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A facile synthesis of (*S*)-felodipine

Kuktae Kwon, Jung A. Shin, Hee-Yoon Lee *

Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon, Republic of Korea

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ABSTRACT

A short and facile synthesis of (*S*)-felodipine was developed starting from (*R*)-glycidol as the source of the chiral auxiliary. 2-Hydroxyethyl esters were found to undergo selective transesterification reactions in the presence of other esters. This selective transesterification reaction was applied to the synthesis of (*S*)-felodipine through selective substitution of the 2-hydroxyethyl group possessing chiral ester with sodium methoxide.

1. Introduction

1,4-Dihydropyridines are involved in a plethora of biological activities in addition to the redox system in nature as NADH coenzymes and their analogs. These various biological activities led 1,4-dihydropyridines being used in the treatment of vascular disorders, cancer, diabetes, AIDS and many other diseases.[1]

1,4-Dihydropyridines have been readily available through the Hantzsch condensation reaction that was first reported in 1882.[2] As a result, many effective drugs known as calcium channel blockers with 1,4-dihydropyridine core structure have been developed for the treatment of high blood pressure (Fig. 1).[3]

Many of these 1,4-dihydropyridine calcium channel blockers exist as mixtures of enantiomers. Apparently, enantiomers of these 1,4-dihydropyridines show different pharmacological effects ranging from moderate difference in pharmacokinetics to complete change of biological activities.[4] Thus, the development of these drugs as single enantiomeric forms would provide a significant improvement in pharmacological effects.[5] However, most 1,4-dihydropyridine calcium channel blockers have been developed as racemic drugs. It is only recent that amlodipine, the leading calcium channel blocker, was developed as a single enantiomeric form.[6] For the preparation of single enantiomeric 1,4-dihydropyridines, there have been only a few reports of asymmetric synthesis using organocatalysts[7] or chiral auxiliaries[8] with limited asymmetric induction. Most of the reports for the

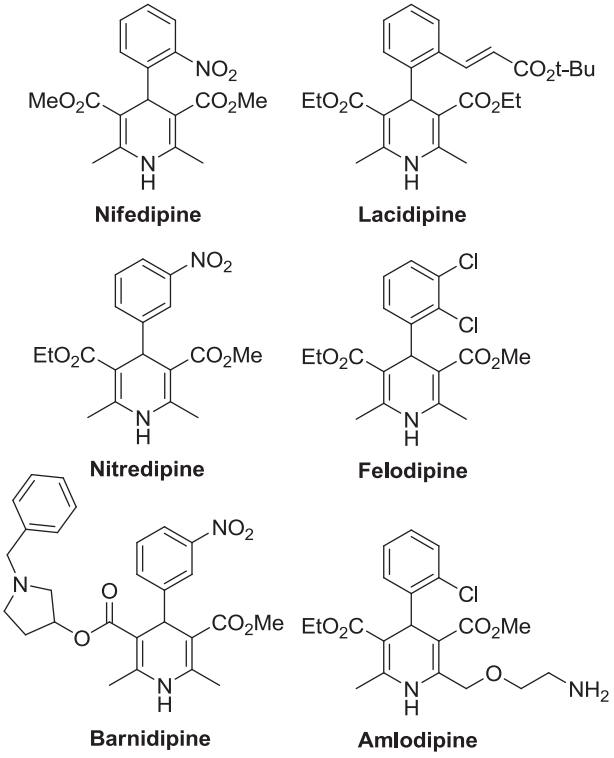

Fig. 1. Dihydropyridine calcium channel blockers.

* Corresponding author. Tel.: +82 42 250 2835; fax: +82 42 250 2810; e-mail address: leehy@kaist.ac.kr (H.-Y. Lee).

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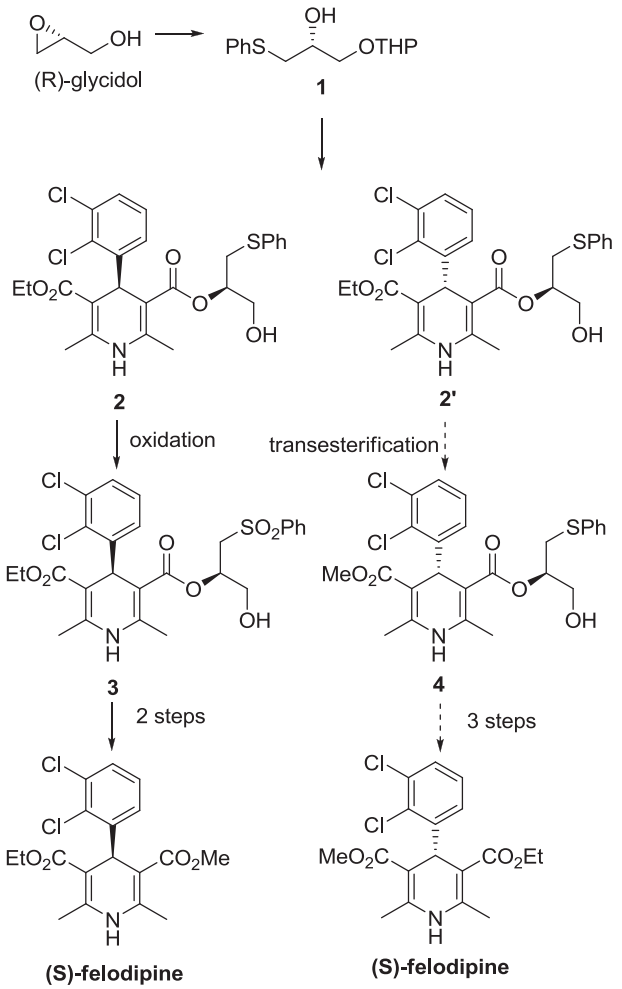
preparation of single enantiomers utilized chiral resolution through separation of diastereomers with chiral auxiliaries[4c,9] or diastereomeric salts,[6,10] or through enzymatic separation.[11] A process for chiral amlodipine was developed using the chiral resolution of two enantiomers through diastereomeric salt formation.[6]

