

# Attrition-Enhanced Deracemization in the Synthesis of Clopidogrel - A Practical Application of a New Discovery

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## Abstract:

The recently discovered technique of deracemization by means of attrition-induced grinding of a solid conglomerate in contact with a solution wherein racemization occurs has been used with a derivative of 2-chlorophenyl glycine, the key chiral component in the synthesis of Clopidogrel (Plavix). Deracemization of the racemate proceeds to a single enantiomer and in essentially absolute enantiomeric excess. Further conversion of enantiomerically pure material to Clopidogrel was achieved in 88% yield.

## Introduction

Racemizable conglomerates can be driven to enantiomeric purity by proper choice of solid/solution contact and use of attrition grinding.<sup>1</sup> Ample evidence for the generality of this remarkable observation is available.<sup>2</sup> An obvious limitation to technological application is the necessity that the racemate be a conglomerate. Only about 5–10% of all crystalline organic compounds occur as conglomerates.<sup>3</sup> Design of conglomerates from first principles is nearly impossible.<sup>4</sup> We have recently reported the deracemization by attrition-enhanced Ostwald ripening of a derivative of naproxen known from the literature to be a conglomerate so that a further search was not necessary.<sup>5</sup> We describe here both a very simple and practical approach for solution of the problem of rapid identification of conglomer-

ates together with application of the grinding technique to the synthesis of Clopidogrel.

(S)-Clopidogrel (Plavix) **1** is a platelet aggregation inhibitor used for treatment of ischemic strokes, heart attacks, atherosclerosis and also for the prevention of thrombosis after placement of intracoronary artery stents. The Plavix market was reported to be US\$7.3 billion in 2007 up 19% relative to 2005.<sup>6</sup> In patent procedures Clopidogrel is either resolved with camphor sulfonic acid (CSA),<sup>7</sup> or the intermediate 2-chlorophenylglycine ester **2** (see Scheme 1) is resolved with tartaric acid.<sup>8</sup> In either approach the undesired enantiomer can be recycled by racemization. Both **1** and **2** as free bases are oils at room temperature and not suitable for deracemization as described above. On the basis of our experience with the imines of amino acid amides (usually solids and racemizable) we envisaged a route starting from readily available racemic 2-chlorophenyl glycine (**5**, Scheme 2) used as amide **3**, which is converted reversibly to imine **4**. We proposed to make a small library of imines **4a–i** derived from **3** using various aromatic aldehydes (Scheme 2), and to scan the library for conglomerate behaviour using second harmonic generation (SHG)<sup>9</sup> and small-scale deracemization experiments.

## Results

Second harmonic generation is a very fast method to scan solids for noncentrosymmetric space groups.<sup>3a,9</sup> A positive effect is strongly indicative that the compound is a conglomerate, but may not be considered a guarantee. Results of SHG observations and nonoptimized grinding experiments are given in Table 1. In this small library significant SHG effects were observed with **4a**, **4c**, and **4d**. Compound **4a**, obtained, it may be noted, from relatively inexpensive benzaldehyde, deracemized immediately. The failure to observe deracemization with **4c** and **4d** in these scouting experiments is probably due to nonoptimized conditions for crystallization. No attempt was made at this stage to optimize conditions. The other imines are presumably racemic

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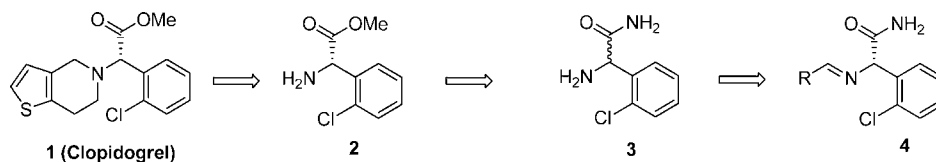
- (1) For NaClO<sub>3</sub>, which forms a solid conglomerate, from a saturated solution in contact with the solid: (a) Viedma, C. *Phys. Rev. Lett.* **2005**, *94*, 065504. for NaClO<sub>3</sub> from supersaturated solution in contact with solid. (b) Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, *250*, 975. first demonstrated for an intrinsically chiral compound. (c) Noorduin, W. L.; Izumi, T.; Millemaggi, A.; Leeman, M.; Meekes, H.; van Enckevort, W. J. P.; Kellogg, R. M.; Kaptein, B.; Vlieg, E.; Blackmond, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 1158.
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(6) MS Global insights, from www.imshealth.com.

