoxyphenyl)-2-hydroxy-4-oxo-butanoate 5d

Compound **5d** (360 mg) was obtained according to Section 4.2.1 from **4d** (700 mg, 2.61 mmol). Yield 55%. ^{1}H NMR: δ 12.38 (s, 1H), 7.63 (d, J = 8.8, 1H), 6.45 (dd, J = 8.8, 2.4, 1H), 6.42 (d, J = 2.4, 1H), 4.66 (dd, J = 6.0, 4.0, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.51 (dd, J = 17.6, 4.0, ^{1}H), 3.42 (dd, J = 17.6, 6.0, 1H); ^{13}C NMR: δ 200.9, 174.2, 166.5, 165.4, 131.6, 113.4, 108.0, 100.9, 67.0, 55.6, 52.8, 41.4; $[\alpha]_D^{20}$ = +26.5 (c 0.3, $CHCl_3$); ee >99%, Chiralpak IA column, n-hexane/ethanol = 60:40, flow rate = 1.0 mL/min, t_R = 9.59 (S) and 15.04 min (R). HRMS calcd for $C_{12}H_{15}O_6^+$ $[M+H]^+$, 255.0863. Found 255.0863.

4.2.6. Methyl (*S*)-4-(2-hydroxy-5-methoxyphenyl)-2-hydroxy-4-oxo-butanoate 5e

Compound **5e** (145 mg) was obtained according to Section 4.2.1 from **4e** (300 mg, 1.19 mmol). Yield 51%. ^{1}H NMR: δ 11.52 (s, 1H), 7.15 (d, J = 2.4, ^{1}H), 7.13 (d, J = 8.8, 1H), 6.94 (dd, J = 8.8, 2.4, 1H), 4.64 (dd, J = 6.0, 4.0, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.57 (dd, J = 17.6, 4.0, 1H), 3.47 (dd, J = 17.6, 6.0, 1H); ^{13}C NMR: 202.6, 174.3, 157.2, 152.1, 125.1, 119.8, 118.9, 112.5, 66.9, 56.2, 53.1, 42.1; $[\alpha]_D^{20}$ = +8.8 (c 0.14, $CHCl_3$); ee >98%, Chiralpak IA column, n-hexane/ethanol = 60:40, flow rate = 1.0 mL/min, t_R = 8.11 (R) and 11.40 min (S). HRMS calcd for $C_{12}H_{15}O_6^+$ $[M+H]^+$, 255.0863. Found 255.0854. (S)-4-(2,5-dihydroxyphenyl)-2-hydroxy-4-oxo-butyric acid methyl ester was also isolated as a side product. Yield 18%. ^{1}H NMR: δ 7.07 (d, J = 2.4, 1H), 6.97 (dd, J = 8.8, 2.4, 1H), 6.77 (d, J = 8.8, 1H), 4.60 (dd, J = 6.0, 4.0, 1H), 3.75 (s, 3H), 3.36 (dd, J = 17.6, 4.0, 1H), 3.45 (dd, J = 17.6, 6.0, 1H).

4.2.7. General procedure for the synthesis of 1a–e

A solution of triphenylphosphine (1.5 equiv) and diethyl azodicarboxylate (1.5 equiv) in THF at 0 °C was stirred for 15 min and then added dropwise to a solution of **5a–e** (1.0 equiv) in THF at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the volatiles removed by evaporation. The crude product was purified using column chromatography (n-hexane/ethyl acetate = 3:1) to afford the product **1a–e** as slightly yellow solids.