In 1989, Lamm reported a preparation of (*S*)-felodipine, that is, the more potent drug than the (*R*)-isomer, using (*R*)-3-chloropropane-1,2-diol as the starting material for the chiral auxiliary.[9] Diastereomers of the 1,4-dihydropyridine obtained through Hantzsch reaction were separated and were converted into enantiomerically pure felodipines. Lamm was able to determine the absolute stereochemistry of the more potent isomer as the (*S*)-isomer. We became interested in developing a practical route to (*S*)-felodipine and decided to modify Lamm's synthetic route in a hope to convert both diastereomeric 1,4-dihydropyridines obtained from Hantzsch reaction into (*S*)-felodipine as shown in the Scheme 1.



Scheme 1. Synthetic plan of (*S*)-felodipine from glycidol.

Since the chiral auxiliary in Lamm's synthesis could be prepared from (*R*)-glycidol that has become commercially available in large quantity, we believed that (*R*)-glycidol would allow this synthetic route to be a practical one. Another modification would be the deferment of the sulfide oxidation to sulfone with a plan to convert both diastereomers obtained through Hantzsch reaction into (*S*)-felodipine. The sulfonyl group that is used to discriminate two esters of the dihydropyridine core would be introduced after the separation of two diastereomeric sulfide intermediates **2** and **2′**. The isomer **2** with desired (*R*)-configuration will be oxidized to the sulfone **3** and will be converted to (*S*)-felodipine. The isomer **2′** with (*S*)-configuration could undergo transesterification reaction[12] to **4** with a hope that the ethyl ester will react faster than the other ester of secondary alcohol. After switching to the methyl ester, **4** will be converted into (*S*)-felodipine through oxidation to sulfone followed by the selective hydrolysis and ethyl ester formation. This synthetic strategy would be a highly efficient one since it does not waste undesired isomer separated through chiral resolution. Herein we report a discovery of hydroxyl group accelerated selective transesterification reaction and its application to the synthesis of (*S*)-felodipine, which was developed into a process for a large scale preparation of (*S*)-felodipine.[13]

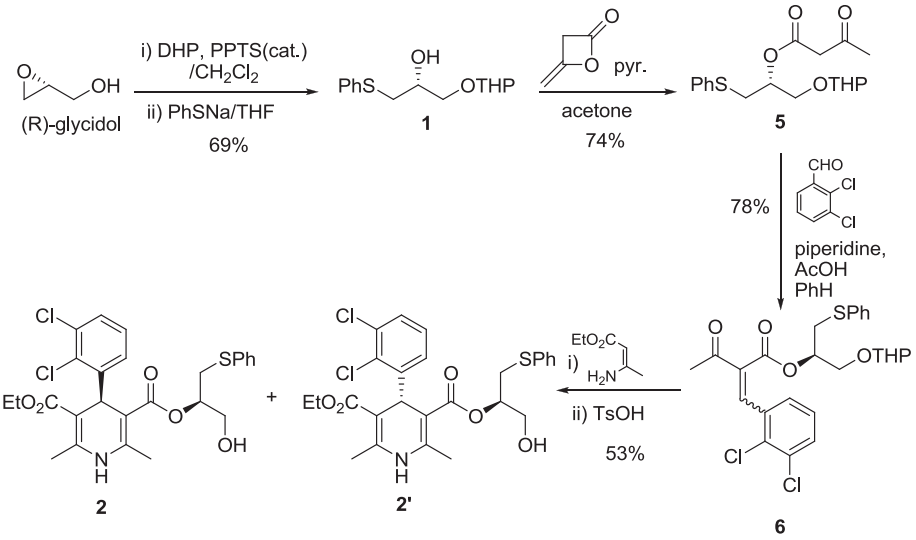
2. Result and discussion

The synthesis of (*S*)-felodipine started with (*R*)-glycidol by protecting the free alcohol as the THP ether (Scheme 2). The choice of (*R*)-glycidol was purely random as either enantiomer would form the same diastereomeric mixture only with mirror images. Though THP ether produced diastereomeric mixture in **1**, the sensitivity of glycidol under basic reaction conditions that were required for the introduction of many other protecting groups made the THP group as the preferred protecting group especially for a large scale reaction. Next, the epoxide was treated with the thiophenoxide anion to produce the secondary alcohol **1**. With the chiral auxiliary **1** in hand, synthesis of 1,4-dihydropyridine was accomplished in three step sequence. Esterification of **1** with diketene produced **5** and it was converted into **6** through Knoevenagel reaction with 2,3-dichlorobenzaldehyde. After the Hantzsch ester synthesis from **6** and ethyl 3-aminocrotonate, the THP protecting group was removed from the 1,4-dihydropyridine to produce diastereomeric products **2** and **2′**. At this stage, since the desired isomer **2** would be converted into the corresponding sulfone that was known to produce (*S*)-felodipine through eliminative hydrolysis of the chiral auxiliary followed by esterification reaction, feasibility of the selective transesterification reaction of the undesired isomer **2′** was examined.

