# A Scalable Synthesis of (±)-2-Oxoclopidogrel

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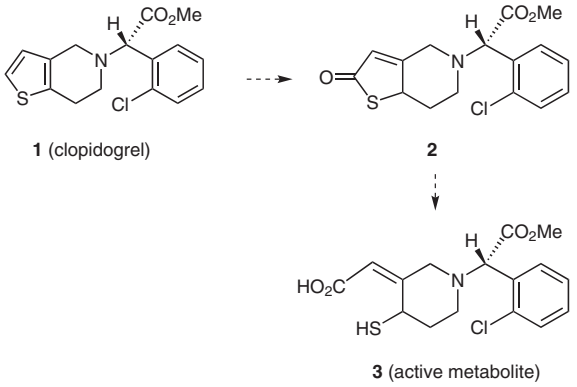
**Abstract:** As a precondition for detailed pharmacological investigations, an efficient chemical method for the conversion of the antiplatelet drug clopidogrel into its first metabolite 2-oxoclopidogrel was developed. The one-pot procedure, which can easily be performed on a gram scale, exploits the selective borylation of a dianionic intermediate derived from clopidogrel with subsequent oxidative workup.

**Key words:** clopidogrel, drugs, lithiation, oxidation, thiophenes

Platelet activation is the major factor in the development of ischemic and thrombotic complications in patients undergoing percutaneous coronary intervention (PCI). Antiplatelet treatment with the thienopyridine derivative clopidogrel (**1**; Plavix®) in addition to aspirin given before PCI is currently considered the gold standard to prevent adverse cardiovascular events.[1] The main clinical limitation of **1**, however, is the high interindividual response variability. Actually, between 5–54% of PCI patients attain insufficient platelet inhibition[2] and thus appear to be at increased risk for cardiovascular events.[3]

The causes of the substantial interpatient differences in response to **1** are incompletely understood. Nevertheless, it has been shown that **1** is actually a prodrug that requires biotransformation to an active metabolite, that is, the sensitive thiol **3** which then binds covalently by a disulfide bridge to its pharmacological target.[4] Preliminary data indicate that the plasma concentration of the active metabolite is a strong determinant of the antiplatelet activity.[5] Based on incubation experiments using liver microsomes, formation of the active metabolite of **1** was suggested to proceed through a two-step mechanism via 2-oxoclopidogrel (**2**) as an intermediate metabolite (Scheme 1).[4] Although genetic polymorphisms of cytochrome P450 enzymes have been linked to individual variability in responsiveness to clopidogrel,[6] no direct in vitro or in vivo assessments of the metabolic pathways leading to clopidogrel activation and the involved enzymes have been performed.

To elucidate these pathways and the variability of clopidogrel metabolism, substantial amounts of 2-oxoclopidogrel (**2**) are needed both as an analytical standard for in vitro and in vivo quantification and as a precursor for studying its biotransformation into the active metabolite **3**. It should be stressed that the enzymatic production of 2-oxoclopidogrel (**2**)[4] starting from **1** is not applicable on a preparative scale because yields are very low and extensive purification is required to obtain only tiny amounts of the product in pure form.

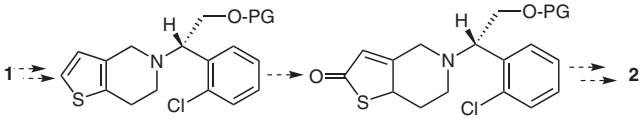



**1** (clopidogrel) **2** **3** (active metabolite)

**Scheme 1** Enzymatic conversion of clopidogrel (**1**) via 2-oxoclopidogrel (**2**) into the active metabolite **3**

Against this background a chemical method for the conversion of **1** into **2** would be highly desirable. Here we disclose an operationally simple, non-enzymatic, time-, and cost-efficient solution for this task, which yields large quantities of analytical grade 2-oxoclopidogrel (*rac*-**2**).

