Organic Process Research & Development **2009**, *13,* 1382–1386

# A Novel Chiral Resolving Reagent, Bis((*S*)-Mandelic acid)-3-nitrophthalate, for Amlodipine Racemate Resolution: Scalable Synthesis and Resolution Process

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**Abstract:**

**A novel bis((*S*)-mandelic acid)-3-nitrophthalate (1), a chiral resolving reagent for the separation of (*S*)-(−)-isomers of amlodipine from the racemate thereof, is designed and synthesized. A simple three-step pilot-scale preparation of 1, along with the optimization of a resolution process on the racemate amlodipine, is reported.**

## Introduction

Amlodipine (Figure 1**)** and its salts are long-acting calcium channel blockers used in the treatment of angina, congestive heart failure, and hypertension. It is being used in its enantiomeric mixture of salt forms, but the two enantiomers of amlodipine and their salts have different pharmacological profiles. The (*S*)-(−)-isomer is the more potent calcium channel blocker showing about 2000-fold potency in in vitro evaluation in the rat aorta than the (*R*)-(+)-isomer.[1] While a number of sources in the literature and patents have reported the separation of (*S*)-(−)-amlodipine from its racemate,[2] four selective diastereomeric salt crystallization methods have showed promising results for industrial application: (i) of (*S*)-amlodipine-hemi-D-tartrate salt in the presence of DMSO,[2d] (ii) of (*S*)-amlodipine-hemiLtartrate salt via processing the filtered solution of (*R*)-amlodipine-hemi-L-tartrate salt in DMSO,[2e] (iii) of (*S*)-amlodipine-hemidibenzoyl-D-tartrate salt,[2f] (iv) of (*S*)-amlodipine-hemi-(1*R*, 3*S*)-camphorate salt.[2g]

However, these methods have some limitations and undesirable aspects to be used in industrial-scale production. For example, DMSO used in methods (i) and (ii) can cause rotten cabbage odor problems by dimethyl sulfide in conventional municipal wastewater treatment.[3] On the manufacturing side, a relatively high freezing point makes the manufacturer's handling unfavorable because at, or just below, room temperature it is a solid, which limits its efficacy in the crystallization process. Furthermore, solvent recovery is inconvenient due to its high boiling point. Method (iii) uses isopropanol as the main crystallization solvent to overcome the problems of DMSO with the relatively expensive dibenzoyl derivative of D-tartaric acid, but we found in our test experiments that this diastereomeric salt has wet, cakelike crystal properties not suitable for industrial-scale filtration. Method (iv) merely demonstrates less than a 10-g scale of (*S*)-amlodipine separation from its racemate which is not a sufficient demonstration for a large-scale application; in addition the corresponding (*S*)-amlodipine-hemi-(1*R*, 3*S*)-camphorate salt has hygroscopic properties and quickly becomes quite wet after filtration. Therefore, it seemed worthwhile to develop and to optimize an alternative method. Our initial approach was to test other resolving reagents commonly used in industry with various solvent systems, but none of those trials was successful. Thus, we decided to design and develop a new resolving reagent. Two criteria were set for the desig of new resolving reagents. The new reagents (1) must be readily prepared from cheap commercial materials and (2) must be useable with solvents more suitable for an industrial crystallization process. Here we now report the scalable and commercially viable preparation and resolution process using our new chiral resolving reagent.

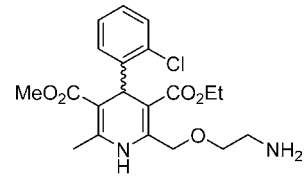


***Figure 1.*** **(*R*,*S*)-Amlodipine.**

## Results and Discussion

There are very few approaches to the rational design of resolving reagents because it is difficult to forecast small and subtle differences in interactions within the diastereoisomeric salts and their effect on crystal structure. Furthermore, the solvent plays a decisive role.[4] Thus, we have begun with the simple approach of incorporating additional functionality around the stereocenter of lactic acid or mandelic acid. Although there was no clear explanation, a literature reference suggested that added functionality—to increase interactions—should enhance rigidity of the compound.[4] We reasoned this is because a flexible resolving reagent can interact indiscriminately with both enantiomers by quickly adopting a structural change, whereas a rigid one would prefer either one of the diastreomeric