4.2.8. Methyl (*R*)-6-fluoro-4-oxochroman-2-carboxylate 1a

Compound **1a** (270 mg) was obtained according to Section 4.2.7 from **5a** (500 mg, 2.06 mmol). Yield 60%. ^{1}H NMR: δ 7.53 (dd, $^3J_{H-F}$ = 8.1, ^4J = 3.1, 1H), 7.25 (ddd, ^3J = 9.1, $^3J_{H-F}$ = 7.7, ^4J = 3.1, 1H), 7.10 (dd, ^3J = 9.1, $^4J_{H-F}$ = 4.2, 1H), 5.09 (dd, J = 8.4, 5.6, 1H), 3.82 (s, 3H), 3.08–3.05 (m, 2H); ^{13}C NMR: δ 188.8 (d, $^4J_{C-F}$ = 1.9), 168.9, 157.6 (d, $^1J_{C-F}$ = 241.7), 156.3 (d, $^4J_{C-F}$ = 1.8), 124.0 (d, $^2J_{C-F}$ = 24.5), 121.4 (d, $^3J_{C-F}$ = 6.5), 119.9 (d, $^3J_{C-F}$ = 7.4), 112.1 (d, $^2J_{C-F}$ = 23.4), 75.3, 52.9, 39.2; $[\alpha]_D^{20}$ = −38.3 (c 0.85, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/ethanol = 98:2, flow rate = 0.8 mL/min, t_R = 24.98 (R) and 25.13 min (S). HRMS calcd for $C_{11}H_{10}FO_4^+$ $[M+H]^+$, 225.0558. Found 225.0571.

4.2.9. Methyl (*R*)-6-chloro-4-oxochroman-2-carboxylate 1b

Compound **1b** (295 mg) was obtained according to Section 4.2.7 from **5b** (400 mg, 1.55 mmol). Yield 80%. ^{1}H NMR: δ 7.98 (d, J = 2.4, 1H), 7.59 (dd, J = 8.8, 2.4, 1H), 7.02 (d, J = 8.8, 1H), 5.10 (dd, J = 8.4, 5.6, 1H), 3.82 (s, 3H), 3.08–3.05 (m, 2H); ^{13}C NMR: δ 188.6, 169.0, 158.7, 136.5, 128.0, 126.5, 121.8, 120.1, 75.1, 53.2, 39.4; $[\alpha]_D^{20}$ = −50.2 (c 1.5, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/ethanol = 98:2, flow rate = 0.8 mL/min, t_R = 25.13 (R) and 26.56 min (S). HRMS calcd for $C_{11}H_{10}ClO_4^+$ $[M+H]^+$, 241.0262. Found 241.0254.

4.2.10. Methyl (*R*)-6-bromo-4-oxochroman-2-carboxylate 1c

Compound **1c** (155 mg) was obtained according to Section 4.2.7 from **5c** (300 mg, 0.99 mmol). Yield 55%. ^{1}H NMR: δ 7.98 (d, J = 2.4, 1H), 7.59 (dd, J = 8.8, 2.4, 1H), 7.02 (d, J = 8.8, 1H), 5.10 (dd, J = 8.4, 5.6, 1H), 3.82 (s, 3H), 3.06–3.05 (m, 2H); ^{13}C NMR: δ 188.4, 169.0, 159.2, 139.3, 129.6, 122.3, 120.4, 115.2, 75.4, 53.2, 39.4; $[\alpha]_D^{20}$ = −47.8 (c 1.5, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/ethanol = 98:2, flow rate = 0.8 mL/min, t_R = 26.37 (S) and 27.73 min (R). HRMS calcd for $C_{11}H_{10}BrO_4^+$ $[M+H]^+$, 284.9757. Found 284.9711.

4.2.11. Methyl (*R*)-7-methoxy-4-oxochroman-2-carboxylate 1d

Compound **1d** (175 mg) was obtained according to Section 4.2.7 from **5d** (250 mg, 0.98 mmol). Yield 74%. ^{1}H NMR: δ 7.84 (d, J = 8.8, 1H), 6.61 (dd, J = 8.8, 2.4, 1H), 6.56 (d, J = 2.4, 1H), 5.08 (dd, J = 8.4, 5.6, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.01–2.99 (dd, J = 5.6, 2.4, 2H); ^{13}C NMR: δ 188.1, 169.2, 166.4, 162.1, 128.7, 114.7, 110.8, 101.0, 75.4, 55.7, 52.9, 39.1; $[\alpha]_D^{20}$ = +12.5 (c 2.2, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 23.63 (S) and 28.20 min (R). HRMS calcd for $C_{12}H_{13}O_5^+$ $[M+H]^+$, 237.0758. Found 237.0756.