Initially, we considered it necessary to first convert the ester function of **1** into a protected alcohol **4**, which could then be selectively oxidized to a thiobutenolide of type **5** prior to the final re-establishment of the ester moiety in **2** (Scheme 2).




**4** **5**

**Scheme 2** Initial concept for the conversion of **1** into **2**

Following this plan, clopidogrel (**1**) was reduced with $LiAlH_4$ in diethyl ether, and the resulting alcohol **6** was converted into the silylether **7** by treatment with TBSCl and $Et_3N$ (88% overall yield). The key thiophene oxida-

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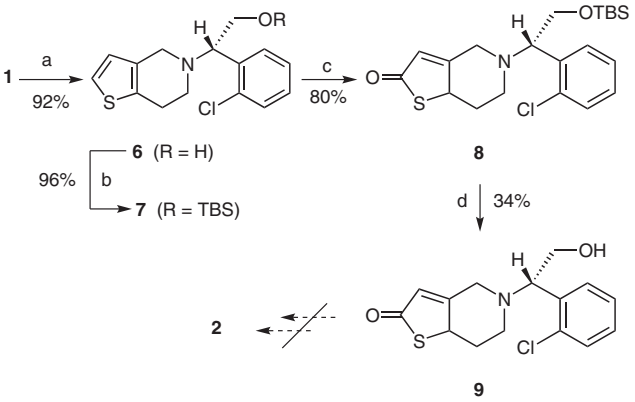
tion was then initiated by lithiation of the thiophene ring using *n*-BuLi in THF in the presence of tetramethylurea (TMU, instead of HMPT[7]) as a co-solvent. After addition of $B(OMe)_3$ the resulting boronate was directly oxidized with $H_2O_2$ to afford compound **8** in good yield as a mixture of diastereomers (Scheme 3). To our surprise, the cleavage of the silyl protecting group then proved to be difficult under various established conditions,[8] and the alcohol **9** was isolated in only 34% yield in the best case. Moreover, the planned oxidation of **9** using either the Dess–Martin periodinane[9] or Jones reagent[10] failed. Nevertheless, compounds **8** and **9** proved of value as references for further structural assignments.

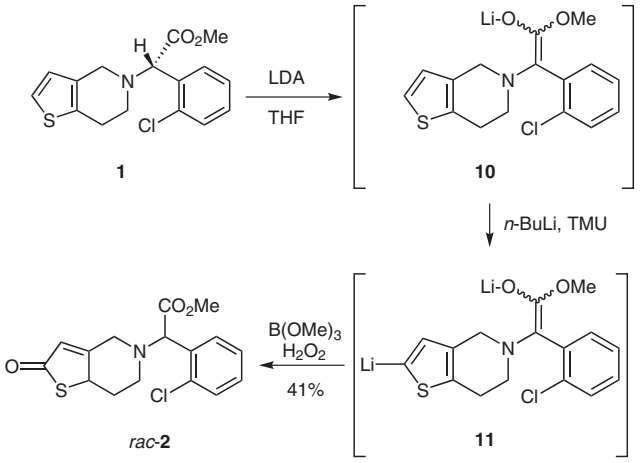



**Scheme 3** Initial approach for the conversion of **1** into **2**. *Reaction conditions*: (a) $LiAlH_4$, $Et_2O$, 20 h, r.t.; (b) TBSCl, $Et_3N$, $CH_2Cl_2$. –10 °C to r.t., 24 h; (c) *n*-BuLi, THF, TMU, –78 °C, 17 min, then $B(OMe)_3$, –60 °C to 0 °C, 3 h, then $H_2O_2$–$H_2O$, 0 °C, 45 min; (d) THF–$H_2O$–AcOH (1:1:2.5), r.t., 30 min, 30 °C, 20 h concept for the conversion of **1** into **2**.