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10.1021/op900070c CCC: $40.75 
Published on Web 10/02/2009

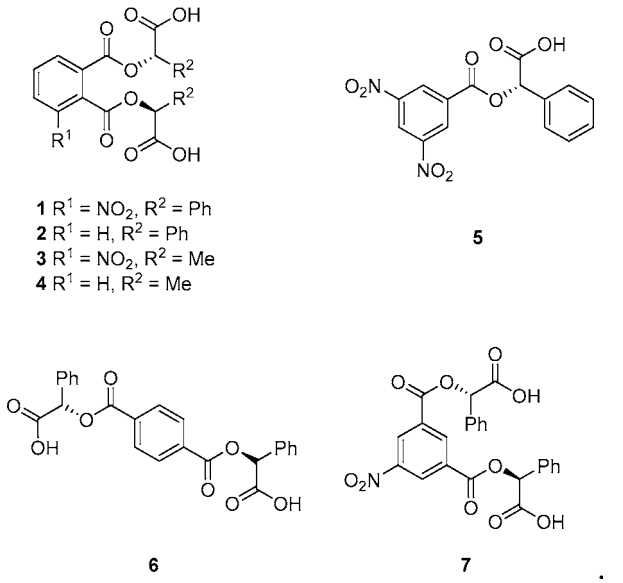


***Figure 2.*** **New chiral resolving reagents bearing phenyl functionality.**

***Table 1.*** **Representative prescreening result of resolving reagents on amlodipine resolution**[a]

| compound | solvent | yield of (*S*)-amlodipine·salt[b] | ee of (*S*)-amlodipine (%)[c] | $S_{exp}$[d] |
|---|---|---|---|---|
| **1** | IPA/MTBE/DCM (1/25/5) | 41 | 70 | 0.29 |
| **2**[e] | – | – | – | – |
| **3** | ACN/IPA (1/9) | 5 | 10 | 0.005 |
| **4**[e] | – | – | – | – |
| **5** | MEK/MTBE (4/1) | 10 | 87 | 0.09 |
| **6** | MEK/MTBE (5/1) | 52 | 20 | 0.10 |
| **7**[e] | – | – | – | – |

[a] Resolution experiments were conducted at temperatures between 15−20 °C. [b] Relative to the theoretical amount, i.e. half of the starting racemic amlodipine. [c] Enantiomeric excess (determined by HPLC) of the amlodipine liberated from the diastereomeric salt. [d] Experimental resolution efficiency or experimental resolvability, calculated from the chemical yield of the precipitated salt and the enantiomeric excess of the amlodipine liberated from the salt. [e] Precipitation was not observed in various solvents and solvent mixture systems.

salts for converse reasons. Phenyl functionality seemed fairly reasonable, considering the availability of various derivatives at low prices. Furthermore, it can add rigidity to a resulting diastereomeric salt. Seven candidates have been prepared by generally known procedures or following the literature preparation protocol (Figure 2),[5] and careful prescreening of these compounds revealed compound **1** as the best candidate (Table 1).[6]

Proton NMR analysis of this isolated salt revealed the ratio of 2:1, salt of (*S*)-amlodipine to compound **1**. Thus, optimization of resolution experiments with compound **1** was conducted in various solvent systems at the temperature range of 15−20 °C. As it is shown in entries 1−5 in Table 2, single polar solvent systems which usually provide good solubility for various organic molecules failed to form precipitates. Mixed solvent systems consisting of solvent and antisolvent generally gave

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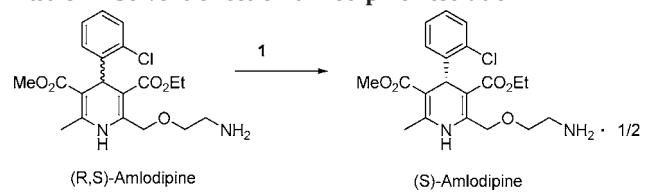
(6) For each of new chiral resolving reagent in Figure 2, about 20 sets of prescreening were run with the solvents chosen from ICH class 2 or class 3 solvents.