4.2.12. Methyl (*R*)-6-methoxy-4-oxochroman-2-carboxylate 1e

Compound **1e** (78 mg) was obtained according to Section 4.2.7 from **5e** (150 mg, 0.59 mmol). Yield 56%. ^{1}H NMR: δ 7.30 (d, J = 2.4, 1H), 7.12 (dd, J = 8.8, 2.4, 1H), 7.02 (d, J = 8.8, 1H), 5.05 (t, J = 7.0, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.05–3.03 (d, J = 7.6, 2H); ^{13}C NMR: δ 189.6, 169.2, 154.7, 154.6, 125.5, 120.7, 119.4, 107.4, 75.3, 55.8, 52.9, 39.5; $[\alpha]_D^{20}$ = −67.3 (c 0.1, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 15.83 (S) and 18.64 min (R). HRMS calcd for $C_{12}H_{13}O_5^+$ $[M+H]^+$, 237.0758. Found 237.0745.

4.2.13. General procedure for the synthesis of 2a, 2d, and 2f

A solution of **1a**–**b** and **1d** in methanol and HCl (5% w/w) was hydrogenolyzed with 5% palladium on charcoal (5% w/w) at room temperature under 1 atmosphere pressure of hydrogen for 5 h. The reaction mixture was filtered through Celite and evaporated under reduced pressure and the colorless oil was purified by using column chromatography (*n*-hexane/ethyl acetate = 4:1) to afford products **2a**, **2d,** and **2f** as colorless oils.

4.2.14. Methyl (*R*)-6-fluorochroman-2-carboxylate 2a

Compound **2a** (30 mg) was obtained according to Section 4.2.13 from **1a** (40 mg, 0.17 mmol). Yield 85%. ^{1}H NMR: δ 6.88–6.79 (m, 2H), 6.74 (dd, ^3J = 8.8, $^4J_{H-F}$ = 2.9, 1H), 4.70 (dd, J = 7.6, 3.5, 1H), 3.79 (s, 3H), 2.86–2.69 (m, 2H), 2.27 (m, 1H), 2.17 (m, 1H); ^{13}C NMR: δ 171.4, 157.3 (d, $^1J_{C-F}$ = 237.4 Hz), 149.6 (d, $^4J_{C-F}$ = 2.1), 122.5 (d, $^3J_{C-F}$ = 7.6), 118.1 (d, $^3J_{C-F}$ = 8.1), 115.5 (d, $^2J_{C-F}$ = 22.6), 114.6 (d, $^2J_{C-F}$ = 23.1), 73.9, 52.7, 24.5, 23.7 (d, $^4J_{C-F}$ = 1.3); $[\alpha]_D^{20}$ = −10.3 (*c* 0.5, $CHCl_3$); ee >99%, Chiralpak ODH column, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 7.65 (*S*) and 13.38 min (*R*). HRMS calcd for $C_{11}H_{11}FO_3^+$ [M]$^+$, 210.0687. Found 210.0681.

4.2.15. Methyl (*R*)-7-methoxychroman-2-carboxylate 2d

Compound **2d** (165 mg) was obtained according to Section 4.2.13 from **1d** (200 mg, 0.84 mmol). Yield 88%. ^{1}H NMR: δ 6.93 (d, J = 8.8, 1H), 6.50 (d, J = 2.4, 1H), 6.47 (dd, J = 8.8, 2.4, 1H), 4.71 (dd, J = 7.6, 3.5, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.77–2.65 (m, 2H), 2.25–2.11 (m, 2H); ^{13}C NMR: δ 171.3, 159.1, 154.0, 129.8, 113.2, 108.0, 101.5, 73.8, 55.2, 54.4, 24.8, 22.6; $[\alpha]_D^{20}$ = +11.6 (*c* 1.8, $CHCl_3$); ee >99%, Chiralcel ODH column, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 13.98 (*S*) and 56.99 min (*R*). HRMS calcd for $C_{12}H_{15}O_4^+$ [M+H]$^+$, 223.0965. Found 223.0963.