In order to circumvent the above-mentioned problems associated to functional-group transformations in the presence of the sensitive thiobutenolide moiety we envisioned that the borylation step (to prepare for the thiophene oxidation) could possibly be achieved employing a dilithiated intermediate of type **11** (Scheme 4). In this case, the ester functionality would be in situ protected as the enolate **10**. And indeed: When clopidogrel (**1**) was first deprotonated with LDA (1 equiv) and subsequently treated with *n*-BuLi/TMU, trimethylborate, and $H_2O_2$, the desired product, that is, 2-oxoclopidogrel (*rac*-**2**), was obtained as a mixture of diastereomers (Scheme 3).

The constitution of *rac*-**2** was unambiguously established through the spectroscopic data, also in comparison to compounds **8** and **9**. Particular characteristic features of the thiobutenolide substructure are the carbonyl proton signal at δ = ca. 5.95 ppm and a $^{13}C$ signal at δ = 198.5 ppm corresponding to the carbonyl group. The doubling of most $^{13}C$ and some $^{1}H$ signals indicated the presence of two diastereomers in a ratio of ca. 1:1.

In conclusion, we have found an astonishingly simple solution for the preparation of 2-oxoclopidogrel (*rac*-**2**).




**Scheme 4** Synthesis of 2-oxoclopidogrel (*rac*-**2**) in a one-pot procedure.

Starting from (inexpensive) clopidogrel (**1**) the transformation is achieved in a one-pot procedure and proceeds with an overall yield of 40% even on a gram scale. While the absolute stereochemical information is lost during this process and the product is formed as a mixture of diastereomers, the method represents the first and sole synthetic entrance to a key metabolite (precursor of the active species) of the important antiplatelet drug clopidogrel. Also the synthetic material proved to be perfectly suited as an analytical standard for detailed pharmacological investigations, the results of which will be separately reported in due course.

**(2-Chlorophenyl)-{2-oxo-2,6,7,7a-tetrahydro-4*H*-thieno[3,2-*c*]pyridin-5-yl}acetic Acid Methyl Ester (*rac*-2)**

To a solution of clopidogrel (**1**, 3.8 g, 11.84 mmol) in THF (80 mL) was added dropwise at –78 °C a 1.8 M solution of LDA (7.2 mL, 13.02 mmol) in THF. After 45 min at –78 °C TMU (2.8 mL, 26.05 mmol) was added, followed by a 1.58 M solution of *n*-BuLi in hexane (16.5 mL, 26.05 mmol). The mixture was stirred for 10 min before $B(OMe)_3$ (2.9 mL, 26.05 mmol) was added at –60 °C. The stirred solution was allowed to slowly warm to 0 °C (4.5 h) before a solution (35% w/w) of $H_2O_2$ in $H_2O$ (1.2 mL, 14.21 mmol, 1.2 equiv) was added and stirring was continued for 45 min at 0 °C. The mixture was then partitioned between $H_2O$ (20 mL) and MTBE (50 mL), and the aqueous layer was re-extracted with MTBE. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc = 3:1) afforded the *rac*-**2** as a solid (1.58 g, 4.8 mmol, 41%). $R_f$ = 0.32 (cyclohexane–EtOAc = 10:1). IR (ATR, $CHCl_3$): 2928 (m), 2857 (m), 1758 (s), 1685 (s), 1469 (m), 1255 (m), 1094 (s), 835 (s) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.72–1.86 (m, 1 H), 2.25–2.35 (m, 1 H), 2.48–2.64 (m, 1 H), 2.94–3.10 (m, 1 H), 3.09–3.23 (m, 1 H), 3.64/3.65 (s, 3 H, $OCH_3$), 3.74–3.87 (m, 1 H), 4.05 (m, 1 H, H-C7a), 4.82/4.84 (s, 1 H, CHN), 5.93 (s, 1 H, HC3), 7.23 (m, 2 $H_{ar}$), 7.35 (m, 1 $H_{ar}$), 7.45 (m, 1 $H_{ar}$). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 33.7/33.9 (C7), 48.9/45.5 (C4), 51.0 (C7a), 52.3 ($OCH_3$), 51.5/52.3 (C6), 67.1 (CH-N), 126.4/126.6 (C-3), 127.0/127.1 ($C_{ar}$4), 129.6/129.7 ($C_{ar}$5), 129.9/130.0 ($C_{ar}$3), 129.5/129.6 ($C_{ar}$6), 132.6/132.8 (C3), 134.5/134.7 ($C_{ar}$1), 167.2/167.4 (C3a), 170.6/170.7 ($CO_2Me$), 198.5 (C=O). ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}ClNO_3S$: 337.0539; found: 337.0538.