***Table 2.*** **Solvent effect on amlodipine resolution**[a]




| entry | solvent | yield of (*S*)-amlodipine· 1/2 **1** (%)[b] | ee of (*S*)-amlodipine (%)[c] | $S_{exp}$[d] |
|---|---|---|---|---|
| 1 | DMSO | – | – | – |
| 2 | DMF | – | – | – |
| 3 | MeOH | – | – | – |
| 4 | acetone | – | – | – |
| 5 | IPA | – | – | – |
| 6 | IPA/ACN (9/1) | – | – | – |
| 7 | MIBK | 86 | 64 | 0.55 |
| 8 | MEK/MTBE (5/1) | 62 | 81 | 0.50 |
| 9 | MEK/MTBE (10/1) | 46 | 80 | 0.37 |
| 10 | MEK/IPE (5/1) | 65 | 79 | 0.51 |
| 11 | MEK/IPE (10/1) | 59 | 88 | 0.52 |
| 12 | MEK | 65 | 96 | 0.62 |

[a] Resolution experiments were conducted at temperatures between 15−20 °C with 0.25 equiv of **1**. [b] Relative to the theoretical amount, i.e. half of the starting racemic amlodipine. [c] Enantiomeric excess (determined by HPLC) of the amlodipine liberated from the diastereomeric salt. [d] Experimental resolution efficiency or experimental resolvability, calculated from the chemical yield of the precipitated salt and the enantiomeric excess of the amlodipine liberated from the salt.

diastereomeric salt in good yields but with only moderate enantiomeric excesses. Finally, methyl ethyl ketone (MEK) gave diastereomeric salt in good yield with satisfactory resolution result (65%, 96% ee, entry 12). Furthermore, this diastereomeric salt showed relevant characteristics suitable for an industrial application: (1) nonhygroscopic and stable under relatively high humidity conditions (i.e., at relative humidities above about 60% and up to about 85%), (2) good filtration property for fast and easy collection of resulting salt. Upon reslurry of this diastereomeric salt in the mixed solvent system MEK/hexane (2/1) enrichment of enantiomeric exess to 97.5% was observed with a 92% recovery of yield. While the enantiomeric exess was improved up to >99% by the MEK/EtOH (5/1) slurry method, the recovery yield was only 80%; thus, this method was discarded. Reslurry of the diastereomeric salt was necessary to consistently obtain the final (*S*)-amlodipine besylate, which is the final ingredient for drug tablet, with >99% ee (Scheme 2). Although theoretical amount required for the resolution is 0.25 equiv, optimal amount of compound **1** was verified. Our experiment confirmed this theoretical amount as it is shown in Table 3. Comparable yield of diastereomeric salt was obtained when 0.5 equiv of compound **1** was used, but still the best resolution result was achieved again with 0.25 equiv of **1** (entry 2 in Table 3). The temperature factor was also investigated with the optimized amount of **1** in MEK single solvent (Table 4). Resolutions were conducted several times at the given temperatures to ensure the results were consistent. Temperatures below 10 °C (entry 1 and 2) or above 24 °C (entry 4), have not exceeded the result previously obtained at the temperature range between 15−20 °C (entry 3).

Since the preparation of compound **1** was done by a lab preparation procedure, we had to develop a scalable preparation

***Table 3.*** **Optimization of compound 1 equivalent[a]**

| entry | equivalent | yield of (*S*)-amlodipine·1/2 **1** (%)[b] | ee of (*S*)-amlodipine (%)[c] | $S_{exp}$[d] |
|---|---|---|---|---|
| 1 | 0.2 | 55 | 93 | 0.51 |
| 2 | 0.25 | 65 | 96 | 0.62 |
| 3 | 0.35 | 59 | 93 | 0.55 |
| 4 | 0.5 | 65 | 85 | 0.55 |

[a] Resolution experiments were conducted in MEK at temperatures between 15−20 °C. [b] Relative to the theoretical amount, i.e. half of the starting racemic amlodipine. [c] Enantiomeric excess (determined by HPLC) of the amlodipine liberated from the salt. [d] Experimental resolution efficiency or experimental resolvability, calculated from the chemical yield of the precipitated salt and the enantiomeric excess of the amlodipine liberated from the salt.

