



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

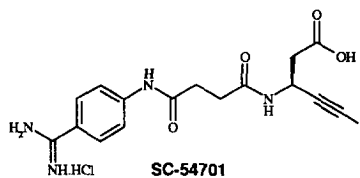
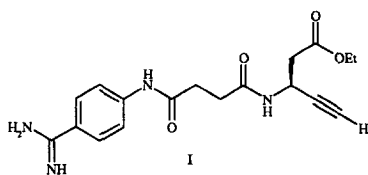
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Abstract : A short and efficient synthesis of the prodrug form of SC-54701A has been achieved from (trimethylsilyl)acetylene in 6 steps with an overall yield of 19%. © 1997 Elsevier Science Ltd.

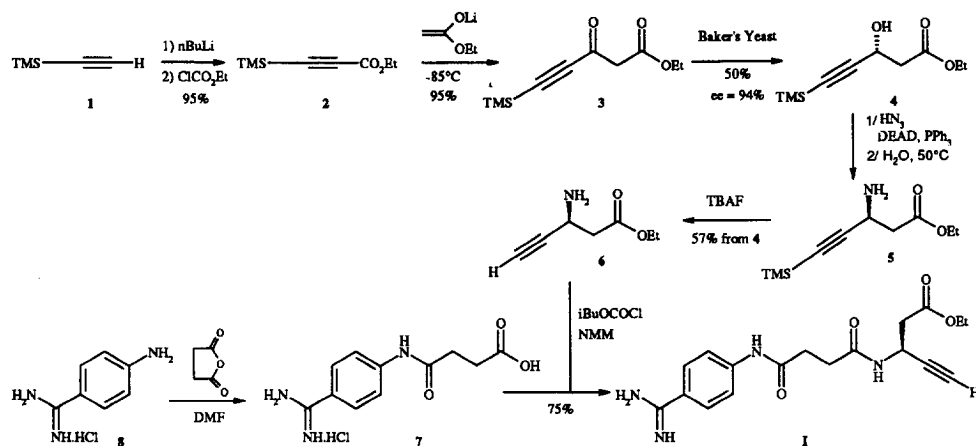
Many new therapeutic approaches for the treatment or prevention of a myocardial infarct, stroke and unstable angina are currently under clinical investigations.¹ Fibrinogen receptor antagonists disrupt the obligatory platelet fibrinogen interaction for white thrombus formation.² Peptide mimetics, based 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



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 chloroformate⁷ 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 (*Saccharomyces cerevisiae*, Sigma type II), [yield = 50%, $[\alpha]_D^{20} +39$ (c 1, CHCl₃), ee = 94%^{10,11}]. A Mitsunobu reaction on **4**, employing phthalimide in the presence of diethylazodicarboxylate (DEAD) and PPh₃ led exclusively to the elimination product, ethyl 5-(trimethylsilyl)pent-2-en-4-ynoate.¹² Fortunately, substituting the phthalimide by HN₃ furnished, after Staudinger reaction¹³, the desired (*S*)-configured amine **5** which was transformed to amine **6**¹⁴

after deprotection, by using tetrabutylammonium fluoride (TBAF) (yield = 57% from 4). When compound 6, was coupled with acid 7 in the presence of isobutyl chloroformate 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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- 6** was transformed to the hydrochloride salt and the $[\alpha]_D^{20}$ was measured in MeOH. $[\alpha]_D^{20}$ -3.1 (c 0.70, CH₃OH).⁶