**(*S*)-5-[2-(*tert*-Butyldimethylsilanyloxy)-1-(2-chlorophenyl)ethyl]-5,6,7,7a-tetrahydro-4*H*-thieno[3,2-*c*]pyridin-2-one (8)**

To a solution of silyl ether **7** (2.0 g, 4.93 mmol) in THF (50 mL) was added dropwise at –78 °C TMU (2.8 mL, 5.91 mmol, 1.2 equiv) followed by addition of a 2.41 M solution of *n*-BuLi in hexane (2.45 mL, 5.91 mmol, 1.2 equiv) over a period of 7 min. Stirring was continued for 10 min under warming to –60 °C before $B(OMe)_3$ (0.6 mL, 5.42 mmol, 1.1 equiv) were added. The mixture was then allowed to warm to 0 °C over a period of 3 h and stirred for 30 min at 0 °C before aq $H_2O_2$ (35% w/w, 0.5 mL, 5.91 mmol, 1.2 equiv) were added. After 45 min at 0 °C the mixture was allowed to warm to r.t. and $H_2O$ (20 mL) and MTBE (50 mL) were added. The layers were separated, and the aqueous layer was re-extracted with MTBE. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc = 10:1) afforded the product **8** as yellow oil (1.67 g, 3.93 mmol, 80%). $R_f$ = 0.29 (cyclohexane–EtOAc = 10:1). IR ($CHCl_3$): 3061 (w), 2950 (m), 2925 (m), 2854 (m), 1569 (w), 1469 (m), 1254 (m), 1099 (s), 834 (s), 775 (m), 699 (m) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = –0.10/–0.05 (s, 3 H, $SiMe_2$), 0.82 [s, 9 H, $SiC(CH_3)_3$], 1.71–1.92 (m, 1 H,), 2.22–2.28 (m, 1 H, H-C7), 2.35–2.44 (m, 1 H, HC4), 2.50–2.60 (m, 1 H, HC4), 2.90–2.97 (m, 1 H, HC6), 3.72 (d, *J* = 11.7 Hz, 1 H, HC6), 3.78–3.98 (m, 2 H, $H_2$COTBS), 4.11–4.21 (m, 2 H, HCN and HC7a), 5.87/6.04 (s, 1 H, HC3), 7.17–7.21 (m, 2 H, Ar), 7.32–107.37 (m, 1 $H_{ar}$), 7.47–7.53 (m, 1 $H_{ar}$). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = –5.6 ($SiMe_2$), 25.7 [$SiC(CH_3)_3$], 34.2/34.7 (C7), 49.4/50.6 (C4), 51.5 (C7a), 52.7/53.5 (C6), 64.6 (CHOTBS), 65.5/66.0 (CHN), 125.8 (C-3), 126.5/126.8 ($C_{ar}$2), 128.4/128.5 ($C_{ar}$4), 129.3/129.4 ($C_{ar}$5), 129.5/129.6 ($C_{ar}$3), 133.8 ($C_{ar}$6), 137.5 ($C_{ar}$1), 168.6/168.9 (C3a), 198.7/198.8 (C=O). MS (EI, 70 eV): *m/z* (%) = 425 (23) [$M^+$], 278 (100).

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