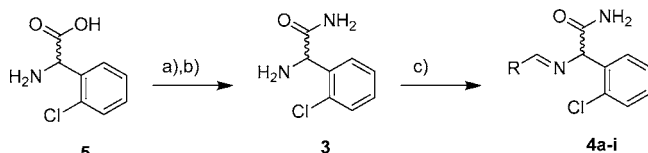
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### Scheme 1. Retrosynthetic approach to clopidogrel 1



### Scheme 2. Synthesis of the Schiff bases<sup>a</sup>



<sup>a</sup> Reagents and conditions: a)  $\text{SOCl}_2/\text{MeOH}$  (95%);  $\text{NH}_3$  (81%); c)  $\text{RCHO}/\text{Na}_2\text{SO}_4$  (90% for **4a**).

**Table 1. Results of second harmonic generation measurements for 4a–i**

entry	R =	SHG <sup>a</sup>	ee in first test (%)
1	Ph ( <b>4a</b> )	large SHG effect	<b>33</b>
2	2-tolyl ( <b>4b</b> )	no SHG effect	0
3	2-chlorophenyl ( <b>4c</b> )	large SHG effect	0
4	2-bromophenyl ( <b>4d</b> )	large SHG effect	0
5	2-nitrophenyl ( <b>4e</b> )	small SHG effect	<i>b</i>
6	2-benzyloxyphenyl ( <b>4f</b> )	no SHG effect	0
7	1-naphthyl ( <b>4g</b> )	small SHG effect	0
8	2-pyridyl ( <b>4h</b> )	small SHG effect	<i>b</i>
9	2,5-difluorophenyl ( <b>4i</b> )	no SHG effect	<i>b</i>

<sup>a</sup> Second harmonic generation. <sup>b</sup> Deracemization not attempted.

compounds that cannot be expected to deracemize. Subsequently, we also established unambiguously that **4a** is a conglomerate by single-crystal structure determination of the racemate (crystallographic data for **4a** (CCDC 734087) can be downloaded free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223033; e-mail [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk))).

Optimal conditions for the deracemization of **4a** involved heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as racemizing agent until complete dissolution at 70 °C, followed by cooling to 20 °C (0.1 °C·min<sup>-1</sup>) with vigorous stirring in the presence of glass beads for attrition and to allow secondary nucleation to propagate the first formed chirality.<sup>10</sup> The enantiomeric excess (ee) reached ~93% after a single night and went to >98% ee after stirring an additional day. In five experiments the (*S*)-enantiomer of **4a** was obtained four times. On use of isothermal grinding of a saturated solution in contact with

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solid<sup>1c</sup> the (*S*)-enantiomer was obtained five times from five experiments. This tendency towards nonrandom behaviour follows previous observations for another imine,<sup>1c</sup> which in more than 100 experiments always gave the same enantiomer, (*R*) in that case. The presence of minor amounts of chiral impurities, perhaps of natural origin, is a possible explanation.

For preparative purposes the deracemization was carried out on a 35 g scale. A few crystals of (*S*)-**4a** were added to ensure that the (*S*)-enantiomer would be formed.<sup>1b</sup> An ee of >99.5% with a yield of 80% was obtained overnight. For the synthesis of Clopidogrel (*S*)-**3a** was converted to methyl ester (*S*)-**2**. Direct conversion with  $\text{H}_2\text{SO}_4$  gave many side products, probably due to liberated benzaldehyde. Therefore, the benzaldehyde was first removed by treatment of imine **4a** with aqueous HCl in acetone, which results in crystallization of the (*S*)-amide **3** as the HCl salt.<sup>12</sup> Subsequently the amide was converted to (*S*)-**2** with  $\text{H}_2\text{SO}_4$  in MeOH.<sup>13</sup> This free amino acid ester **2** is sensitive to racemisation and must be stored as salt or used immediately in the next reaction. The ee remained >99%. Reaction with dibromide **6** gave (*S*)-Clopidogrel in 88% yield with an ee of >99% (Scheme 3).

## Conclusions

This short synthesis of an enantiomerically pure popular drug without any chiral aid demonstrates the practical potential of this new approach for preparing pure enantiomers. Measurements by SHG provide a remarkably simple solution to the problem of finding a suitable conglomerate by fast screening of small libraries. We expect further improvements in and applications of this new technology.

## Experimental Section

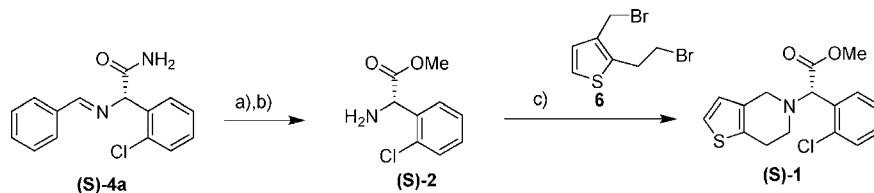
**(+/-)-2-Chlorophenylglycine Methyl Ester Hydrochloride (2·HCl).** To 2-chlorophenylglycine **2** (100 g, 539 mmol) in MeOH (270 mL) was added  $\text{SOCl}_2$  (47 mL, 647 mmol, 1.2 equiv) dropwise. After complete addition, the mixture was stirred overnight at room temperature and subsequently heated with a hot water bath for 3 h. Complete conversion was indicated by NMR analysis. About 50 mL of the MeOH solvent was evaporated, and the remaining reaction mixture was poured in *tert*-butyl methyl ether (TBME, 700 mL). The resulting white solid was collected by filtration and was washed with TBME to give, after drying, ester **2·HCl** (120.3 g, 510 mmol, 95%) as a white solid.