***Table 4.*** **Optimization of temperature[a]**

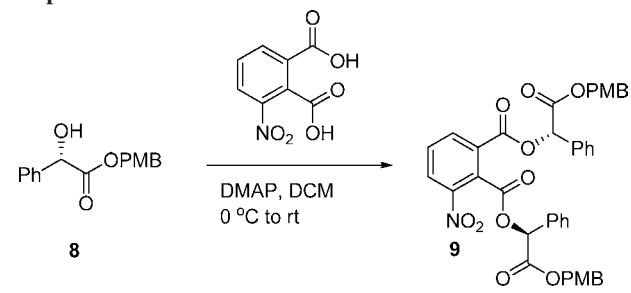
| entry | temperature | yield of (*S*)-amlodipine·1/2 **1** (%)[b] | ee of (*S*)-amlodipine (%)[c] | $S_{exp}$[d] |
|---|---|---|---|---|
| 1 | −2–5 °C | 85 | 0 | 0 |
| 2 | 5–10 °C | 76 | 71 | 0.32 |
| 3 | 15–20 °C | 61 | 96 | 0.59 |
| 4 | 24–26 °C | 54 | 90 | 0.49 |

[a] Resolution experiments were conducted 3 times at the given temperature in MEK with 0.25 equiv of **1**, and calculated mean values were recorded. [b] Relative to the theoretical amount, i.e. half of the starting racemic amlodipine. [c] Enantiomeric excess (determined by HPLC) of the amlodipine liberated from the salt. [d] Experimental resolution efficiency or experimental resolvability, calculated from the chemical yield of the precipitated salt and the enantiomeric excess of the amlodipine liberated from the salt.

procedure for compound **1**. Synthesis of our chiral resolving reagent began with (*S*)-mandelic acid protection with the *p*-methoxybenzyl (PMB) group. Initial preparation of compound **8** was done by using MeOH/water (5/1) cosolvent system following the literature protocol. While this preparation method was acceptable for lab-scale preparation, a significant amount of byproduct due to a PMB alkylation on the secondary alcohol of both starting compound and compound **8** were problematic for scale up. The cause of this byproduct formation was attributed to the unwanted cesium salt formation on the secondary alcohol; thus, we decided to remove water in order to take advantage of cesium carbonate's poor solubility in MeOH solvent. This slight change has made a significant difference in the reaction, and we were successfully able to obtain compound **8** without the byproduct problem in 89% yield. Next, the coupling reaction between compound **8** and 3-nitrophthalic acid was examined. Compound **9** was initially prepared by converting 3-nitrophthalic acid to the corresponding reactive acid chloride followed by the coupling reaction of this with compound **8** in the presence of weak bases, such as $Et_3N$ or pyridine, and column purification. This preparation method was also problematic because the phthalic anhydride formation took place prior to the coupling reaction. More than half of 3-nitrophthalic acid was converted to the corresponding phthalic anhydride. The nitro group on the 3-position would probably be responsible for this significant byproduct formation by increasing the reactivity of carboxylic acid chloride on the 2-position. Thus, we have decided to try less reactive carboxylic acid activating reagents (Table 5).

As can be seen in entry 5, mixed anhydride activation using ethyl chloroformate clearly gave disappointing results, offering no product after the reaction. Other mixed anhydride activations,

