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A Very Short, Efficient and Inexpensive Synthesis of the Prodrug Form of SC-54701A A Platelet Aggregation Inhibitor

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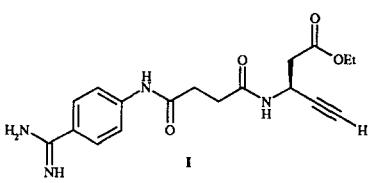
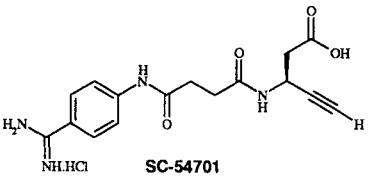
Abstract : A short and efficient synthesis of the prodrug form of SC-54701A has been achieved from (trimethylsilyl)acetylene in 6 steps with an overall yield of 19%. © 1997 Elsevier Science Ltd.

Many new therapeutic approaches for the treatment or prevention of a myocardial infarct, stroke and unstable angina are currently under clinical investigations.[1] Fibrinogen receptor antagonists disrupt the obligatory platelet fibrinogen interaction for white thrombus formation.[2] Peptide mimetics, based on the RGD sequence of fibrinogen that effectively disrupt platelet aggregation and possess short half-lives ideally suitable for critical intervention in combination with fibrinolytic agent, have been designed.[3,4] Administration of an orally active fibrinogen receptor antagonist has the potential to prevent vascular complications which has led to a continued interest in the RGD mimetic area. Recently, several structurally unique fibrinogen receptor antagonists, that have oral activity in animals,[5] especially SC-54701A and its prodrug ester **I** have been disclosed.[6]



I



SC-54701

Contrary to the previously reported synthesis of **I** which is expensive and tedious,[6] we would like to report here a short, convergent, efficient and inexpensive synthesis of **I** using an enzymatic reduction of an acetylenic β-ketoester. Our synthesis started with (trimethylsilyl)acetylene which was treated with *n*-BuLi (1 eq). The so-formed 1-lithio-2-(trimethylsilyl)acetylene was reacted with ethyl chloroformiate[7] to afford ethyl 3-(trimethylsilyl)prop-2-ynoate **2** (95% yield). Claisen condensation of ethyl lithioacetate with **2** gave, after distillation (83-85 °C, 2 mm/Hg) the ketoester **3** (95%)[8] which was then reduced to the corresponding chiral alcohol **4** by employing lyophilized baker's yeast[9] (*Saccharomyces cerevisiae*, Sigma type II), [yield = 50%, $[\alpha]_D^{20}$ +39 (*c* 1, $CHCl_3$), ee = 94%[10,11]]. A Mitsunobu reaction on **4**, employing phthalimide in the presence of diethylazodicarboxylate (DEAD) and PPh_3 led exclusively to the elimination product, ethyl 5-(trimethylsilyl)pent-2-en-4-ynoate.[12] Fortunately, substituting the phtalimide by HN_3 furnished, after Staudinger reaction[13], the desired (*S*)-configurated amine **5** which was transformed to amine **6**[14]

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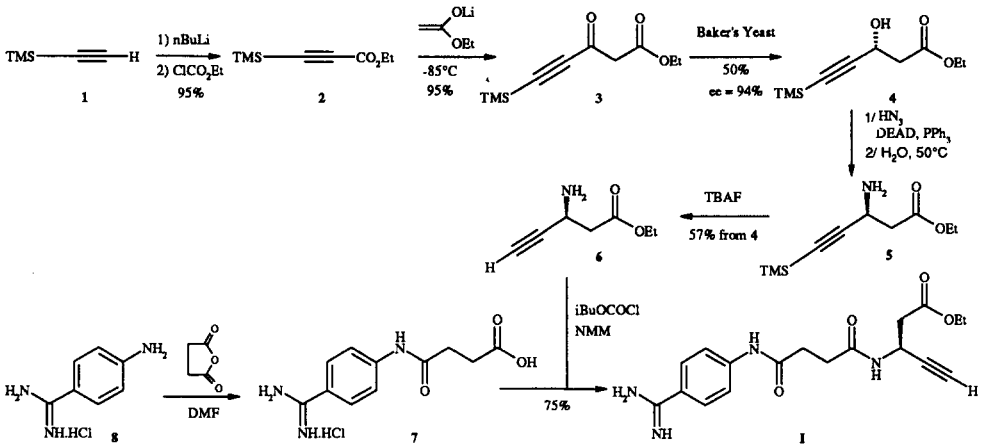
after deprotection, by using tetrabutylammonium fluoride (TBAF) (yield = 57% from **4**). When compound **6**, was coupled with acid **7** in the presence of isobutyl chloroformiate and N-methylmorpholine (NMM), the expected prodrug ester **I** was obtained in 75% yield after purification by flash-chromatography.[6] We have to point out that **7** was obtained by reacting the commercially available 4-aminobenzamidine hydrochloride **8** with succinic anhydride using 4-(dimethylamino)pyridine (DMAP) in warm DMF.

The prodrug ester **I** was obtained from (trimethylsilyl)acetylene in 6 steps with an overall yield of 19%.



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10. The ee of **4** was measured by GC after esterification with (*S*)-O-acetylpropanoyl chloride and calibration with racemic material.
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14. **6** was transformed to the hydrochloride salt and the $[\alpha]_D$ was measured in MeOH. $[\alpha]_D^{20}$ -3.1 (*c* 0.70, CH_3OH).[6]

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