(11) Noorduin, W. L.; Meekes, H.; van Enkevort, W. J. P.; Millemaggi, A.; Leeman, M.; Kaptein, B.; Kellogg, R. M.; Vlieg, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 6445.

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(13) (Sanofi-Synthelabo). U.S. Patent 6,670,486, 2005.

### Scheme 3. Synthesis of clopidogrel<sup>a</sup>



<sup>a</sup> Reagents and conditions: a) HCl/acetone (95%); b) H<sub>2</sub>SO<sub>4</sub>/MeOH (94%); c) 6/MeCN (95%, ee > 99%).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.36 (2H, b), 7.67 (1H, m), 7.57 (1H, m), 7.45 (2H, m), 5.44 (1H, s), 3.76 (3H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.7, 134.0, 132.1, 131.1, 130.7, 130.5, 128.7, 54.1, 53.0; [M + 1] (TOF/ESI) calculated for C<sub>9</sub> H<sub>10</sub>NO<sub>2</sub>Cl: 200.05, found: 200.1.

(+/-)-2-Chlorophenylglycinamide (**3**). To ester **2**·HCl (100 g, 424 mmol) was added concentrated aqueous ammonia (315 mL), and the resulting mixture was stirred overnight at room temperature. The mixture was cooled with ice, and the solids were collected by filtration, washed with water, and stripped 3× with toluene to give 57.2 g of amide **3**. The mother liquor was extracted with dichloromethane (2 × 300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, combined with the solid amide, and concentrated to give amide **3** (63.6 g, 344 mmol, 81%) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.22–7.46 (5H, m), 7.18 (1H, b), 4.61 (1H, s), 2.31 (2H, b); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 175.3, 141.3, 133.3, 129.8, 129.5, 129.2, 127.8, 56.8; [M + 1] (TOF/ESI) calculated: 185.05, found: 185.1.

(+/-)-2-(Benzylideneamino)-2-(2-chlorophenyl)acetamide (**4a**). To amide **3** (58.7 g, 318 mmol) in dichloromethane (DCM, 480 mL) was added benzaldehyde (35.3 mL, 350 mmol, 1.1 equiv) and Na<sub>2</sub>SO<sub>4</sub> (73.4 g, 517 mmol, 1.63 equiv), and the mixture was stirred overnight at room temperature. The mixture was then heated with a hot water bath, and the solids were removed by filtration. The residue was washed with warm dichloromethane, and the combined mother liquors were concentrated to give 88.3 g, 324 mmol crude imine **4a**, which was recrystallized from CH<sub>3</sub>CN (500 mL) to give **4a** (77.9 g, 286 mmol, 90%) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.45 (1H, s), 7.87 (2H, dd), 7.63, (1H, dd), 7.44–7.51 (6H, m), 7.32–7.38 (2H, m), 5.43 (1H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 172.1, 164.17, 138.1, 136.3, 133.4, 132.0, 130.9, 130.0, 129.8, 129.4, 129.2, 128.0, 73.6; [M + 1] (TOF/ESI) calculated: 273.08, found: 273.2. The imines **3b–i** were prepared in a similar manner.

**Deracemization Following Protocol of ref 10. (S)-(E)-2-(Benzylideneamino)-2-(2-chlorophenyl)acetamide (4a).** In a 1 L round-bottom flask with a 5 × 2 cm stirring egg was loaded racemic-imine **4a** (35 g, 128 mmol). MeCN (315 mL) and the mixture were stirred at 1050 rpm. Glass beads (borosilicate, 0.2 mm, 87.5 g) were added, followed by the addition of DBU (5.1 mL, 38.5 mmol, 0.3 equiv). The mixture was heated to 70 °C to form a homogeneous solution and subsequently cooled to 20 °C with a rate of 0.1 °C/min using a thermostat (Huber ministat cc). To the mixture were added a few milligram-sized crystals of enantiopure imine **4a**, obtained in a previous experiment, at 68, 67, 66, and 64 °C. After stirring overnight at 20 °C, chiral HPLC analysis revealed an ee > 99.5%, and the solids were collected by filtration and washed with TBME

to give (*S*)-**4a** (115.6 g, including glass beads, 28.1 g, 103 mmol, corrected, 80%) as a white solid.