***Table 5.*** **Coupling reagent test for the preparation of compound 9**

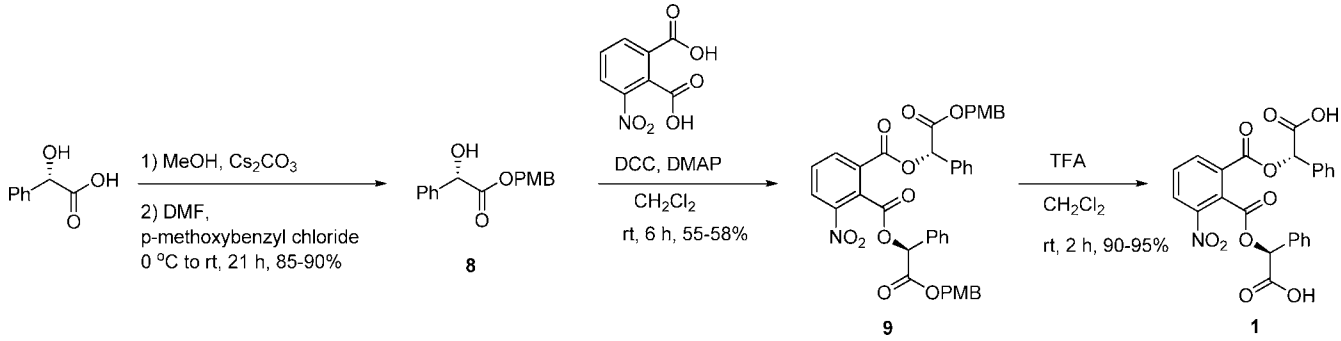



| entry | coupling reagent[a] | % yield[b] |
|---|---|---|
| 1 | $(EtO)_2P(O)Cl$ | 45 |
| 2 | $(EtO)_2P(S)Cl$ | 42 |
| 3 | $(MeO)_2P(S)Cl$ | 10 |
| 4 | $(PhO)_2P(O)Cl$ | 45 |
| 5 | ethyl chloroformate | no rxn |
| 6 | DCC | 58 |

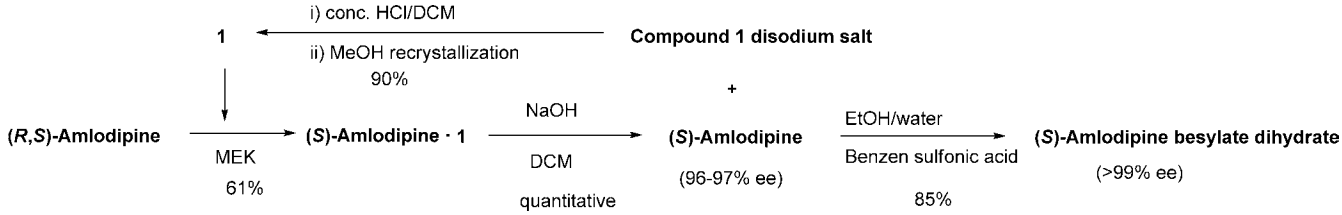
[a] DMAP (0.3 equiv), DCM (g/10 mL), 12 h, room temperature. [b] Isolation yield.

such as alkoxy chlorophosphate or thiophosphate, have been employed and gave a range of low to moderate yields (entry 1−4), leading us to employ the DCC method (entry 6). DCC activation consistently gave 10% higher yield than other methods, and removal of dicyclohexyl urea (DCU) was unexpectedly easy. Unlike the conventional DCC activation at 0 °C, activation was conducted at room temperature and stirred for 2 h prior to the addition of alcohol compound **8** to complete the activation of sterically congested diacids. After the reaction, DCU was filtered off, and residual DCU in the crude was further removed by hexane slurry followed by filtration. Crystallization of the crude mixture in MeOH gave the desired product in 58% (>99% purity) yield. Deprotection of PMB on compound **9** with TFA/DCM went smoothly, giving compound **1** in 92% as pale, yellowish solid after simple workup procedure (Scheme 1). These reaction steps repeatedly gave desired quality of product up to a kilogram scale in our pilot reactor without further complications. Pilot-scale resolution of racemic amlodipine with compound **1** also proceeded smoothly, giving consistent quality and quantity of (*S*)-amlodipine diastereomeric salt (Scheme 2). Further treatment of this diastereomeric salt with NaOH followed by salt formation with benzenesulfonic acid gave (*S*)-amlodipine besylate dihydrate, which is the active pharmaceutical ingredient (API) used in final dosage form, in 85% (>99% ee). About 90% of compound **1** was recovered by acidification of corresponding disodium salt followed by back extraction of aqueous layer with DCM. The purity of compound **1** after DCM extraction was the same as that of the initially used compound **1**, showing over 99% purity with the retention of chiral purity (>97% ee). Recovered compound **1** was subjected to reusability test. As it is expected by recovered compound's purity, the results showed no differences in quality and quantity of (*S*)-amlodipine as well as recovered compound **1**. The cycles of recovery and reuse of compound **1** were done three times without introducing new impurities while maintaining those impurities below 0.1%. More than three times of cycles increased existing impurities to just over 0.1%. Since our goal

***Scheme 1.*** **Optimal process for compound 1 synthesis**




***Scheme 2.*** **Chiral resolution process on (*R*,*S*)-amlodipine with compound 1**




was to control all unknown impurities below 0.1%, more than three times of recovery and reuse was not desirable.