4.2.16. Methyl (*R*)-chroman-2-carboxylate 2f

Compound **2f** (190 mg) was obtained according to Section 4.2.13 from **1b** (250 mg, 1.04 mmol). Yield 80%. ^{1}H NMR: δ 7.11 (t, J = 7.6, 1H), 7.01 (d, J = 7.3, 1H), 6.92 (d, J = 7.3, 1H), 6.86 (t, J = 7.6, 1H), 4.73 (dd, J = 7.6, 3.5, 1H), 3.78 (s, 3H), 2.83–2.74 (m, 2H), 2.30–2.12 (m, 2H); ^{13}C NMR: δ 171.3, 153.3, 129.3, 127.5, 121.2, 120.8, 116.9, 73.7, 52.3, 24.6, 23.3; $[\alpha]_D^{20}$ = −6.9 (*c* 3.0, $CHCl_3$); ee >99%, Chiralcel ODH column, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 7.63 (*S*) and 10.67 min (*R*). HRMS calcd for $C_{11}H_{13}O_3^+$ [M+H]$^+$, 193.0859. Found 193.0858.

4.2.17. General procedure for the synthesis of 2b–c and 2e

A solution of **1b**–**c**, **1e** (1.0 equiv) in trifluoroacetic acid (20.0 equiv) was treated with triethylsilane (4.0 equiv) and the resulting reaction mixture was heated at 55 °C for 6 h. The reaction mixture was then cooled to room temperature, neutralized with solid sodium bicarbonate, diluted with water, and extracted with diethyl ether. The organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give a colorless oil, which was purified by using column chromatography (*n*-hexane/ethyl acetate = 5:1) to afford the product **2b**–**c**, and **2e** as colorless oils.

4.2.18. Methyl (*R*)-6-chlorochroman-2-carboxylate 2b

Compound **2b** (36 mg) was obtained according to Section 4.2.17 from **1b** (75 mg, 0.31 mmol). Yield 51%. ^{1}H NMR: δ 7.05 (dd, J = 8.8, 2.4, 1H), 6.85 (d, J = 8.8, 1H), 6.78 (d, J = 2.4), 4.72 (dd, J = 7.6, 3.5, 1H), 3.78 (s, 3H), 2.87–2.70 (m, 2H), 2.26 (m, 1H), 2.16 (m, 1H); ^{13}C NMR: δ 171.0, 152.0, 128.9, 127.5, 125.5, 122.7, 118.2, 73.7, 52.3, 24.1, 23.1; $[\alpha]_D^{20}$ = −6.9 (*c* 3.0, $CHCl_3$); ee >99%, Chiralcel ODH column, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 7.68 (*S*) and 10.88 min (*R*). HRMS calcd for $C_{11}H_{11}ClO_3^+$ [M]$^+$, 226.0391. Found 226.0403.

4.2.19. Methyl (*R*)-6-bromochroman-2-carboxylate 2c

Compound **2c** (78 mg) was obtained according to Section 4.2.17 from **1c** (150 mg, 0.53 mmol). Yield 54%. ^{1}H NMR: δ 7.20 (dd, J = 8.8, 2.4, 1H), 7.16 (d, J = 2.4, 1H), 6.82 (d, J = 8.8, 1H), 4.73 (dd, J = 7.6, 3.5, 1H), 3.71 (s, 3H), 2.85–2.68 (m, 2H), 2.23–2.15 (m, 2H); ^{13}C NMR: δ 171.2, 152.7, 132.1, 130.7, 123.5, 118.9, 113.1, 73.9, 52.7, 24.3, 23.2; $[\alpha]_D^{20}$ = −7.1 (*c* 0.5, $CHCl_3$); ee >98%, Chiralcel ODH column, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, t_R = 7.87 (*S*) and 10.54 min (*R*). HRMS calcd for $C_{11}H_{11}BrO_3^+$ [M]$^+$, 269.9886. Found 269.9879.

4.2.20. Methyl (*R*)-6-methoxychroman-2-carboxylate 2e

Compound **2e** (20 mg) was obtained according to Section 4.2.17 from **1e** (60 mg). Yield 35% (24 mg of **1e** was recovered). ^{1}H NMR: δ 6.87 (d, J = 8.8, 1H), 6.69 (dd, J = 8.8, 2.4, 1H), 6.57 (d, J = 2.4, 1H), 4.68 (dd, J = 7.6, 3.5, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.87–2.70 (m, 2H), 2.30–2.12 (m, 2H); ^{13}C NMR: δ 171.5, 153.6, 147.3, 121.7, 117.5, 113.9, 113.5, 73.8, 55.6, 52.3, 24.7, 23.6; $[\alpha]_D^{20}$ = −5.6 (*c* 0.2, $CHCl_3$); ee >99%, Chiralcel ODH column, *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, t_R = 9.14 (*S*) and 73.01 min (*R*). HRMS calcd for $C_{12}H_{14}O_4^+$ [M]$^+$, 222.0887. Found 222.0892.