The transesterification reaction by NaOMe was tested using varying amount of NaOMe, concentration, and reaction time (Table 1). To our surprise, completely unexpected selectivity of the transesterification reaction was observed. In all cases, transesterification reaction proceeded faster at the ester of the chiral auxiliary. When 3 equiv of NaOMe was used, equal mixture of felodipine and dimethyl ester **9** was obtained with complete conversion after 20 h (entry 1). When the reaction time was shortened to 6 h, the conversion was still complete and the amount of **9** was reduced substantially. When the amount of NaOMe was reduced, the ratio of **8**/**9** improved further (entries 3 and 4). When the concentration of the reaction was doubled to expedite the reaction, conversion was complete in 5.5 h without the formation of **9** (entry 7). For comparison, when **7** was treated under the transesterification reaction condition, no transesterification product was observed (entry 8). This result indicated that the free hydroxyl group of **2** not only facilitate the hydrolysis of the chiral ester but also affected the transesterification reaction of the ethyl ester of **2**.

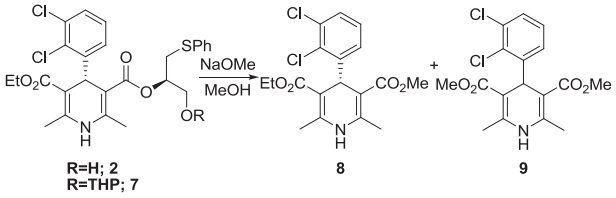
To further confirm the role of the free hydroxyl group in the transesterification reaction, a sterically hindered model substrate **10** was subjected to the transesterification reaction with NaOMe. The transesterification reaction proceeded cleanly to produce the corresponding methyl ester. When the free hydroxyl group of **10** was protected as THP ether, no transesterification reaction was observed (Scheme 3).

These results clearly demonstrated that the free hydroxyl group played an activating role in the transesterification reaction. It is presumed that the alkoxide generated from the free hydroxyl group coordinated to the ester carbonyl group intramolecularly to activate

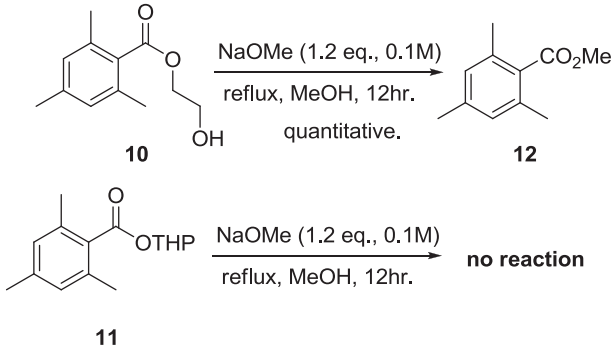


Scheme 2. Preparation of the 1,4-dihydropyridine intermediates for (*S*)-felodipine.

Table 1
Selectivity and reactivity of the transesterification reaction



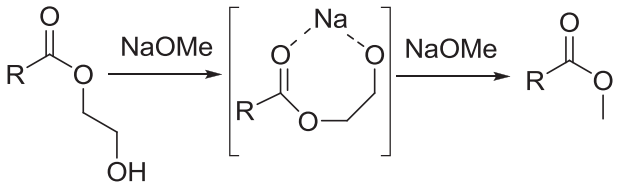
Entry	Substrate	Equiv/concn	Time (h)	Conversion (%)	**8/9**
1	**2**	3/0.2	20	100	1/1.7
2	**2**	3/0.2	6	100	1/0.4
3	**2**	1.1/0.2	16	100	1/0.2
4	**2**	1.1/0.2	9	100	1/0.1
5	**2**	1.1/0.4	8	100	1/0.3
6	**2**	1.1/0.4	6	100	1/0.2
7	**2**	1.1/0.4	5.5	100	1/0
8	**7**	3/0.2	20	0	—



Scheme 3. Hydroxyl group promoted transesterification reaction.

the ester group that would react with methoxide or methanol faster than the unactivated ester group (Scheme 4). A similar observation was reported for the selective transesterification reaction of β-ketoesters presumably through a same type of activation mechanism.[14]

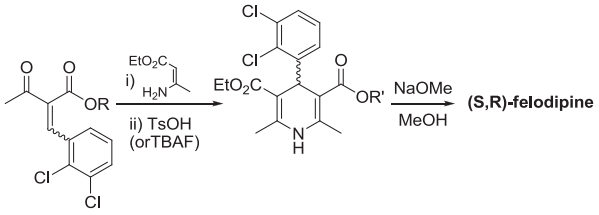
The selective transesterification reaction of 2-hydroxyethyl esters changed the synthetic strategy of asymmetric synthesis of

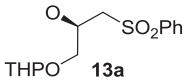
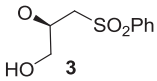
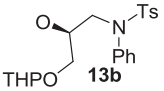
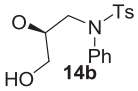
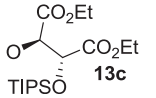
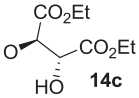


Scheme 4. Plausible activation pathway of the ester group.