## Conclusion

In summary, we have designed and synthesized a new chiral resolving reagent specifically aimed at the separation of (*S*)-amlodipine from the enantiomeric mixture of amlodipine. A scalable and commercially viable preparation of compound **1** and a robust resolution process proved its efficacy by providing more than 99% pure (*S*)-amlodipine besylate salt, which is the final ingredient for the drug tablet, with over 99% ee. Furthermore, up to three times of recovery and reuse of compound **1** in resolution eased our concerns over the cost of production.

## Experimental Section

**General.** Melting points were determined on an open capillary apparatus and are uncorrected. $^1$H spectra and $^{13}$C spectra were obtained in the solvent indicated on a Bruker DPX 400 spectrometer. All purity values were obtained by HPLC analysis.

**HPLC methods.** (A) Chiral HPLC method. Ultron Es-OVM, 4.6 mm × 250 mm, isocratic elution with 78:22 pH 7 buffer solution/ACN over 20 min, 1.0 mL/min flow at 25 °C with detection at 237 nm.

(B) Novapack C18, 4.6 mm × 150 mm, isocratic elution with 50:35:15 pH 3.0 buffer solution/MeOH/ACN over 40 min, 1.0 mL/min flow at 25 °C with detection at 237 nm.

(C) Chiral HPLC method. ChiralCel OD, 4.6 mm × 250 mm, isocratic elution with 90:10 hexane/IPA containing 0.4% TFA over 40 min, 2.0 mL/min at 25 °C with detection at 230 nm.

(D) Novapack C18, 4.6 mm × 150 mm, isocratic elution with 70:30 pH 3.0 buffer solution/ACN over 40 min, 1.0 mL/min flow at 25 °C with detection at 230 nm.

**(*S*)-4-Methoxybenzyl 2-hydroxy-2-phenyl Acetate (8).** To a cooled (0−5 °C) solution of (*S*)-mandelic acid (2 kg, 13.12 mol) in MeOH (4 L) was transferred $Cs_2CO_3$ (2.12 kg, 6.48 mol) in MeOH (12 L) and stirred for 30 min. The solution was concentrated under reduced pressure, charged with DMF (8 L), and *p*-methoxybenzylchloride (2.68 kg, 17.12 mol) was added while keeping the temperature of the reaction no more than 30 °C. The reaction mixture was stirred for 21 h at between 20−25 °C. Insoluble inorganic salts were filtered off, and the filtrate was transferred in ethyl acetate/hexane (16 L/4 L). Organic layer was washed with aq 10% $NH_4Cl$ (20 L × 3) followed by 10% $NaHCO_3$ (8 L) and concentrated under reduced pressure. Hexane (40 L) slurry of this concentrate at between 0−5 °C and filtration gave compound **8** in 89% (3.2 kg, 11.72 mol) as white solid. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.36−7.38 (m, 5H), 7.27. (d, $J$ = 1.5 Hz, 2H), 6.87 (d, $J$ = 1.7 Hz, 2H), 5.11 (s, 2H), 4.26 (m, 1H), 3.76 (s, 3H). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.21; H, 5.82.

**Bis((*S*)-2-(4-methoxybenzyloxy)-2-oxo-1-phenylethyl)-3-nitrophthalate (9).** 3-Nitrophthalic acid (1 kg, 4.8 mol), in DCM (21.2 L) was treated with DCC (2.56 kg, 12.4 mol), and stirred for 2 h at room temperature. To this solution was added compound **8** (2.84 kg, 10.4 mol) followed by DMAP (0.24 kg, 1.96 mol) and stirred for 3 h. Reaction mixture was filtered, and the filter cake was washed with hexane (4.24 L). Filtrate was stirred for 1 h, and insoluble solids were filtered again. Filtrate was concentrated and crystallized in MeOH (5.28 L) to give compound **9** in 55% yield (1.92 kg, 2.64 mol). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.55 (d, $J$ = 5.2 Hz, 1H), 8.03 (d, $J$ = 7.2 Hz, 1H), 7.64 (t, $J$ = 8.0 Hz, 1H), 7.51−7.44 (m, 5H), 7.26−7.40 (m, 5H), 7.20−7.02 (m, 4H), 6.94−6.80 (m, 4H), 6.65 (s, 2H), 6.60 (s, 2H), 6.22 (s, 1H), 6.01 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H). Anal. Calcd for $C_{40}H_{33}NO_{12}$: C, 66.75; H, 4.62; N, 1.95 Found: C, 66.71; H, 4.65; N, 1.92.

