A Facile Solid-Phase Synthesis of (+)-(*S*)-Clopidogrel

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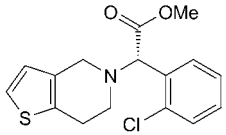
Enantiomerically pure (+)-(*S*)-clopidogrel was prepared by solid-phase synthesis using the commercially available *Wang* resin. This method offers mild reaction conditions and provides the (+)-(*S*)-clopidogrel in overall 52% yield over six steps and with optical purity of 98.0% ee.

Introduction. – Solid-phase reactions play an important role in combinatorial chemistry in the area of medicinal chemistry, where their potential has emerged due to the possibility of automated synthesis [1–3]. A growing number of pharmacologically active molecules have been actively prepared by the solid phase synthesis.

Clopidogrel is a thienopyridine-class antiplatelet agent targeted to inhibit blood clots in coronary-artery, peripheral vascular, and cerebrovascular diseases [4–6]. Clopidogrel is marketed as clopidogrel bisulfate ((+)-(*S*)-clopidogrel hydrogen sulfate), most commonly under the trade names *Plavix*®, as 75 mg oral tablets. *Plavix*® is sold in nearly 110 countries, with sales of US$ 9.43 billion in 2010 (The 2nd top selling drug in the world) [7]. The current synthetic process of (+)-(*S*)-clopidogrel (**1**) by *Sanofi–Aventis* suffers from low overall yields and moreover, tedious purification methods are required to obtain the chemical and enantiomerical purity to be used as a pharmaceutical substance [8][9].

We report herein the first solid-phase synthesis of the enantiomerically pure (+)-(*S*)-clopidogrel (**1**) in good yields.

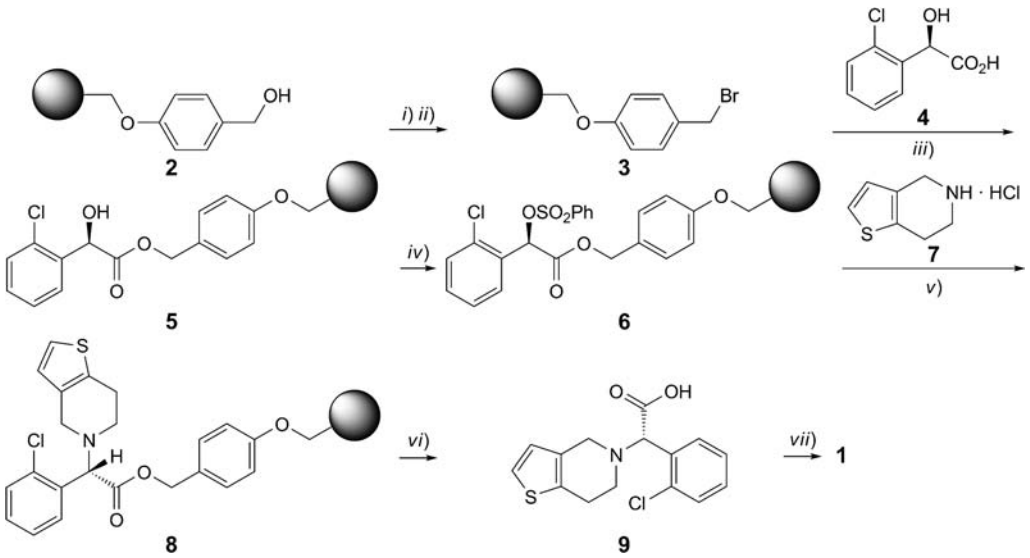


1

Results and Discussion. – To develop a sequence for the solid-phase synthesis, we selected the commercially available *Wang* resin **2**. Thus, as illustrated in *Scheme*, the Br-containing resin **3** was first prepared from **2** using the standard OH-to-Br conversion conditions involving Ph_3P and Br_2 (*Scheme*). The resin **3** was further reacted with (*R*)-2-chloromandelic acid (**4**) and $CsCO_3$ to give [4-({[(2*R*)-2-(2-chlorophenyl)-2-hydroxy-

acetyl]oxy}methyl)phenoxy]methyl resin (**5**). The OH group in the resin **5** was then converted to the $PhSO_2$ group for further functionalization by reacting **5** with benzenesulfonyl chloride and Et_3N. A nucleophilic displacement of the $PhSO_2$ group in the resin **6** was carried out with 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride (**7**) to afford the [4-({[(2*S*)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetyl]oxy}methyl)phenoxy]methyl resin **8**.