1,4-dihydropyridine compounds. This reaction eliminated the requirement of an electron-withdrawing group for the selective hydrolysis and allowed exploration of a possible asymmetric induction during Hantzsch dihydropyridine synthesis using various chiral auxiliaries. Substituting thiophenyl group with seemingly bulkier groups, such as sulfone, tartrate or sulfonamide of aniline for the Hantzsch reaction did not induce any diastereoselectivity (Table 2). From the substituent similar in size (entry 1) to larger

Table 2
Chiral induction in Hantzsch reaction



Entry	OR	OR′	Yield[a] (ratio)	Yield (%)
1	 **13a**	 **3**	54% (1/1)	80[b]
2	 **13b**	 **14b**	52% (1/1)	84
3	 **13c**	 **14c**	44% (1/1)	—

[a] Yield for Hantzsch reaction and deprotection.
[b] Yield for transesterification reaction of the (*R*)-isomer.

substituents (entries 2 and 3), no bias was observed. Nevertheless, in all cases except tartrate ester (entry 3), transesterification reaction of the 2-hydroxyethyl esters, **14a** and **14b** produced felodipine selectively. Inability of the selective transesterification reaction with the tartrate ester also supports the mechanism in the Scheme 4 as other coordination structures, which do not activate the ester group are possible in **14c** for the selective transesterification reaction.

Since we have discovered that 2-hydroxyethyl esters undergo transesterification reaction with NaOMe selectively, **2** was converted into (*S*)-felodipine directly through the transesterification reaction with NaOMe. Thus the synthetic steps of (*S*)-felodipine from (*R*)-glycidol was shortened to seven step sequence.

3. Conclusion

We have discovered that esters containing 2-hydroxyethyl groups undergo selective transesterification reaction in the presence of other alkyl esters. This selective transesterification reaction was applied to the synthesis of (*S*)-felodipine starting from (*R*)-glycidol in seven step sequence through resolution of two isomers obtained via Hantzsch reaction. The selective transesterification reaction eliminated the introduction of electron-withdrawing group in the ester group and selective hydrolysis–esterification steps. We are currently probing the activation mechanism, scope, and limitation of the selective transesterification reaction of 2-hydroxyethyl esters.

4. Experimental

4.1. General methods

All oxygen or moisture sensitive reactions were carried out in oven-dried glassware under the positive pressure of argon. Sensitive liquids and solutions were transferred by syringe or cannula and introduced through rubber septa through which a high flow of argon was maintained. Unless otherwise stated, reactions were carried out at room temperature.

Concentration of solution was accomplished by using a Buchi rotary evaporator with an air pump. This was generally followed by removal of residual solvents on a vacuum line held at 0.1–1 Torr. Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Chromatography grade hexane and EtOAc were technical grade and distilled before used. Et_2O and THF were distilled from sodium–benzophenone ketyl under nitrogen. Triethylamine was distilled from sodium. Dichloromethane and dimethylformamide were distilled from P_2O_5. Benzene and toluene were washed with concentrated sulfuric acid and water, and then dried over sodium for more than 12 h before distillation. Concentration of alkyl lithium solutions was determined by titration against diphenylacetic acid. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. Visualization on TLC was achieved by use of UV light (254 nm), exposure to iodine vapor, or treatment with acidic anisaldehyde, potassium permanganate, 5% phosphomolybdic acid in ethanol, or ceric ammonium molybdate stain followed by heating. Flash column chromatography was undertaken on silica gel (Merck 60, 230–400 mesh ASTM). Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) was recorded on Bruker FT AM 300 (300 MHz) and Bruker FT AM 400 (400 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the singlet at 7.24 ppm for chloroform-*d*. The following abbreviations were used to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet. Coupling constant, *J* was reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on Brucker FT AM 300 (75 MHz) and Brucker FT AM 400 (100 MHz) and was fully decoupled by broad band decoupling. Chemical shifts were reported in parts per million referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Mass spectra were recorded on a VG AUTOSPEC Ultma GC/MS system using direct insertion probe (DIP) and electron impact (EI) (70 eV) method.

4.1.1. 2-(Oxiran-2-ylmethoxy)-tetrahydro-2H-pyran. Pyridinium *p*-toluenesulfonate (1.00 g, 4.05 mmol) and 3,4-dihydro-2*H*-pyran (11.3 mL, 121.5 mmol) were added to a stirred solution of oxiran-2-ylmethanol (6.00 g, 80.99 mmol) in dichloromethane (80 mL) at 0 °C under argon atmosphere. After 6 h, aqueous $NaHCO_3$ solution (60 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3×50 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/5). Product (9.22 g, 72%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 4.54–4.51 (m, 2H), 4.03–4.01 (m, 1H), 3.05–3.03 (m, 2H), 2.68–2.65 (m, 2H), 2.54–2.51 (m, 1H), 1.51–1.48 (m, 2H), 1.45–1.39 (m, 4H); Isomer 2; ^{1}H NMR (300 MHz, $CDCl_3$) 4.54–4.51 (m, 2H), 3.99–3.97 (m, 1H), 3.05–3.03 (m, 2H), 2.68–2.65 (m, 2H), 2.48–2.46 (m, 1H), 1.51–1.48 (m, 2H), 1.45–1.39 (m, 4H).

*4.1.2. (2S)-1-(Phenylthio)-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-ol (**1**).* Benzenethiol (6.87 mL, 67.2 mmol) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 2.65 g, 67.2 mmol) in THF (50 mL) at 0 °C under argon atmosphere. After 30 min, a solution of 2-(oxiran-2-ylmethoxy)-tetrahydro-2*H*-pyran (9.22 g, 58.3 mmol) in THF (50 mL) was added to the reaction mixture at 0 °C and gradually warmed to room temperature. After 5 h, aqueous NH_4Cl solution (30 mL) was added and the layers were separated. Aqueous layer was extracted with EtOAc (3×50 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/5). Product (14.23 g, 96%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.36–7.35 (d, *J*=7.3 Hz, 2H), 7.26–7.21 (t, *J*=7.8 Hz, 2H), 7.16–7.11 (t, *J*=7.1 Hz, 1H), 4.52–4.51 (m, 1H), 3.85–3.78 (m, 2H), 3.67–3.62 (m, 2H), 3.5–3.48 (m, 1H), 3.38 (br s, 1H), 3.08–3.01 (m, 2H), 1.73–1.68 (m, 2H), 1.55–1.47 (m, 4H); Isomer 2; ^{1}H NMR (300 MHz, $CDCl_3$) 7.36–7.35 (d, *J*=7.3 Hz, 2H), 7.26–7.21 (t, *J*=7.8 Hz, 2H), 7.16–7.11 (t, *J*=7.1 Hz, 1H), 4.5–4.77 (m, 1H), 3.85–3.78 (m, 2H), 3.67–3.62 (m, 2H), 3.5–3.48 (m, 1H), 3.35 (br s, 1H), 3.08–3.01 (m, 2H), 1.73–1.68 (m, 2H), 1.55–1.47 (m, 4H).

