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Synthesis of the stabilized active metabolite of clopidogrel

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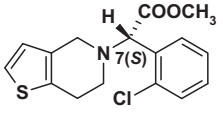
ABSTRACT

The convergent synthesis of the stabilized active metabolite of clopidogrel was achieved in eleven steps from commercially available 1,2,3,6-tetrahydropyridine and 2-bromo-3′-methoxy acetophenone (MPBr). This synthetic route used a standard Horner–Wadsworth–Emmons reaction allowing the introduction of a *Z* exocyclic double bond. A selective hydrolysis of an acrylic methyl ester moiety, isolated by an efficient and reliable preparative chiral chromatography at gram scale, released the title compound with a 98% LC purity and d.e. >99%.

1. Introduction

Clopidogrel **1** is an oral antiplatelet agent from the thienopyridine family indicated for the prevention of artherothrombotic events (Fig. 1).[1] Clopidogrel is a P2Y12-ADP receptor antagonist and a prodrug, requiring two distinct metabolic transformations to produce the active metabolite responsible for the anti-aggregating effect.



1

Fig. 1. Chemical structure of clopidogrel.

The main metabolic pathway converts **1** into an inactive carboxylic acid derivative **2** by hydrolysis (Scheme 1). In vitro studies showed that the pharmacologically active metabolite is generated by a two-step hepatic pathway involving multiple cytochrome P450 isoenzymes.[2] The first step involves oxidation of **1** to the inactive 2-oxo-clopidogrel intermediate **3**. Next, the thiolactone ring is opened, via the sulfinate intermediate, **3′** to give the active metabolite species **4**. Two additional elements of stereogenicity are thus added to the stereocenter already present at position 7: a new stereocenter at position 4 and a stereogenic exocyclic double bond, suggesting that the active metabolite may be one component of a mixture of diastereoisomers.

In vitro metabolism studies on **3** showed that the metabolic transformation led to a mixture of four stereoisomers, referred to as H1, H2, H3 and H4. All four were isolated and characterized: isomers H1 and H2 **4a** are the *E* compounds while isomers H3 and H4 **4b** have *Z* configuration at the exocyclic double bond (Scheme 2).[3] The thiol moiety of the active metabolite **4** binds specifically and irreversibly to cysteine residues of the platelet P2Y12 purinergic receptor, thus inhibiting ADP-mediated platelet activation and aggregation.

In addition, it has been demonstrated by analysis of clinical samples that only metabolites H4 and H3 are formed in vivo, and that H4 was found to be the only biologically active isomer.[4] These various metabolism studies showed that the expression of the anti-aggregant activity of clopidogrel depends on the configuration of the three stereochemical sites: C7, C3–C16 and C4. The *S* configuration at C7 and the *Z* configuration of the C3–C16 double bond are considered to be crucial for expression of activity and only isomers H3 and H4 had these features.

Since only metabolite H4 was active in vivo, it appeared that the activity was also closely linked to the *R* or *S* configuration at

