An Asymmetric Synthesis of Clopidogrel Hydrogen Sulfate

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Abstract: An asymmetric synthesis of (*S*)-(+)-clopidogrel hydrogen sulfate has been developed through application of a Strecker reaction with [(1*S*)-1-(4-methoxyphenyl)ethyl]amine hydrochloride as a chiral auxiliary. Addition of 2-chlorobenzaldehyde to a solution of sodium cyanide and [(1*S*)-1-(4-methoxyphenyl)ethyl]amine hydrochloride gave diastereoisomerically pure (2*S*)-(2-chlorophenyl){[(1*S*)-1-(4-methoxyphenyl)ethyl]amino}acetonitrile hydrochloride. Cleavage of the chiral auxiliary and concomitant hydrolysis of the nitrile group then gave enantiomerically pure (2*S*)-2-(2-chlorophenyl)glycine hydrochloride, a key intermediate for (*S*)-(+)-clopidogrel.

Key words: asymmetric synthesis, heterocycles, Strecker reaction, cyclizations, chiral auxiliaries, stereoselective synthesis

Clopidogrel (**1**; Plavix®) is an antiaggregatory and antithrombotic drug administered for the treatment of atherosclerotic events, such as myocardial infarction, ischemic stroke, or peripheral vascular disease, that is widely used in combination with aspirin after insertion of intravascular stents.[1–4] Of the two possible stereoisomers of clopidogrel, only the *S*-enantiomer is suitable for pharmaceutical use, as the *R*-enantiomer shows no antithrombotic activity and causes convulsions in animal experiments.[5] 2-(2-Chlorophenyl)glycine [amino(2-chlorophenyl)acetic acid], an unnatural amino acid that is commercially available as a racemic mixture, is a valuable intermediate for the synthesis of clopidogrel (**1**; Figure 1).

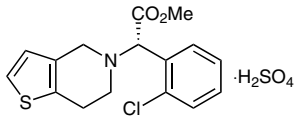

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Figure 1 Clopidogrel hydrogen sulfate

Various methods have been reported for the synthesis of this potent antithrombotic drug, most of which involve either the *ortho*-chloromandelate or 2-(2-chlorophenyl)glycine derivatives as starting materials. The final product is usually obtained in a racemic form and resolved through fractional crystallization with a resolving agent such as tartaric acid[6] or camphorsulfonic acid.[7] Economically, the use of an enantiomerically pure reagent at the start of a synthetic sequence would be more cost-effective and less polluting. For this reason, several strategies have recently been developed for the preparation of enantiomerically pure *ortho*-chloromandelate by enzymatic routes, such as kinetic resolution with hydrolases[8,9] or enantioselective reduction of a prochiral keto acid.[10] Although enantioselective hydrolysis of a 2-(2-chlorophenyl)glycine amide by microbes possessing amidase activity has been reported,[11,12] the low solubility of the amide in water and necessity of fermenting a specific bacterial strain limit the application of this process on a large scale.

Although numerous examples of successful enzyme-catalyzed resolutions of phenylglycine have recently been reported in the literature,[13–17] only a few instances of resolution of 2-(2-chlorophenyl)glycines have been described. D-Phenylglycine and several of its analogues, variously substituted on the aromatic ring [including 2-(2-chlorophenyl)glycine], that are useful as starting material for semisynthetic penicillins and cephalosporins, have been prepared by using D-hydantoinase.[18] (*R,S*)-2-(2-Chlorophenyl)glycine has been successfully resolved by Fadnavis and co-workers,[19] who used an immobilized pencillin G acylase, and by Ferraboschi and co-workers, who adopted a chemo-enzymatic approach.[20] The common drawback of these resolutions is that half the material is lost as the unwanted isomer, which greatly diminishes their synthetic utility when scaled up. Recently, Pérez-Fuertes and co-workers[21] prepared enantiopure α-arylglycines by an asymmetric Strecker reaction. This asymmetric synthesis encouraged us to attempt a preparation of enantiomerically pure (*S*)-clopidogrel (**1**) by a similar stereoselective route.

Our retrosynthetic analysis for (*S*)-(+)-clopidogrel hydrogen sulfate (**1**) is shown in Scheme 1. Methyl (*S*)-2-(2-chlorophenyl)glycinate (**6**) and 2-(2-bromoethyl)-3-(bromomethyl)thiophene (**7**) are precursors of (*S*)-(+)-clopidogrel (**1**). Glycinate **6** might be obtained from (2*S*)-(2-chlorophenyl){[(1*S*)-1-(4-methoxyphenyl)ethyl]amino}acetonitrile hydrochloride (**4**), which, in turn, could be prepared from 2-chlorobenzaldehyde (**2**).

