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A new synthesis of the GPIIb/IIIa receptor antagonist SB-214857-A

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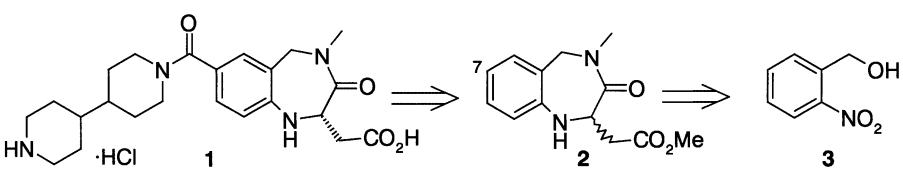
Abstract—A new synthesis of lotrafiban SB-214857-A is reported. The key steps are the preparation of racemic (4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)-acetic acid methyl ester from 2-nitrobenzyl alcohol, a resolution using an immobilised lipase enzyme and a palladium-catalysed aminocarbonylation reaction.

SB-214857-A (lotrafiban) **1** is a potent non-peptidic glycoprotein IIb/IIIa antagonist and consequently inhibits platelet aggregation ex vivo.[1,2] Previous syntheses of SB-214857-A starting from L-aspartic acid[3–5] have been reported. In this letter we report an alternative enantioselective synthesis of **1** in which the key intermediate, racemic 1,4-benzodiazepine ester **2**, is prepared from 2-nitrobenzyl alcohol **3** using a novel tetrahydroquinazoline to diazepine rearrangement. Enzyme-catalysed resolution of **2** followed by functionalisation at C-7 of the aromatic ring enabled a palladium-catalysed aminocarbonylation process to complete the synthesis (Scheme 1).[6]

The preparation of the racemic 1,4-benzodiazepine ester **2** is outlined in Scheme 2. 2-Nitrobenzyl alcohol **3** was converted to the sulfonate ester and then displacement with aqueous methylamine gave **4**. Reaction of **4** with dimethyl acetylenedicarboxylate gave the intermediate nitro-alkene **5**. Attempted reduction of the nitro group of **5** over palladium on carbon led to partial alkene reduction, however, hydrogenation using Raney-Nickel as catalyst led to clean and selective nitro reduction to an intermediate aniline. This intermediate aniline was not isolated and subsequent treatment with mild acid caused cyclisation to the tetrahydroquinazoline **6**. Conversion of tetrahydroquinazoline **6** to benzodiazepine **7** could be achieved under a variety of different basic conditions such as DBU in ethyl acetate, but the preferred conditions used sodium methoxide in methanol. This particular reaction is thought to proceed via a retro-Michael reaction and then lactam formation. Benzodiazepine **7** was isolated as a single double bond isomer as shown, with the geometry determined by ^{1}H NMR. Hydrogenation of **7** over palladium on carbon gave the key intermediate **2**. Overall **2** could be prepared from **3** in 77% yield and if required without isolation of any intermediates.

Resolution of the racemic 1,4-benzodiazepine ester **2** could be achieved using *Candida antarctica* lipase B (supplied as Novozym 435 resin) which selectively



Scheme 1. Strategy for the synthesis of SB-214857-A **1**.

Keywords: asymmetric synthesis; benzodiazepine; carbonylation; enzyme reaction; epimerisation; hydrogenation.

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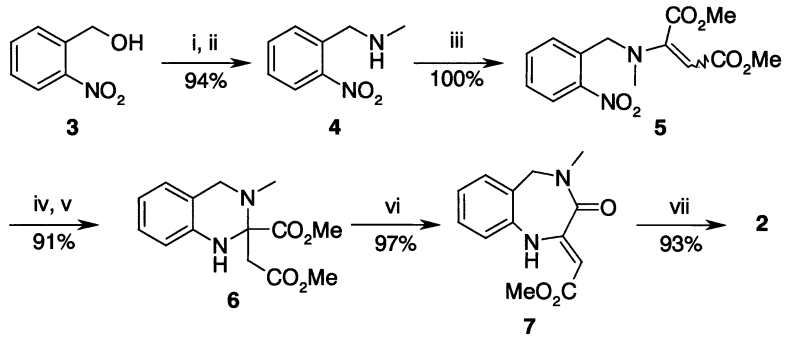
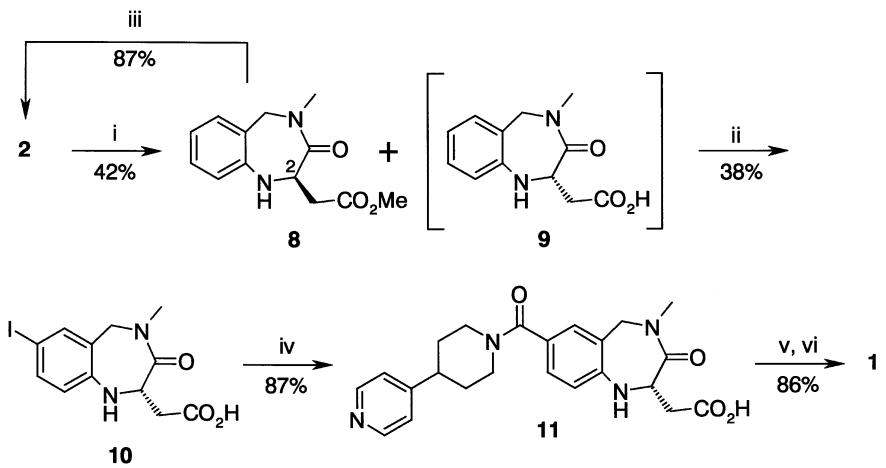