**Bis((*S*)-mandelic acid)-3-nitrophthalate (1).** Compound **9** (1.76 kg, 2.44 mol) in DCM (9 L) was treated with TFA (2.84 kg, 24.8 mol) and stirred for 2 h. Reaction mixture was concentrated under reduced pressure and dissolved again in DCM (9 L). DCM layer was basified with 10% $NaHCO_3$ (16 L), and the aqueous phase was separated. The aqueous layer

was further washed with DCM (4 L), and pH was adjusted to 1.1−1.2 with conc. HCl. Back-extraction of the aqueous phase with DCM (10.8 L) followed by concentration of the organic phase gave compound **1** in 92% (1.08 kg, 2.24 mol) as pale, yellowish solid (>99% pure by HPLC method D, >97% ee by chiral HPLC method C). HPLC retention time: **1** = 12.29 min, Chiral HPLC retention times: (*R*)-**1** = 13.57 min, (*S*)-**1** = 19.17 min. **1**: mp 60−62 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.32 (d, $J$ = 5.2 Hz, 1H), 8.31 (d, $J$ = 7.2 Hz, 1H), 7.64 (t, $J$ = 8.0 Hz, 1H), 7.51−7.44 (m, 5H), 7.26−7.40 (m, 5H), 6.36 (s, 1H), 6.12 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 173.59, 173.25, 163.84, 163.03, 146.49, 135.85, 132.58, 132.41, 130.83, 129.91, 129.73, 129.68, 129.40, 129.08, 128.82, 128.71, 128.08, 127.90, 75.80, 75.75. Anal. Calcd for $C_{24}H_{17}NO_{10}$: C, 60.13; H, 3.57; N, 2.92. Found: C, 59.73; H, 3.55; N, 2.95.

**Chiral Resolution of (*R*,*S*)-Amlodipine.** Compound **1** (293 g) in MEK (1.25 L) was gradually added to (*R*,*S*)-amlodipine (1 kg) suspension in MEK (1.25 L), and heated to 55 °C over 20 min. The mixture was cooled to 15−20 °C and stirred for 63 h. The precipitate formed was filtered, washed with *tert*-butyl methyl ether (1 L) to give (*S*)-amlodipine·0.5 compound **1** diastereomeric salt as yellow solid in 65% yield (519 g, 96.4% ee). Reslurry of the solid in MEK/hexane (1.5 L/0.75 L) for 16 h, filtration followed by filter cake wash with MEK/hexane (1.5 L/0.75 L) gave solid (*S*)-amlodipine·0.5 compound **1** diastereomeric salt as pale-yellow solid in 61% yield (475 g, 97.5% de by chiral HPLC method A) after drying *in vacuo* for 16 h. Chiral HPLC retention times: (*R*)-amlodipine = 5.22 min, (*S*)-amlodipine = 7.42 min. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.82 (bs, 1H), 8.33 (d, $J$ = 8.04 Hz, 2H), 7.86 (t, $J$ = 8.04 Hz, 1H), 7.47 (d, $J$ = 6.76 Hz, 2H), 7.36 (d, $J$ = 6.76 Hz, 2H), 7.17−7.30 (m, 13H), 7.06−7.10 (m, 2H), 5.83 (s, 1H), 5.69 (s, 1H), 5.25 (s, 2H), 4.44−4.60 (dt, $J$ = 32.49 Hz, 4H), 3.91−3.96 (m, 4H), 3.55−3.56 (m, 5H), 3.46−3.47 (m, 5H), 2.94 (t, $J$ = 5.48 Hz, 4H), 2.20 (s, $J$ = 4.56 Hz, 6H), 1.07 (t, $J$ = 7.12 Hz, 6H). Anal. Calcd for $C_{64}H_{67}Cl_2N_5O_{20}$: C, 59.26; H, 5.21; Cl, 5.47; N, 5.40. Found: C, 59.21; H, 5.18; Cl, 5.51; N, 5.43.