*4.1.3. (R)-1-(Phenylthio)-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-yl 3-oxobutanoate (**5**).* Pyridine (0.875 mL, 10.6 mmol) and diketene (5.35 g, 63.62 mmol) were added to a stirred solution of (2*S*)-1-(phenylthio)-3-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-ol (14.23 g, 53.02 mmol) in acetone (106 mL) at room temperature and refluxed under argon atmosphere. After 4 h, the mixture was cooled to room temperature and then water (50 mL) was added to the reaction mixture and the layers were separated. Aqueous layer was extracted with EtOAc (3×50 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/5). Product (13.81 g, 74%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.39–7.34 (d, *J*=7.2 Hz, 2H), 7.28–7.23 (t, *J*=8.3 Hz, 2H), 7.19–7.15 (t, *J*=6.9 Hz, 1H), 5.16–5.13 (m, 1H), 4.57–4.56 (m, 1H), 3.90–3.88 (d, *J*=4.7 Hz, 1H), 3.76–3.72 (m, 1H), 3.61–3.57 (m, 1H), 3.5–3.48 (m, 1H), 3.33–3.32 (d, *J*=4.7 Hz, 2H), 3.2–3.15 (m, 2H), 2.21 (s, 3H), 1.7–1.62 (m, 2H), 1.56–1.22 (m, 4H); Isomer 2; 7.39–7.34 (d, *J*=7.2 Hz, 2H), 7.28–7.23 (t,

J=8.3 Hz, 2H), 7.19–7.15 (t, J=6.9 Hz, 1H), 5.16–5.13 (m, 1H), 4.51–4.49 (m, 1H), 3.87–3.85 (d, J=4.6 Hz, 1H), 3.76–3.72 (m, 1H). 3.61–3.57 (m, 1H), 3.5–3.48 (m, 1H), 3.33–3.32 (d, J=4.7 Hz, 2H), 3.2–3.15 (m, 2H), 2.21 (s, 3H), 1.7–1.62 (m, 2H), 1.56–1.22 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.1, 166.4, 135.4129.8, 129.0, 128.9, 128.9, 128.8, 126.5, 99.0, 98.5, 72.9, 72.6, 66.7, 66.4, 62.0, 61.9, 49.9, 34.2, 34.1, 30.3, 30.2, 30.0, 29.9, 25.2, 19.1, 19.0; High resolution mass (ESI): calculated for $C_{18}H_{24}O_5S$ $[M+Na]^+$: 375.1242, found: 375.1251.

*4.1.4. (R)-1-(Phenylthio)-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-yl 2-(2,3-dichlorobenzylidene)-3-oxobutanoate (**6**).* 2,3-Dichlorobenzaldehyde (8.23 g, 47.02 mmol), piperidine (1.16 mL, 17.75 mmol), and acetic acid (1.02 mL, 17.75 mmol) were slowly added to a stirred solution of (*R*)-1-(phenylthio)-3-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl 3-oxobutanoate (13.81 g, 39.18 mmol) in benzene (80 mL) at room temperature under argon atmosphere. The resulting mixture was refluxed and water was removed using Dean–Stark apparatus. After 2 h, mixture was cooled to room temperature and then water (80 mL) was added and the layers were separated. Aqueous layer was extracted with EtOAc (3×50 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/5). Product (15.57 g, 78%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81–7.79 (d, J=7.8 Hz, 1H), 7.42–7.31 (m, 2H), 7.32–7.29 (d, J=6.8 Hz, 1H), 7.27–7.24 (m, 3H), 7.19–7.15 (m, 2H), 5.32–5.27 (m, 1H), 4.54–4.51 (d, J=11.4 Hz, 1H), 3.99–3.96 (m, 1H), 3.82–3.8 (m, 1H), 3.46–3.43 (m, 2H), 3.27–3.25 (m, 1H), 3.12–3.1 (m, 1H), 2.2 (s, 3H), 1.63–1.6 (m, 2H), 1.5–1.46 (m, 4H); Isomer 2; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81–7.79 (d, J=7.8 Hz, 1H), 7.42–7.31 (m, 2H), 7.32–7.29 (d, J=6.8 Hz, 1H), 7.27–7.24 (m, 3H), 7.19–7.15 (m, 2H), 5.22–5.15 (m, 1H), 4.45–4.42 (d, J=11.3 Hz, 1H), 3.8–3.79 (m, 1H), 3.74–3.7 (m, 1H), 3.46–3.43 (m, 2H), 3.27–3.25 (m, 1H), 3.12–3.1 (m, 1H), 2.2 (s, 3H), 1.63–1.6 (m, 2H), 1.5–1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.9, 194.0, 194.0, 171.1, 165.9, 136.9, 135.3, 133.6, 131.6, 131.6, 131.6, 129.7, 129.7, 129.4, 129.3, 129.0, 129.0, 129.0, 129.0, 128.3, 127.8, 127.4, 127.4, 126.4, 98.8, 98.6, 73.4, 73.1, 66.3, 66.1, 62.0, 61.9, 60.3, 33.8, 31.5, 31.1, 30.2, 30.2, 27., 25.3, 25.2, 25.2, 25.2, 22.5, 20.9, 19.1, 19.0, 18.9, 14.1, 14.0; High resolution mass (ESI): calculated for $C_{25}H_{26}Cl_2O_5S$ $[M+Na]^+$: 531.0776, found: 531.0774.