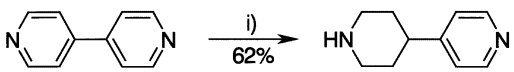
Scheme 2. Preparation of the racemic 1,4-benzodiazepine ester **2**. (i) MsCl, NEt_3, THF, rt; (ii) $MeNH_2$, H_2O, rt; (iii) dimethyl acetylenedicarboxylate, PhMe, rt; (iv) H_2, Raney-Ni, MeOH, 50 psi, 50°C; (v) AcOH, MeOH, 65°C; (vi) NaOMe, MeOH, 65°C; (vii) H_2, Pd/C, MeOH, 60 psi, 60°C.

hydrolysed the (*S*)-enantiomer to the corresponding acid **9**, addition of ammonia solution to maintain the pH 7.0 enhanced the rate of reaction[7] (Scheme 3). With a chemical conversion of 48% the acid **9** was obtained in 99.5% e.e., as determined by chiral HPLC. At the end-point of the reaction the Novozym 435 was removed by filtration and the unreacted (*R*)-ester **8** was obtained in 42% yield by crystallisation from aqueous sodium bicarbonate solution. Typically the acid **9** was not isolated but the aqueous solution used directly in the next reaction, which was the electrophilic iodination at C-7. A range of iodinating reagents[8] were studied for the conversion of **9** to **10**, from which pyridine iodine monochloride complex[9] was selected. Maintaining the reaction at pH 7.0 using sodium hydroxide solution gave a totally regioselective iodination and no unwanted over oxidation by-products. Iodo-acid **10** was isolated in 38% yield (over two steps) by crystallisation from aqueous acid, this procedure increased the chiral purity to 99.9% e.e., as determined by chiral capillary electrophoresis. Recycling of the unreacted (*R*)-ester **8** to the racemic ester **2** was not straightforward. No epimerisation at C-2 was observed when **8** was treated under acidic conditions such as acetic acid or HCl in methanol. Likewise no epimerisation was observed by the treatment of **8** under typical basic conditions, e.g. catalytic sodium methoxide in methanol or DBU. The key to success was the use of dimethyl carbonate as either solvent or as co-solvent with toluene. Treatment of **8** with catalytic sodium methoxide in dimethyl carbonate produced racemic ester **2** in 87% isolated yield after 4 h at 50°C. The exact role of the dimethyl carbonate is not clear, but its inclusion proved to be essential. The efficient recovery and a single recycling of the unreacted ester **8** effectively increased the yield of iodo-acid **10** from racemic ester **2** to 60%.

The next key reaction was the palladium-catalysed aminocarbonylation of aryl iodide **10** with 4,4′-bipiperidine. This reaction was attempted under a wide variety of reaction conditions, although the required product **1** was obtained, a considerable amount of unwanted by-product arising from the addition of two molecules of **10** to one of 4,4′-bipiperidine was always obtained. To overcome this problem, a range of protected 4,4′-bipiperidines were studied. Although the mono *N*-BOC 4,4′-bipiperidine[3,4,10] and mono *N*-CBZ 4,4′-bipiperidine[11] could be prepared and utilised, the low yielding formation from 4,4′-bipiperidine precluded their use here. The solution came in the form of 4,4′-pyridylpiperidine **13**,[12] which could be selectively prepared by the partial hydrogenation of 4,4′-bipyridine **12**



Scheme 3. Preparation of SB-214857-A **1**. (i) Novozym 435, *t*-BuOH, H_2O, NH_3, pH 7.0, 50°C; (ii) pyridineiodine monochloride complex, H_2O, NaOH, pH 7.0, 10°C; (iii) NaOMe, MeOH, $(MeO)_2CO$, 50°C; (iv) $PdCl_2(PPh_3)_2$, CO, **13**, anisole, dicyclohexylamine, 15 psi, 100°C; (v) H_2, Pd/C, *iso*-propanol, H_2O, 60 psi, 75°C; (vi) $C_5H_5N{\cdot}HCl$, EtOH, CH_2Cl_2, H_2O, 40°C.



12 13

Scheme 4. Preparation of 4,4′-pyridylpiperidine **13**. (i) H_2, Pd/C, H_2O, citric acid, 60 psi, 75°C.

over palladium on carbon[13] in the presence of a catalytic quantity of citric acid (Scheme 4). Aminocarbonylation of aryl iodide **10** with a palladium(II) catalyst,[6] carbon monoxide and pyridylpiperidine **13** gave amide **11** in 87% yield. Reduction of the pyridine ring of **11** was achieved by hydrogenation over palladium on carbon to give **1** as a zwitterion in 91% yield. The required drug substance was the hydrochloride salt, however, **1** was unstable with respect to acid, so conversion of the zwitterionic form to the hydrochloride salt was achieved under buffered conditions in 94% yield by treatment with pyridine hydrochloride in $EtOH/CH_2Cl_2$.

In conclusion, a new efficient synthesis of SB-214857-A **1** has been achieved starting from 2-nitrobenzyl alcohol in 12 linear steps, the overall yield is 35% (based on the recovery and recycling on the unreacted ester **8**) and the target molecule is obtained with >99.9% e.e., as determined by chiral capillary electrophoresis. This route has been scaled up to produce kilogram quantities.[14]

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14. Issues relating to the scale up of this route will be reported elsewhere.