4.2.21. General procedure for the synthesis of 6a–f

To a stirred solution of **2a**–**f** in THF (2 mL) and MeOH (1 mL), 0.25 M aqueous LiOH (1.05 equiv) was added dropwise at room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and then acidified with dil HCl. The crude product was extracted with ethyl acetate and concentrated. This organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The concentrate was further purified by crystallization with *n*-hexane to afford **6a**–**f**.

4.2.22. (*R*)-6-Fluorochroman-2-carboxylic acid 6a

Compound **6a** (89 mg) was obtained according to Section 4.2.21 from 2**a** (100 mg, 0.47 mmol). Yield 96%. ^{1}H NMR: δ 6.88–6.80 (m, 2H), 6.75 (dd, ^3J = 8.7, $^4J_{H-F}$ = 2.6, 1H), 4.74 (dd, 1H, J = 7.6, 3.5), 2.90–2.75 (m, 2H), 2.33 (m, 1H), 2.18 (m, 1H); ^{13}C NMR: δ 175.8, 157.2 (d, $^1J_{C-F}$ = 237.9), 148.9 (d, $^4J_{C-F}$ = 2.1), 122.3 (d, $^3J_{C-F}$ = 7.5), 117.8 (d, $^3J_{C-F}$ = 8.1), 115.4 (d, $^2J_{C-F}$ = 22.7), 114.5 (d, $^2J_{C-F}$ = 23.2), 73.2, 24.1, 23.5 (d, $^4J_{C-F}$ = 1.1); $[\alpha]_D^{20}$ = −12.6 (*c* 1.0, DMF) {lit.[9] $[\alpha]_D^{20}$ = −13.4 (*c* 1.0, DMF)}; ee >99%, Chiralcel ODH column, *n*-hexane/2-propanol/trifluoroacetic acid = 90:10:0.5, flow rate = 1.0 mL/min, t_R = 6.92 (*S*) and 9.62 min (*R*). HRMS calcd for $C_{10}H_9FO_3^+$ [M]$^+$, 196.0530. Found 196.0531.

4.2.23. (*R*)-6-Chlorochroman-2-carboxylic acid 6b

Compound **6b** (91 mg) was obtained according to Section 4.2.21 from **2b** (100 mg, 0.44 mmol). Yield 97%. ^{1}H NMR: δ 7.10 (dd, J = 8.8, 2.4, 1H), 7.04 (d, J = 2.4, 1H), 6.86 (d, J = 8.8, 1H), 4.76 (dd, J = 7.6, 3.5, 1H), 2.90–2.74 (m, 2H), 2.35 (m, 1H), 2.18 (m, 1H); ^{13}C NMR: δ 175.8, 151.5, 129.0, 127.9, 125.9, 122.6, 118.2, 73.2, 24.1, 23.1; $[\alpha]_D^{20}$ = −15.5 (*c* 1.0, MeOH) {lit.[20] $[\alpha]_D^{20}$ = −16.4 (*c* 2.1, MeOH)}; ee >98%, Chiralcel ODH column, *n*-hexane/2-propanol/trifluoroacetic acid = 90:10:0.5, flow rate = 1.0 mL/min, t_R = 6.66 (*S*) and 8.14 min (*R*). HRMS calcd for $C_{10}H_9ClO_3^+$ [M]$^+$, 212.0235. Found 212.0242.

4.2.24. (*R*)-6-Bromochroman-2-carboxylic acid 6c

Compound **6c** (87 mg) was obtained according to Section 4.2.21 from **2c** (100 mg, 0.37 mmol). Yield 92%. ^{1}H NMR: δ 7.23 (dd,

J = 8.8, 2.4, 1H), 7.18 (d, J = 2.4, 1H), 6.78 (d, J = 8.8, 1H), 4.77 (dd, J = 7.6, 3.5, 1H), 2.88–2.74 (m, 2H), 2.33 (m, 1H), 2.18 (m, 1H); ^{13}C NMR: δ 174.9, 152.5, 132.1, 130.6, 125.9, 123.6, 118.6, 73.2, 24.0, 23.0; $[\alpha]_D^{20} = -7.8$ (c 0.5, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/2-propanol/trifluoroacetic acid = 90:10:0.5, flow rate = 1.0 mL/min, t_R = 6.79 (S) and 8.07 min (R). HRMS calcd for $C_{10}H_9BrO_3^+$ [M]$^+$, 255.9730. Found 255.9738.