Scheme. *Synthesis of* **1**



i) PPh_3, CH_2Cl_2. *ii*) Br_2. *iii*) Cs_2CO_3, DMF. *iv*) $PhSO_2Cl$, Et_3N, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2. *v*) Et_3N, CH_2Cl_2. *vi*) CF_3COOH (TFA) 50% in CH_2Cl_2. *vii*) $SOCl_2$, MeOH.

The desired product **9** was cleaved from the resin **8** using CF_3COOH (TFA) 5% in CH_2Cl_2, and the enantiomerically pure (2*S*)-(2-chlorophenyl)(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetic acid (**9**) was obtained in 62% overall yield over 5 steps.

The acid **9** was further methylated under the typical acetylation conditions using $SOCl_2$ to furnish the target compound, (+)-(*S*)-clopidogrel (**1**), in 84% yield. The HPLC analysis revealed the optical purity (ee) of 98.0% for this compound.

Conclusions. – We have successfully prepared (+)-(*S*)-clopidogrel (**1**) from the commercially available *Wang* resin with overall 52% yield in six steps and optical purity of 98.0% ee. Regarding the ease of chemistry, the elimination of purification steps *en route*, and the straightforward nature of parallel synthesis, this work suggests that the solid-phase reactions can be used for commercial production of clopidogrel.

Experiment Part

General. All chemicals including *Wang* resin, *(*R*)-2-chloromandelic acid* (**4**), and *4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride* (**7**) were obtained from *Daehe Biopharma* (http://www.daehe.co.kr/) and were used without further purification. Solvents were purified and dried by

standard procedures. A chiral HPLC method was used for determination of the enantiomeric purity. As a stationary phase, an *Ultron ES-OVM* column (5 μm; 4.6 mm × 150 mm i.d.) was used. The mobile phase consisted of a mixture of MeCN and 0.01M KH_2PO_4 soln. (25 : 75 (*v*/*v*)); further conditions: flow rate, 1.0 ml/min; column temp., 17°; injection volume, 10 μl; detection wavelength, 220 nm. ^{1}H-NMR Spectra: *Varian Unity 300* NMR spectrometer at 300 MHz; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz.

[4-(Bromomethyl)phenoxy]methyl Resin (**3**). *Wang* resin (**2**; 0.87 mmol/g, 1 g, 0.87 mmol) and Ph_3P (0.684 g, 2.7 mmol) in CH_2Cl_2 (20 ml) was stirred for 10 min, and Br_2 (0.134 ml, 2.61 mmol) was added slowly to this suspension. After 5 min at r.t., the resin was washed consecutively with H_2O, H_2O/DMF 1 : 1, DMF, MeOH, MeOH/CH_2Cl_2 1 : 1, and CH_2Cl_2 (50 ml each), and dried under vaccum.

*[4-({[(2*R*)-2-(2-Chlorophenyl)-2-hydroxyacetyl]oxy}methyl)phenoxy]methyl Resin* (**5**). A mixture of **3**, *(*R*)-2-chloromandelic acid* (**4**; 647.3 mg, 3.48 mmol), and $CsCO_3$ (5.1 g, 15.7 mmol) was dissolved in DMF (50 ml) and stirred for 4 h at r.t. The resulting resin was then washed with H_2O, H_2O/DMF 1 : 1, DMF, MeOH, MeOH/CH_2Cl_2 1 : 1, and CH_2Cl_2 (50 ml each), and dried under vacuum.