*4.1.5. 3-Ethyl 5-(S)-1-(phenylthio)-3-(tetrahydro-2H-pyran-2-yloxy) propan-2-yl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**7**).* Ethyl 3-aminocrotonate (4.63 mL, 36.63 mmol) was added to a stirred solution of (*R*)-1-(phenylthio)-3-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl 2-(2,3-dichlorobenzylidene)-3-oxobutanoate (15.57 g, 30.56 mmol) in pyridine (31 mL) and then refluxed. After 4 h, mixture was cooled to room temperature and aqueous $CuSO_4$ solution (50 mL) was added and the layers were separated. Aqueous layer was extracted with EtOAc (3×50 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/1). Product (13.65 g, 72%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.36–7.26 (m, 2H), 7.23–7.2 (m, 4H), 7.18–7.12 (m, 1H), 7.06–7.03 (m, 1H), 5.68 (br s, 1H), 5.42 (s, 1H), 5.12–5.1 (m, 1H), 4.57–4.5 (m, 1H), 4.06–4.02 (q, J=6.9 Hz, 2H), 3.76–3.67 (m, 2H), 3.42–3.4 (m, 2H), 3.2–3.16 (m, 1H), 3.01–2.97 (m, 1H), 2.26 (s, 6H), 1.6–1.49 (m, 2H), 1.55–1.43 (m, 4H) 1.18–1.13 (t, J=3.1 Hz, 3H); Isomer 2; ^{1}H NMR (300 MHz, $CDCl_3$) 7.36–7.26 (m, 2H), 7.23–7.2 (m, 4H), 7.18–7.12 (m, 1H), 7.06–7.03 (m, 1H), 5.64 (br s, 1H), 5.33–5.29 (d, J=12.2 Hz, 1H), 5.12–5.1 (m, 1H), 4.4–4.1 (m, 1H), 4.06–4.02 (q, J=6.9 Hz, 2H), 3.98–3.92 (m, 1H), 3.86–3.74 (m, 2H), 3.31–3.29 (m, 1H), 3.2–3.16 (m, 1H), 3.06–3.05 (m, 1H), 2.26 (s, 6H), 1.6–1.49 (m, 2H), 1.55–1.43 (m, 4H) 1.18–1.13 (t, J=3.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.4, 167.3, 166.4, 157.2, 147.9, 147.5, 144.0, 136.0, 132.8, 132.7, 130.2, 129.8, 129.6, 129.6, 129.1, 129.1, 128.8, 128.8, 128.2, 128.1, 128.1, 126.9, 126.8, 126.1, 125.9, 103.8, 103.5, 98.9, 98.8, 98.2, 71.0, 70.9, 70.5, 66.7, 61.6, 61.6, 59.7, 39.0, 38.7, 38.6, 30.3, 30.2, 25.3, 25.3, 19.9, 19.8, 19.5, 19.4, 19.1, 19.0, 14.2; High resolution mass (ESI): calculated for $C_{31}H_{35}Cl_2NO_6S$ $[M+Na]^+$: 642.1460, found: 642.1461.

*4.1.6. (R)-3-Ethyl 5-((S)-1-hydroxy-3-(phenylthio)propan-2-yl) 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2**).* *p*-Toluenesulfonic acid monohydrate (395 mg, 2.075 mmol) was added to a stirred solution of 3-ethyl 5-(*S*)-1-(phenylthio)-3-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (644 mg, 1.038 mmol) in ethanol (4 mL) at room temperature under argon atmosphere. After 2 h, water (8 mL) was added and the layers were separated. Aqueous layer was extracted with EtOAc (3×5 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/benzene=1/2). Product (412 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) 7.36–7.33 (d, J=7.6 Hz, 1H), 7.3–7.28 (m, 1H), 7.27–7.22 (m, 4H), 7.15–7.12 (m, 1H), 7.06–7.03 (m, 1H), 6.05 (s, 1H), 5.39 (s, 1H), 4.98–4.95 (m, 1H), 4.09–4.02 (m, 2H), 3.81–3.77 (m, 1H), 3.59–3.57 (m, 1H), 3.18–3.14 (m, 1H), 2.92–2.87 (m, 1H), 2.26–2.23 (d, J=6.1 Hz, 6H), 1.2–1.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.3, 166.7, 147.9, 146.2, 143.8, 135.4, 132.7, 130.6, 129.8, 129.5, 129.0, 128.8, 128.2, 127.0, 126.2, 103.2, 102.0, 77.3, 76.9, 76.6, 73.1, 63.1, 60.3, 59.7, 38.6, 34.0, 19.6, 19.2, 14.2; High resolution mass (ESI): calculated for $C_{26}H_{27}Cl_2NO_5S$ $[M+Na]^+$: 558.0885, found: 558.0912.