4.2.25. (*R*)-7-Methoxychroman-2-carboxylic acid 6d

Compound **6d** (50 mg) was obtained according to Section 4.2.21 from **2d** (60 mg, 0.27 mmol). Yield 89%. ^{1}H NMR: δ 6.95 (d, J = 8.8, 1H), 6.52 (d, J = 2.4, 1H), 6.49 (d, J = 2.4, 1H), 4.73 (dd, J = 7.6, 3.5, 1H), 3.76 (s, 3H), 2.81–2.74 (m, 2H), 2.33 (m, 1H), 2.16 (m, 1H); ^{13}C NMR: δ 175.8, 159.2, 153.5, 129.9, 113.1, 108.3, 101.5, 73.3, 55.3, 24.6, 22.7; $[\alpha]_D^{20}$ = +54.5 (c 1.25, $CHCl_3$) {lit.[17b] $[\alpha]_D^{20} = -38.7$ (c 1.0, $CHCl_3$) for the (S)-isomer}; ee >98%, Chiralcel ODH column, n-hexane/2-propanol/trifluoroacetic acid = 90:10:0.5, flow rate = 1.0 mL/min, t_R = 13.28 (S) and 31.90 min (R). HRMS m/z calcd for $C_{11}H_{13}O_4^+$ [M+H]$^+$, 209.0808. Found 209.0808.

4.2.26. (*R*)-6-Methoxychroman-2-carboxylic acid 6e

Compound **6e** (30 mg) was obtained according to Section 4.2.21 from **2e** (40 mg, 0.18 mmol). Yield 80%. ^{1}H NMR: δ 6.87 (d, J = 8.8, 1H), 6.72 (dd, J = 8.8, 2.4, 1H), 6.59 (d, J = 2.4, 1H), 4.68 (dd, J = 7.6, 3.5, 1H), 3.75 (s, 3H), 2.75–2.91 (m, 2H), 2.35 (m, 1H), 2.16 (m, 1H); ^{13}C NMR: δ 175.4, 153.9, 146.9, 121.7, 117.5, 113.9, 113.7, 73.2, 55.6, 24.6, 23.8; $[\alpha]_D^{20} = -11.2$ (c 1.35, $CHCl_3$); ee >99%, Chiralcel ODH column, n-hexane/2-propanol/trifluoroacetic acid = 90:10:0.5, flow rate = 1.0 mL/min, t_R = 10.41 (S) and 38.76 min (R). HRMS calcd for $C_{11}H_{12}O_4^+$ [M]$^+$, 208.0730. Found 208.0741.

4.2.27. (*R*)-Chroman-2-carboxylic acid 6f

Compound **6f** (31 mg) was obtained according to Section 4.2.21 from **2f** (40 mg, 0.21 mmol). Yield 86%. ^{1}H NMR: δ 10.55 (br s, 1H), 7.12 (t, J = 7.6, 1H), 7.05 (d, J = 7.3, 1H), 6.93 (d, J = 7.3, 1H), 6.86 (t, J = 7.6 1H), 4.76 (dd, J = 7.6, 3.5, 1H), 2.90–2.75 (m, 2H), 2.33 (m, 1H), 2.19 (m, 1H); ^{13}C NMR: δ 176.3, 152.9, 129.5, 127.7, 121.1, 116.8, 73.2, 24.4, 23.3; $[\alpha]_D^{20} = -6.3$ (c 1.05, MeOH {lit.[21] $[\alpha]_D^{20} = -6.0$ (c 1.1, MeOH)}; ee >99%, Chiralcel ODH column, n-hexane/2-propanol/trifluoroacetic acid = 90:10:0.5, flow rate = 1.0 mL/min, t_R = 6.68 (S) and 8.19 min (R). HRMS calcd for $C_{10}H_{11}O_3^+$ [M+H]$^+$, 179.0703. Found 179.0731.