**Deracemization Following Isothermal Protocol of ref 1c. (S)-(E)-2-(Benzylideneamino)-2-(2-chlorophenyl)acetamide (4a).** A scintillation vial was charged with 2 mm glass beads (10 g), Schiff-base **3a** (389 mg, 1.43 mmol) and MeCN (3.5 mL). The flask was placed in an ultrasonic bath, fitted with a thermostat (keeping the temperature at 20 °C), and was sonicated for 5 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.10 g, 0.76 mmol, 0.53 equiv) was added, and the mixture was sonicated at 20 °C overnight. After 1 night, ee was >80%, after 2 nights ee was 91–98%. This experiment was carried out as described above five times, and each time similar results were obtained; in all cases the (*S*)-enantiomer of **4a** was obtained.

**(S)-2-Chlorophenylglycinamide Hydrochloride (4·HCl).** To (*S*)-**4a** (28.0 g, 103 mmol) was added a mixture of concentrated aqueous HCl (10.1 mL) and acetone (1.8 L), and the resulting mixture was stirred for 1 h at room temperature. The suspension was decanted from the glass beads from the previous step, and the solids were collected by filtration, washed with acetone, and dried to give (*S*)-**3**·HCl (21.6 g, 97 mmol, 95%) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.60 (3H, b), 7.75 (2H, d), 7.46–7.62 (m, 4H), 5.14 (1H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.6, 134.2, 132.4, 131.7, 130.5, 130.2, 128.4, 53.0; [M + 1] (TOF/ESI) calculated C<sub>8</sub>H<sub>9</sub>ON<sub>2</sub>Cl: 185.05, found: 185.0.

**(S)-2-Chlorophenylglycine Methyl Ester (2).** H<sub>2</sub>SO<sub>4</sub> (26.0 mL, 487 mmol, 5 equiv) was added dropwise under ice cooling to MeOH, and the resulting mixture was heated at reflux for 30 min. Amide (*S*)-**3**·HCl (21.6 g, 97 mmol) was added, and the resulting mixture was stirred for 4 h. at reflux and then overnight at room temperature. After NMR analysis revealed complete conversion, MeOH was evaporated, and water (175 mL) was added. The aqueous layer was basified with 1 M NaOH and extracted with DCE (3 × 50 mL). The combined organic layers were washed with water (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give (*S*)-**2** (16.9 g, 85 mmol, 94%) as a pale oil.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.48 (1H, dd), 7.42 (1H, dd), 7.26–7.7.36 (2H, m), 4.84 (1H, s), 3.58 (3H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 174.4, 139.3, 133.0, 130.0, 129.8, 129.6, 128.1, 56.2, 52.7; [M + 1] (TOF/ESI) calculated: 200.05, found: 200.1.

**(S)-Clopidogrel (1).** To 2-(2-bromoethyl)-3-(bromomethyl)thiophene, prepared by a literature procedure,<sup>14</sup> (4.3 g, 15.1 mmol) in MeCN (45 mL) was added a mixture of ester (*S*)-**2** (3.3 g, 17.8 mmol, 1.18 equiv) and di-isopropylethyl amine

(14) (Patent Hanmi Pharm. Co.). WO2005/87779, 2005.

(DIPEA, 4.4 mL, 26.7 mmol, 1.77 equiv) in MeCN (20 mL) dropwise, and the resulting mixture was heated at reflux overnight. The mixture was concentrated, and the residue was taken up in EtOAc (80 mL) and washed with water (2x 60 mL), brine (60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give clopidogrel **1** (4.3 g, 13.4 mmol, 88%) as a yellow oil with a purity of 94–95% according to HPLC and an ee >99% determined by chiral HPLC.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.7 (1H, m), 7.41 (1H, m), 7.24–7.32 (2H, m), 7.06 (1H, d), 6.67 (1H, d), 4.93 (1H, s), 3.61–3.79 (5H, m), 2.89 (4H, bs); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 171.6, 134.9, 134.1, 133.5, 133.5, 130.2, 130.0, 129.7, 127.4, 125.5, 123.0, 68.1, 52.4, 50.9, 48.5, 25.8; [M + 1] (API/ES) calculated: 322.07, found: 322.0.

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Crystal structure determination of **4a** was carried out by A. Meetsma and J. Baas (Univ. of Groningen). The SHG experiments were kindly performed by Prof. G. Coquerel and his group (Univ. Rouen). The analytical department at Syncom BV carried out the analyses. We are grateful both to the Samenwerkingsverband Noord-Nederland (Cooperation Northern Netherlands) together with the European Fund for Regional Development (EFRO) as well as the European Commission (seventh Framework Program NMP4-SL-2008-214340) for partial funding of this work.

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