*4.1.7. (S)-3-Ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**8**).* Sodium (5 mg, 0.2174 mmol) was added to a methanol (0.5 mL) and stirred for 30 min. That NaOMe solution in methanol (0.5 mL) was added to a neat (*R*)-3-ethyl 5-((*S*)-1-hydroxy-3-(phenylthio)propan-2-yl) 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (107 mg, 0.1995 mmol) and mixture was refluxed. After 5.5 h, solvent was removed using evaporator, and aqueous ammonium chloride solution (10 mL) was added. Aqueous layer was extracted with EtOAc (3×10 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/2). (*S*)-Felodipine (64.4 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) 7.37–7.28 (m, 2H), 7.14–7.09 (t, J=7.9 Hz, 1H), 5.87 (br s, 1H), 5.52 (s, 1H), 4.16–4.09 (q, J=7.4 Hz, 2H), 3.66 (s, 3H), 2.39–2.35 (d, J=3.1 Hz, 6H), 1.26–1.21 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.8, 167.3, 148.1, 144.2, 144.2, 132.7, 130.9, 129.6, 128.1, 126.9, 103.8, 103.4, 59.8, 50.8, 38.5, 19.4, 19.4, 14.2; High resolution mass (ESI): calculated for $C_{18}H_{19}Cl_2NO_4$ $[M+Na]^+$: 406.0589, found: 406.0583; $[\alpha]_D^{24.5}$ −7.13 (*c* 1.0 in CH_3OH, 589 nm)[lit.: $[\alpha]_D^{24.5}$ −7.3 (*c* 1.0 in CH_3OH, 589 nm)].

*4.1.8. (4R)-3-Ethyl 5-((2R)-1-(phenylsulfonyl)-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-yl) 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3**).* Oxone (196 mg, 0.318 mmol) was added to a stirred solution of 3-ethyl 5-(*S*)-1-(phenylthio)-3-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (68 mg, 0.127 mmol) in DMF (5.0 mL) at room temperature under argon atmosphere. After 12 h, $NaHSO_3$ (250 mg) was added and stirred for 5 min. Water (5 mL) and saturated NaCl solution (2.5 mL) were added and the layers were separated. Aqueous layer was extracted with Et_2O (20×3 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane=2/1). Product (52 mg, 72%); ^{1}H NMR (300 MHz, $CDCl_3$) 7.87–7.85 (d, J=7.3 Hz, 2H),

7.57–7.52 (m, 1H), 7.51–7.46 (m, 2H), 7.26–7.2 (m, 2H), 7.09–7.05 (t, *J*=5.8 Hz, 1H), 6.06 (s, 1H), 5.34–5.32 (m, 1H), 4.82 (s, 1H), 4.07–4.02 (m, 2H), 3.71–3.65 (dd, *J*=14.8 Hz, 8.4 Hz, 1H), 3.48–3.44 (dd, *J*=14.8 Hz, 3.3 Hz, 1H), 3.37–3.36 (m, 2H), 2.25–2.22 (d, *J*=2.9 Hz, 6H), 1.54–1.52 (br s, 1H), 1.17–1.12 (m, 3H).

*4.1.9. (S)-3-Ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**8**) from compound **3**.* 0.3 M KOH solution (0.305 mL, 0.0909 mmol) was added to a stirred solution of (4*R*)-3-ethyl 5-((2*R*)-1-(phenylsulfonyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl) 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (53 mg, 0.0909 mmol) in anhydrous MeOH (1 mL) at room temperature under argon atmosphere. After 1 h, solvent was removed. MeI (0.012 mL, 0.1818 mmol) was added to a stirred solution of crude mixture in DMF (1 mL) at room temperature under argon atmosphere. After 1 h, mixture was diluted with EtOAc (2 mL) and water (2 mL) was added. Aqueous layer was extracted with EtOAc (3×3 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane=1/2). (*S*)-Felodipine (32 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) 7.37–7.28 (m, 2H), 7.14–7.09 (t, *J*=7.9 Hz, 1H), 5.87 (br s, 1H), 5.52 (s, 1H), 4.16–4.09 (q, *J*=7.4 Hz, 2H), 3.66 (s, 3H), 2.39–2.35 (d, *J*=3.1 Hz, 6H), 1.26–1.21 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.8, 167.3, 148.1, 144.2, 144.21, 132.7, 130.9, 129.6, 128.1, 126.9, 103.8, 103.4, 59.8, 50.8, 38.5, 19.4, 19.4, 14.2; High resolution mass (ESI): calculated for $C_{18}H_{19}Cl_2NO_4$ $[M+Na]^+$: 406.0589, found: 406.0583; $[\alpha]_D^{24.5}$ −5.2 (*c* 1.0 in CH_3OH, 589 nm) [lit.: $[\alpha]_D^{24.5}$ −7.3 (*c* 1.0 in CH_3OH, 589 nm)].

*4.1.10. General procedure for compound **3** and **14b** from **13a** and **13b**.* Ethyl 3-aminocrotonate (1.2 equiv) was added to a stirred solution starting material (1 equiv) in pyridine (1.0 M) and then refluxed. After 4 h, mixture was cooled to room temperature and aqueous $CuSO_4$ solution was added and the layers were separated. Aqueous layer was extracted with EtOAc three times. Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel to give dicarboxylate product.