Here we report a strategy involving a chiral auxiliary-based Strecker reaction as the key step for the synthesis of (2*S*)-2-(2-chlorophenyl)glycine hydrochloride (**5**), followed by esterification to give the methyl ester **6**, a key intermediate for the synthesis of clopidogrel (**1**).

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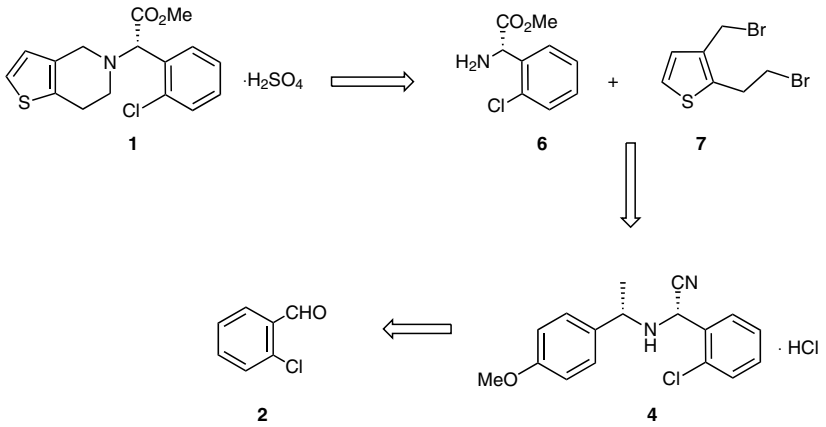
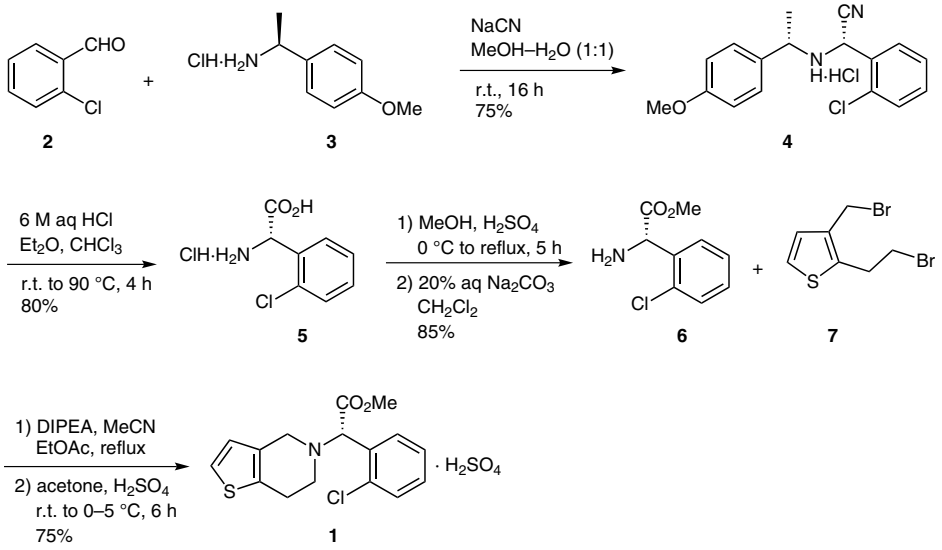


Scheme 1 Retrosynthetic analysis of Clopidogrel hydrogen sulfate **1**

As outlined in Scheme 2, addition of 2-chlorobenzaldehyde (**2**) to a solution of sodium cyanide and (1*S*)-1-(4-methoxyphenyl)ethanamine hydrochloride (**3**)[20] gave diastereomerically pure (2*S*)-(2-chlorophenyl){[(1*S*)-1-(4-methoxyphenyl)ethyl]amino}acetonitrile hydrochloride (**4**). In this step, cyanide undergoes preferential nucleophilic attack at the *re*-face of the imine intermediate formed from 2-chlorobenzaldehyde (**2**) and chiral auxiliary **3** to give the diastereomerically pure nitrile **4**. The NMR spectrum of product **4** confirmed that it was obtained with a high diastereoselectivity (>95%). Removal of the chiral auxiliary and concomitant hydrolysis of the nitrile group in aqueous hydrochloric acid gave enantiopure (2*S*)-2-(2-chlorophenyl)glycine hydrochloride (**5**). The pure compound **5**, washed with chloroform, had a specific optical rotation of $[\alpha]_D^{25}$ +88.2 (*c* 1, 1 M aq HCl).