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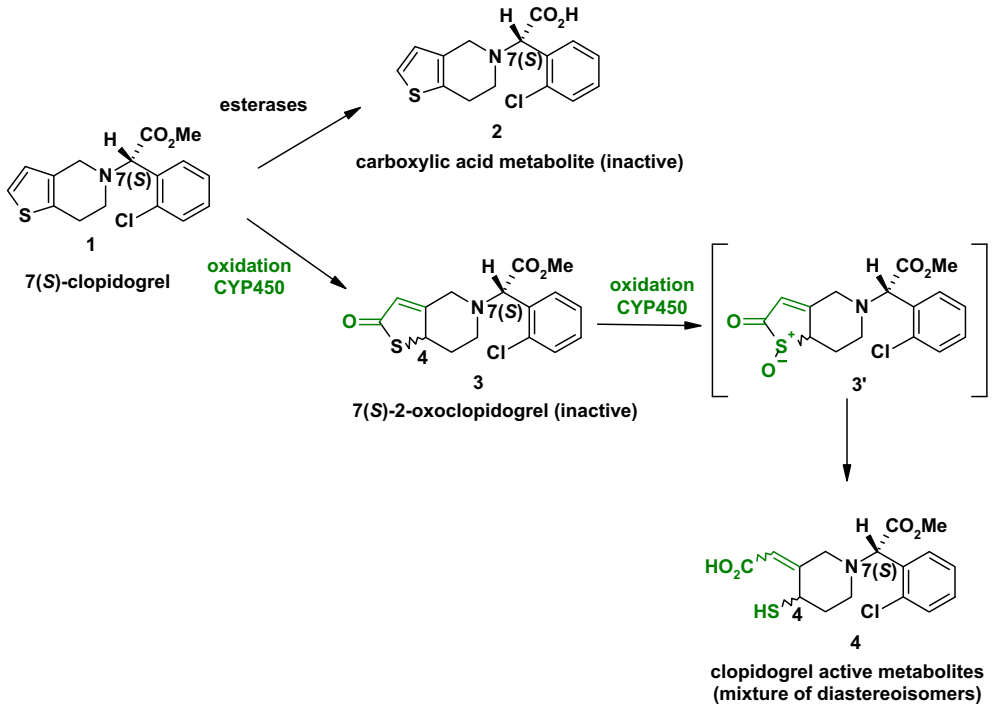
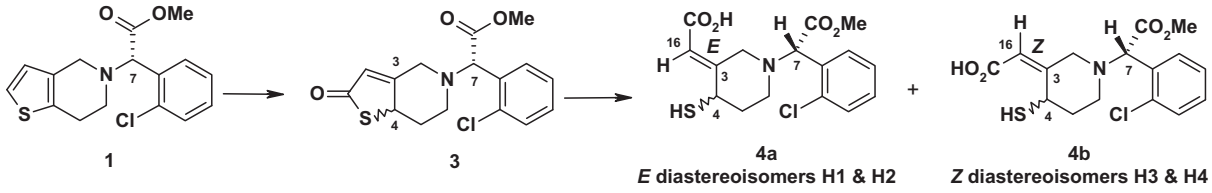


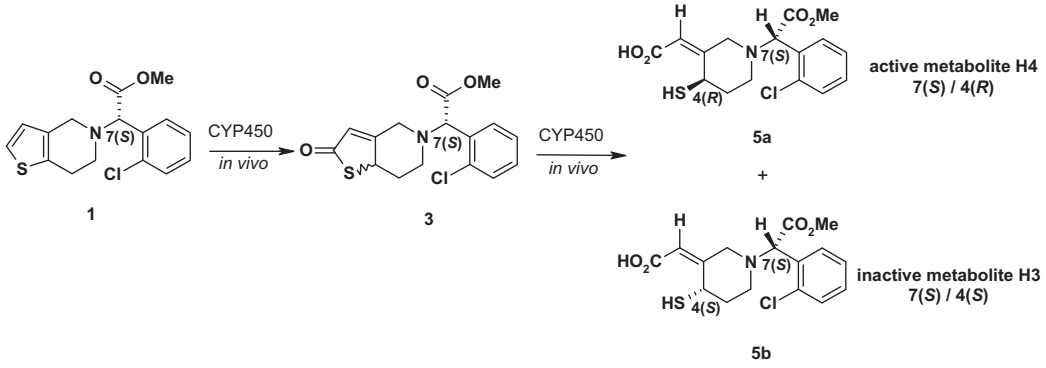
Scheme 1. Metabolic pathway of clopidogrel.



Scheme 2. Active metabolites of clopidogrel: possible set of four stereoisomers generated from clopidogrel **1**.

C4. At the beginning of this project, the absolute configuration at C4 in H4 had not been clearly elucidated. Further structural analysis performed concomitantly with this study, allocated the (*R*) configuration to the C4 centre in active metabolite H4 **5a** (Scheme 3).[5]

Takahashi et al., showed that direct trapping of metabolites H3 and H4 in human plasma with 2-bromo-3′-methoxy acetophenone **6** as alkylating agent overcomes this instability and allows quantification of the derivatized stable forms of both active metabolite **7** and inactive metabolite **8** in clinical samples (Scheme 4).[6]



Scheme 3. In vivo metabolism: structure of both active metabolite H4 **5a** and inactive metabolite H3 **5b** of **1**.

The presence of a free thiol group makes the clopidogrel metabolites H3 and H4 unstable in human plasma, hampering their quantification in clopidogrel-treated patients.

Derivatized active metabolite **7** has never been synthetized preparatively by chemical means to the best of our knowledge. Previous work relied on microsomal incubation with human liver