Acknowledgments

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by MEST (#2012-006431).

References

1. (a) Ramunno, A.; Cosconati, S.; Sartini, S.; Maglio, V.; Angiuoli, S.; La Pietra, V.; Di Maro, S.; Giustiniano, M.; La Motta, C.; Da Settimo, F.; Marinelli, L.; Novellino, E. *Eur. J. Med. Chem.* **2012**, *51*, 216; (b) Yadav, U. C.; Aguilera-Aguirre, L.; Ramana, K. V.; Boldogh, I.; Srivastava, S. K. *PLoS One* **2010**, *5*, e14440.
2. Unno, R.; Yamaguchi, T.; Usui, T.; Kakigami, T.; Fukushima, M.; Mizuno, K.; Baba, Y.; Kurono, M. *Chem. Pharm. Bull.* **1994**, *42*, 1474.
3. Lutsep, H. L. *Curr. Opin. Invest. Drugs* **2002**, *3*, 924.
4. Planas, A. M.; López-Rodríguez, M. L. *J. Med. Chem.* **2011**, *54*, 7986.
5. Vinaya, K.; Kavitha, C. V.; Chandrappa, S.; Prasanna, D. S.; Raghavan, S. C.; Rangappa, K. S. *Chem. Biol. Drug Des.* **2011**, *78*, 622.
6. Siva Kumar, B. V.; Vaidya, S. D.; Kumar, R. V.; Bhirud, S. B.; Mane, R. B. *Eur. J. Med. Chem.* **2006**, *41*, 599.
7. Kwak, J.-H.; Won, S.-W.; Kim, T.-J.; Roh, E.; Kang, H.-Y.; Lee, H. W.; Jung, J.-K.; Hwang, B. Y.; Kim, Y.; Cho, J.; Lee, H. *Arch. Pharm. Res.* **2008**, *31*, 133.
8. Lee, H.; Lee, K.; Jung, J.-K.; Cho, J.; Theodorakis, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2745.
9. Xhonneux, R. M.; Van Lommen, G. R. E. EP 0334429, 1989.
10. de Boer, R. A.; Voors, A. A.; van Veldhuisen, D. J. *Expert Opin. Pharmacother.* **2007**, *8*, 1539.
11. Van de Water, A.; Xhonneux, R. S.; Reneman, R. S.; Janssen, P. A. J. *Eur. J. Pharmacol.* **1988**, *156*, 95.
12. Witiak, D. T.; Stratford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. R. *J. Med. Chem.* **1971**, *14*, 758.
13. (a) Wu, C.; Huang, Z.; Shang, Z.; Zhou, M.; Deng, Y. *Chin. J. Org. Chem.* **2011**, *31*, 1262; (b) Qian, S.; Wu, Y. *Zhongguo Yiyao Gongye Zazhi* **2011**, *42*, 721; (c) Gross, J. L. *Tetrahedron Lett.* **2003**, *44*, 8563.
14. Czompa, A.; Kovács, T.; Antus, S. *J. Heterocycl. Chem.* **2000**, *37*, 991.
15. Yuan, H.-J.; Qian, S.; Hai, L.; Chen, Y.-Y.; Wu, Y. *Synth. Commun.* **2007**, *37*, 3773.
16. Chandrasekhar, S.; Venkat Reddy, M. *Tetrahedron* **2000**, *56*, 6339.
17. (a) Song, X.-G.; Zhu, S.-F.; Xie, X.-L.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2555; (b) Song, S.; Zhu, S.-F.; Pu, L.-Y.; Zhou, Q.-L. *Angew. Chem.* **2013**, *125*, 6188; (c) Uyanik, M.; Hayashi, H.; Ishihara, K. *Science* **2014**, *345*, 291.
18. Zhang, Y.; Khan, M. N. A.; Gong, P.; Lee, Y. S. *Chin. Chem. Lett.* **2009**, *20*, 898.
19. Henrot, S.; Larcheveque, M.; Petit, Y. *Synth. Commun.* **1986**, *16*, 183.
20. Loiodice, F.; Longo, A.; Bianco, P.; Tortorella, V. *Tetrahedron: Asymmetry* **1995**, *6*, 1001.
21. Dolle, Roland E.; Chu, Guo-Hua, US 2005/54630 A1, 2005.