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A synthesis of the platelet aggregation inhibitor xemilofiban from L-aspartic acid. Confirmation of the absolute configuration.

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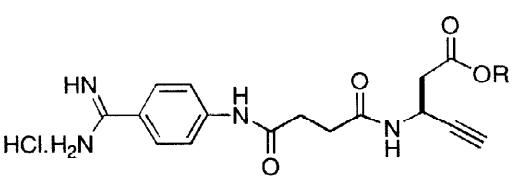
Abstract

A synthesis of xemilofiban (SC-54684A) from L-aspartic acid has been achieved in an overall yield of 18 %, and the absolute configuration has been confirmed.

Xemilofiban (SC-54684A) is one of a class of potent and orally active agents under development for the prevention of thrombotic complications (myocardial infarct, urgent revascularization, death) following coronary revascularization [1]. SC-54684A **1a** is the prodrug form of SC-54701A **1b**, a peptide mimetic based on the RGD sequence of fibrinogen, which effectively disrupts the platelet-fibrinogen interaction thus inhibiting platelet aggregation and preventing thrombus formation [1].



1a R=Et
1b R=H

Different methods for the synthesis of **1b** or its prodrug form **1a** have been reported previously [1-3]. These procedures suffer either from the inefficient resolution of racemates or from the use of expensive and hazardous reagents. The absolute configuration of the β-aminoester moiety had been assigned by analogy with the asparagine residue in the natural ligand. It was therefore decided to carry out a synthesis starting from the readily available L-aspartic acid in order to confirm the absolute configuration and to avoid the requirement for asymmetric synthesis or resolution. A recent report prompted this disclosure [4].

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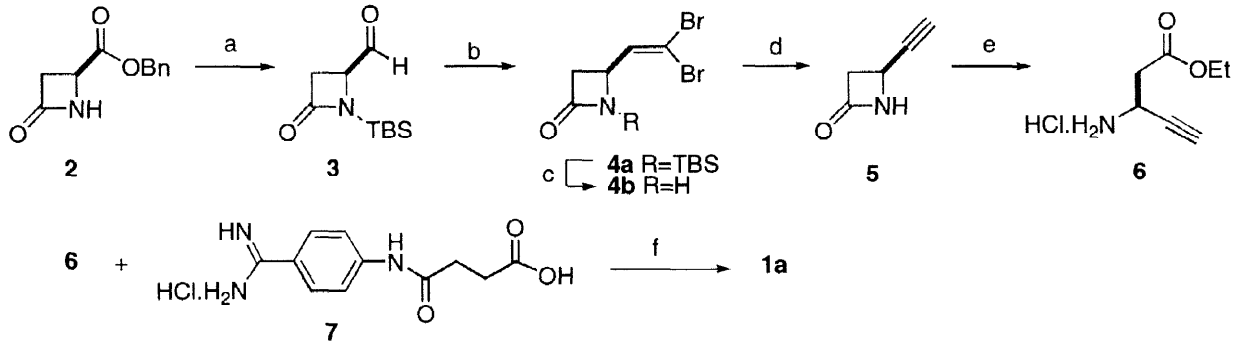
Azetidinone **2** was prepared from L-aspartic acid in 62 % yield via known procedures [5]. Conversion of **2** to the known protected aldehyde **3** was carried out according to the procedure of Labia and Morin [6]. Aldehyde **3** was then homologated to the terminal alkyne **5** using the method of Corey and Fuchs [7]. Removal of the silyl protecting group from azetidinone **4a** prior to elimination of the dibromide **4b** reduced the possibility of epimerization. Treatment of alkynyl azetidinone **5** with hydrogen chloride in ethanol gave the desired β-amino ester intermediate **6**. Comparison with material prepared via resolution using mandelic acid [2] allowed confirmation of the absolute configuration. Using a chiral stationary phase HPLC method, the two were shown to have identical retention times. Comparison with a racemic sample showed that there had been no loss of enantiopurity during the synthesis. Recrystallization from acetonitrile/methyl t-butyl ether gave analytically pure **6** in 70 % yield (>99 % ee). Finally, coupling of **6** with 4-aminobenzamidine succinate **7** under standard conditions [1-3] gave authentic **1a** [8].

In conclusion the synthesis of the prodrug SC-54684A **1a** from L-aspartic acid has been demonstrated in 18 % overall yield and the absolute configuration has been confirmed [9].



a (i) TBSCl, Et_3N, 97 % (ii) $NaBH_4$, MeOH, 83 % (iii) $(COCl)_2$, DMSO, Et_2i-PrN; b. CBr_4, PPh_3, 77 % (from **2**); c. 2N HCl, AcOH, 87 %; d. BuLi, -78 °C, 88 %; e. HCl, EtOH, 74 %; f. i-BuOCOCl, NMM, 70 %

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[8] The author would like to thank Mr R. Salzmann for his expert technical assistance.

[9] New compounds were characterised by ^1H NMR, ^{13}C NMR, IR, optical rotation and microanalysis.