*{4-[({(2*R*)-2-(2-Chlorophenyl)-2-[(phenylsulfonyl)oxy]acetyl}oxy)methyl]phenoxy}methyl Resin* (**6**). A stirred suspension of resin **5** in CH_2Cl_2 (30 ml) was dissolved in $PhSO_2Cl$ (0.23 ml, 1.74 mmol), Et_3N (0.36 ml, 2.61 mmol) and a cat. amount of DMAP were added, and the mixture was stirred for 12 h at r.t. The resin was washed with H_2O, H_2O/DMF 1 : 1, DMF, MeOH, MeOH/CH_2Cl_2 1 : 1, and CH_2Cl_2 (50 ml each), and dried under vacuum.

*[4-({[(2*S*)-2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetyl]oxy}methyl)phenoxy]methyl Resin* (**8**). A stirred soln. of *4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride* (**7**; 454 mg, 2.61 mmol) in CH_2Cl_2 (30 ml) was dissolved in Et_3N (0.73 ml, 5.22 mmol) and stirred for 30 min at r.t., resin **6** was added, and the mixture was stirred for 12 h at r.t. The resin was washed with H_2O, H_2O/DMF 1 : 1, DMF, MeOH, MeOH/CH_2Cl_2 1 : 1, and CH_2Cl_2 (50 ml each), and dried under vacuum.

*(2*S*)-2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetic Acid* (**9**). A mixture of the resin **8** in TFA/CH_2Cl_2 1 : 4 (20 ml) was stirred for 6 h at r.t. The mixture was then filtered and washed with MeOH (2 × 10 ml). The resulting soln. was evaporated *in vacuo* to reduce the volume (1/3), the soln. was carefully filtered through a SiO_2 pad and washed with 5% MeOH in CH_2Cl_2 (30 ml). The filtrate was evaporated and solidified by the addition of Et_2O and hexane. The vacuum drying gave **9** [10]; 165 mg, overall yield 62% over 5 steps). Solid. $[\alpha]_D = +7.4$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 10.61 (br. *s*, 1 H); 7.81 – 7.84 (*m*, 1 H); 7.37 – 7.40 (*m*, 1 H); 7.20 – 7.31 (*m*, 2 H); 7.16 (*d*, *J* = 5.1, 1 H); 6.66 (*d*, *J* = 5.1, 1 H); 5.29 (*s*, 1 H); 4.17 – 4.30 (*m*, 2 H); 3.44 – 3.64 (*m*, 2 H); 3.06 (br. *s*, 2 H). ESI-MS: 308 (100, $[M + H]^+$).

*(+)-(*S*)-Clopidogrel* (= *Methyl (2*S*)-2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetate*; **1**). To a stirred soln. of **9** (40 mg, 0.13 mmol) in MeOH (2 ml) was added $SOCl_2$ (0.013 ml, 0.16 mmol), and the mixture was stirred at 70° for 6 h. After cooling to r.t., the solvent was evaporated *in vacuo*. Sat. $NaHCO_3$ (aq.) was then added, and the mixture was extracted with CH_2Cl_2. The org. layers were collected, evaporated, filtered through a SiO_2 pad, and washed with AcOEt/hexane 1 : 6 to give **1** (84%). Pale yellow oil. [11]: $[\alpha]_D = +44.8$ ($c = 1$, MeOH). ^{1}H-NMR ($CDCl_3$): 7.66 – 7.70 (*m*, 1 H); 7.37 – 7.44 (*m*, 1 H); 7.27 – 7.31 (*m*, 2 H); 7.07 (*d*, *J* = 5.1, 1 H); 6.66 (*d*, *J* = 5.1, 1 H); 4.92 (*s*, 1 H); 3.73 (*s*, 3 H); 3.60 – 3.80 (*m*, 2 H); 2.89 (br. *s*, 4 H). ESI-MS: 322 (100, $[M + H]^+$).

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