The degree of asymmetric induction was assessed by ^{1}H NMR analysis of the diastereomeric mixtures, and the absolute stereochemistry of the (2*S*)-(2-chlorophenyl){[(1*S*)-1-(4-methoxyphenyl)ethyl]amino}acetonitrile hydrochloride (**4**) was determined by conversion into its methyl ester **6** by treatment with methanol and sulfuric acid.[20] The absolute configuration was confirmed by comparison of the measured optical rotation with that of a known sample of methyl (2*S*)-2-(2-chlorophenyl)glycinate (**6**).[20] Condensation of glycinate **6** with 2-(2-bromoethyl)-3-(bromomethyl)thiophene **7** in the presence of *N*,*N*-diisopropylethylamine[22] to give clopidogrel, followed by salt formation with sulfuric acid in acetone gave enantiopure (*S*)-(+)-clopidogrel hydrogen sulfate (**1**). The physical and spectroscopic data for all the compounds were in good agreement with the proposed structures and with literature data.

In conclusion, we achieved an asymmetric synthesis of (*S*)-(+)-clopidogrel hydrogen sulfate by means of an asymmetric Strecker reaction.



Scheme 2 Synthesis of clopidogrel hydrogen sulfate through an asymmetric Strecker reaction

The ^{1}H and ^{13}C spectra were recorded in DMSO-d_6 or D_2O at 400 MHz with a Varian Gemini 400-MHz FT NMR spectrometer. Chemical shifts are relative to TMS. The FTIR spectra were recorded in the solid state as KBr dispersions by using a PerkinElmer 1650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on an Agilent 6310 LC-MS spectrometer. Organic solvents were distilled before use or, if otherwise noted, dried according to the usual procedures.

(2*S*)-(2-Chlorophenyl){[(1*S*)-1-(4-methoxyphenyl)ethyl]amino}acetonitrile Hydrochloride (4)

CAUTION: *Cyanide salts can be absorbed through the skin and are extremely toxic*.

(1*S*)-1-(4-Methoxyphenyl)ethylamine hydrochloride (**3**; 6.76 g, 36.0 mmol) and NaCN (1.85 g, 38.0 mmol) were dissolved in a mixture of H_2O (5.0 mL) and MeOH (5.0 mL). 2-Chlorobenzaldehyde (**2**; 5.0 g, 36.0 mmol) was added, and the soln was stirred for 16 h at 25–30 °C. When the reaction was complete (TLC), the mixture was diluted with H_2O (12.5 mL) and stirred for 30 min at 25–30 °C. The solid that separated was collected by filtration, washed with H_2O (5.0 mL), and dried under vacuum at 70 °C to give a cream-colored powder; yield: 9.0 g (75%, >95% de); mp 112–114 °C; $[\alpha]_D^{25}$ –129 (*c* 0.5, MeOH).

IR (KBr): 3312, 3064, 2983, 2226, 1613, 1584, 1243, 1036, 756, 559 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.75–7.76 (m, 1 H), 7.49–7.52 (m, 3 H), 7.31–7.39 (m, 2 H), 6.84–6.94 (m, 2 H), 4.56 (d, 1 H), 3.99 (q, *J* = 4.0 Hz, 1 H), 3.74 (s, 3 H), 3.61–3.64 (d, *J* = 2.5 Hz, 1 H), 1.31–1.33 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1, 135.5, 132.5, 131.0, 130.3, 129.7, 128.7, 128.4, 127.9, 119.1, 114.4, 56.2, 55.3, 49.3, 24.8.

MS: *m/z* = 301.5 $[M + H]^+$ (free base).

Anal. Calcd for $C_{17}H_{18}Cl_2N_2O$: C, 60.54; H, 5.38; N, 8.31. Found: C, 60.66; H, 5.55; N, 8.32.

(2*S*)-2-(2-Chlorophenyl)glycine Hydrochloride (5)

A mixture of hydrochloride **4** (5.0 g, 15.0 mmol) and 6 M aq HCl (160.0 mL) was stirred for 4.0 h at 90 °C until the reaction was complete (TLC). The mixture was then cooled to 25–30 °C and extracted with Et_2O (2 × 30 mL). The organic extracts were discarded, and the aqueous layer was concentrated under reduced pressure to give the crude product, which was stirred with $CHCl_3$ (10.0 mL) for 30 min at 25–30 °C. The solid was collected by filtration, washed with $CHCl_3$ (2.5 mL), and dried under vacuum to give a white solid; yield: 2.66 g, (80%, 95.5% ee); mp 200–202 °C; $[\alpha]_D^{25}$ +88.2 (*c* 1, 1 M aq HCl).