**(*S*)-Amlodipine.** (*S*)-Amlodipine·compound **1** diastereomeric salt (475 g, 97.5% ee) was suspended in DCM (2.4 L). One M NaOH (1.10 L) was added and stirred for 30 min at 20 °C. Organic phase was separated, washed with $H_2O$ (1.10 L), and dried over $MgSO_4$. The $MgSO_4$ was filtered off and further washed with DCM (1 L). Organic phase was concentrated and dried at 50 °C *in vacuo* to give (*S*)-amlodipine free base in 93% yield (278 g, 99% pure by HPLC method B, optical purity 98.3% ee by HPLC method A). HPLC retention time: amlodipine = 6.9 min. Chiral HPLC retention time: (*R*)-amlodipine = 5.22 min. (*S*)-amlodipine = 7.42 min. $^1$H NMR (400 MHz, MeOD) $\delta$ 7.41 (dd, $J$ = 7.76 Hz, 1H), 7.24 (dd, $J$ = 7.92 Hz, 1H), 7.15−7.17 (m, 1H), 4.07−7.10 (m, 1H), 5.42 (s, 1H), 7.69 (dd, $J$ = 47.53 Hz, 2H), 4.02−4.05 (m, 2H), 3.57−3.60 (m, 5H), 2.88 (t, $J$ = 4.72 Hz, 3H), 2.35 (s, 3H), 1.17 (t, $J$ = 7.12 Hz, 3H).

**Recovery of Compound 1.** Aqueous phase was acidified to pH 1.0−1.5 using conc. HCl (150 mL) and extracted with DCM (1 L). Organic phase was separated and dried over $MgSO_4$. The suspension was filtered, concentrated by evaporator to give compound **1** in 90% yield (177 g, 99% pure by HPLC method D, >97% ee by chiral HPLC method C). HPLC retention time: **1** = 12.29 min, Chiral HPLC retention times: (*R*)-**1** = 13.57 min, (*S*)-**1** = 19.46 min.

**Synthesis of (*S*)-Amlodipine Besylate.** (*S*)-Amlodipine (270 g) was dissolved in EtOH (1.25 L) at 20 °C and cooled to 0−5 °C. Benzenesulfonic acid in $H_2O$ (0.6 L) was transferred gradually, and the reaction mixture was further diluted with $H_2O$ (8.7 L). Reaction mixture was stirred for 22 h at 20 °C. Precipitate was collected by filtration, washed with cold $H_2O$ (4 L) to give (*S*)-amlodipine besylate·$2H_2O$ as white solid in 85% yield (340 g, 99% pure by HPLC method B, >99% ee by HPLC method A, moisture 6.2%). HPLC retention time: amlodipine = 6.92. Chiral HPLC retention time: (*R*)-amlodipine = 5.22 min; (*S*)-amlodipine = 7.42 min; mp 68−70 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.35 (s, 1H), 7.70−7.90 (bs, 3H), 7.39−7.51 (m, 2H), 7.22−7.37 (m, 6H), 7.05−7.12 (m, 1H), 5.27 (s, 1H), 4.60 (q, $J$ = 51.57 Hz, 2H), 3.88−4.00 (m, 2H), 3.68 (s, 2H), 3.47 (s, 2H), 3.05 (t, $J$ = 5.44 Hz, 2H), 2.11 (s, 3H), 1.07 (t, $J$ = 7.12 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 167.22, 165.47, 149.62, 145.37, 143.24, 132.50, 131.10, 130.04, 128.75, 128.14, 127.64, 127.10, 126.76, 126.43, 104.01, 100.64, 73.22, 30.26, 61.41, 52.32, 41.52, 38.83, 19.04, 14.40.

## Supporting Information Available

Experimental details of the synthesis of compounds **2**−**7**, $^1$H NMR data for compounds **2**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review March 25, 2009.

OP900070C