p-Toluenesulfonic acid monohydrate (2 equiv) was added to a stirred solution of dicarboxylate (1 equiv) in ethanol (0.25 M) at room temperature under argon atmosphere. After 2 h, water was added and the layers were separated. Aqueous layer was extracted with EtOAc three times. Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel to give the product. Compound **14b** (65%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.41–7.39 (d, *J*=8.5 Hz, 1H), 7.36–7.34 (d, *J*=7.9 Hz, 1H), 7.24–7.16 (m, 7H), 7.02–7.00 (m, 1H), 6.93–6.9 (m, 1H), 6.89–6.85 (m, 1H), 6.48 (s, 1H), 5.29 (s, 1H), 4.82–4.79 (m, 1H), 4.02–3.99 (m, 2H), 3.9–3.85 (m, 2H), 3.81–3.79 (d, *J*=5.3 Hz, 1H), 3.7–3.66 (m, 1H), 3.13–3.11 (m, 1H), 2.38–2.37 (d, *J*=8.6 Hz, 3H), 2.19–2.17 (d, *J*=7.9 Hz, 3H), 2.12–2.09 (d, *J*=7.6 Hz, 3H), 1.15–1.1 (m, 3H); Isomer 2; 7.41–7.39 (d, *J*=8.5 Hz, 1H), 7.36–7.34 (d, *J*=7.9 Hz, 1H), 7.24–7.16 (m, 7H), 7.02–7.00 (m, 1H), 6.93–6.9 (m, 1H), 6.89–6.85 (m, 1H), 6.36 (s, 1H), 5.0 (s, 1H), 4.74–4.71 (m, 1H), 4.02–3.99 (m, 2H), 3.9–3.85 (m, 2H), 3.81–3.79 (d, *J*=5.3 Hz, 1H), 3.6–3.52 (m, 1H), 2.8–2.79 (m, 1H), 2.38–2.37 (d, *J*=8.6 Hz, 3H), 2.19–2.17 (d, *J*=7.9 Hz, 3H), 2.12–2.09 (d, *J*=7.6 Hz, 3H), 1.15–1.1 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.6, 147.4, 145.7, 145.6, 143.8, 143.8, 143.6, 139.7, 139.0, 134.9, 134.4, 132.9, 132.7, 130.9, 130.3, 130.3, 129.5, 129.5, 129.1, 128.9, 128.5, 128.3, 128.2, 127.9, 127.7, 126.9, 126.8, 103.7, 103.5, 102.3, 102.0, 72.5, 71.7, 61.5, 60.4, 59.9, 59.8, 49.8, 48.8, 39.0, 38.8, 21.6, 21.0, 20.0, 19.8, 19.4, 14.2, 14.1; High resolution mass (ESI): calculated for $C_{33}H_{34}Cl_2N_2O_7S$ $[M+Na]^+$: 695.1361, found: 695.1392.

*4.1.11. 3-(2R,3R)-1,4-Diethoxy-3-hydroxy-1,4-dioxobutan-2-yl 5-ethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**14c**).* Ethyl 3-aminocrotonate (0.062 mL, 0.486 mmol) was added to a stirred solution of (2*R*,3*R*)-diethyl 2-(2-(2,3-dichlorobenzylidene)-3-oxobutanoyloxy)-3-(triisopropylsilyloxy) succinate (266 mg, 0.4417 mmol) in pyridine (2 mL) and then refluxed. After 6 h, mixture was cooled to room temperature and aqueous $CuSO_4$ solution (4 mL) was added and the layers were separated. Aqueous layer was extracted with EtOAc (3×3 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexane=1/2). Product (200 mg, 64%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.28 (m, 1H), 7.27–7.15 (m, 1H), 7.01–6.98 (m, 1H), 6.28 (s, 1H), 5.535.52 (d, *J*=2.8 Hz, 1H), 5.44 (s, 1H), 4.89–4.88 (m, 1H), 4.15–4.09 (m, 2H), 4.01–3.98 (m, 4H), 2.28 (s, 6H), 1.22–1.18 (m, 6H), 1.16–1.14 (m, 3H), 1.00–0.82 (m, 2H); Isomer 2; ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.28 (m, 1H), 7.27–7.15 (m, 1H), 7.01–6.98 (m, 1H), 6.21 (s, 1H), 5.49–5.48 (d, *J*=2.7 Hz, 1H), 5.53 (s, 1H), 4.89–4.88 (m, 1H), 4.01–3.98 (m, 1H), 3.80–3.77 (m, 2H), 2.22 (s, 6H), 1.22–1.18 (m, 6H), 1.16–1.44 (m, 3H), 1.00–0.82 (m, 2H).

1.0 M solution of tetrabutylammonium fluoride (1.0 mL) was added to a stirred solution of 3-(2*R*,3*R*)-1,4-diethoxy-1,4-dioxo-3-(triisopropylsilyloxy)butan-2-yl 5-ethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (150 mg, 0.21 mmol) in THF (2 mL) at room temperature under argon atmosphere. After 5 min, water (3 mL) was added and layers were separated. Aqueous layer was extracted with EtOAc (3×3 mL). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane=1/1). Product (80 mg, 68%); Isomer 1; ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.21 (m, 2H), 7.07–7.04 (m, 1H), 6.19 (s, 1H), 5.56–5.55 (d, *J*=2.3 Hz, 1H), 5.44 (s, 1H), 4.69–4.67 (m, 1H), 4.08–3.99 (m, 4H), 2.26–2.25 (d, *J*=3.7 Hz, 6H), 1.26–1.09 (m, 6H); Isomer 2;; ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.21 (m, 2H), 7.07–7.04 (m, 1H), 6.14 (s, 1H), 5.49–5.48 (d, *J*=2.3 Hz, 1H), 5.40 (s, 1H), 4.69–4.67 (m, 1H), 4.08–3.99 (m, 4H), 2.26–2.25 (d, *J*=3.7 Hz, 6H), 1.26–1.09 (m, 6H). High resolution mass (ESI): calculated for $C_{25}H_{29}Cl_2NO_9$ $[M+Na]^+$: 580.1117, found: 580.1137.

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References and notes

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