IR (KBr) 3415, 3171, 3033, 1679, 1639, 1506, 750 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 7.5 (d, 1 H), 7.3–7.4 (m, 3 H), 5.15 (s, 1 H).

^{13}C NMR (100 MHz, D_2O): δ = 172.4, 133.7, 131.7, 131.2, 130.3, 130.2, 128.0, 55.6.

MS: *m/z* = 185.9 $[M + H]^+$ (free base).

Anal. Calcd for $C_8H_9Cl_2NO_2$: C, 43.27; H, 4.08; N, 6.31. Found: C, 43.3; H, 4.12; N, 6.41.

Methyl (2*S*)-2-(2-Chlorophenyl)glycinate (6)

H_2SO_4 (11.27 g, 115.0 mmol) was slowly added to MeOH (30.0 mL) at 0–5 °C. To this soln was added amino acid **5** (5.0 g, 23.0 mmol), and the resulting mixture was stirred and refluxed for 5.0 h. When the reaction was complete (TLC), the MeOH was completely removed by distillation, H_2O (20.0 mL) was added to the mixture, and the pH was adjusted to 7.0–8.0 with 20% aq Na_2CO_3. The product was extracted with CH_2Cl_2 (3 × 10.0 mL) and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a pale oil; yield: 3.78 g (85%, 99% ee); $[\alpha]_D^{25}$ +122 (*c* 1, MeOH) (Lit.[20] +123).

IR (neat): 3383, 3061, 2952, 1747, 1593, 1574, 1463, 1169, 751 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (s, 3 H), 7.61–7.64 (m, 2 H), 7.46–7.50 (m, 2 H), 5.5 (s, 1 H), 3.72 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.5, 133.7, 131.9, 130.9, 130.5, 130.3, 128.5, 53.9, 52.9.

MS: *m/z* = 199.9 $[M + H]^+$.

(*S*)-(+)-Clopidogrel Hydrogen Sulfate (1)

2-(2-Bromoethyl)-3-(bromomethyl)thiophene (**7**; 5.0 g, 18.0 mmol) was added to a mixture of ester **6** (4.31 g, 21.6 mmol) and MeCN (50.0 mL), and the resulting mixture was stirred for 15 min at 25–30 °C. A mixture of DIPEA (3.28 g, 32.0 mmol) and MeCN (5.0 mL) was added, and the mixture was stirred overnight at the reflux. When the reaction was complete (TLC), the solvents were completely evaporated under reduced pressure. EtOAc (100.0 mL) was added to the residue and the mixture was washed with H_2O (3 × 75.0 mL). The combined organic layers were washed with sat. aq NaCl (75.0 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give clopidogrel as a yellow oil. The oil was mixed with acetone (50.0 mL), carbon (0.25 g), and Hyflo filter aid (0.3 g), and the mixture was stirred for 10–15 min at 25–30 °C. The solids were collected by filtration and washed with acetone (5.0 mL). The filtrate was mixed with H_2O (0.7 mL) and cooled to 0–5 °C. H_2SO_4 (1.94 g, 19.8 mmol) was added slowly over 1.5 h and the mixture was stirred for 6.0 h at 0–5 °C. The solid that separated was collected by filtration, washed with acetone (5.0 mL), and dried under vacuum to give (*S*)-clopidogrel hydrogen sulfate **(1)** as an off-white powder; yield: 5.6 g (75%, 99.9% ee); $[\alpha]_D^{25}$ +55 (*c* 1, MeOH) (Lit.[20] +54.8).

IR (KBr): 3446, 3121, 2956, 1752, 1439, 1188, 750, 569 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.68–7.70 (m, 2 H), 7.53–7.57 (m, 2 H), 7.44–7.45 (m, 1 H), 6.88–6.90 (d, *J* = 5.0 Hz, 1 H), 5.62 (br s, 2 H), 4.93 (br s, 2 H), 4.2 (br s, 2 H), 3.76 (s, 3 H), 3.08 (br s, 2 H).

MS: *m/z* = 322.0 $[M + H]^+$ (free base).

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