An Alternative Synthesis of a Potent GPIIb/IIIa Receptor Antagonist

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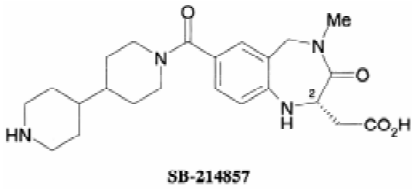
Dedicated to Professor Albert Eschenmoser

Abstract: A key intermediate to SB-214857 was prepared via an oxidative cyclization of a hydroquinone with a flanking aspartate side chain using Fremy's salt.

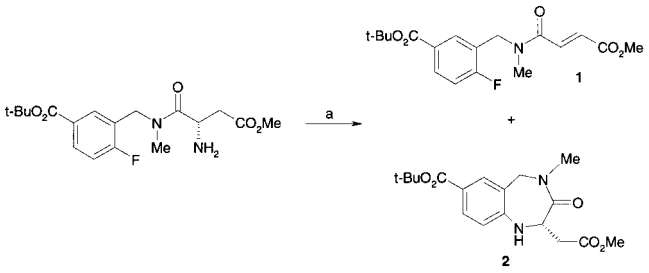
Key words: benzodiazepine, cyclization, quinone, hydroquinone, oxidation

Benzodiazepine SB-214857 is a potent GPIIb/IIIa receptor antagonist and as a consequence disrupts the binding interaction of fibrinogen with the GPIIb/IIIa receptor on activated platelets.[1] This results in inhibition of platelet aggregation and possibly thrombosis. In fact SB-214857 has just completed successful phase II clinical trials and is targeted to enter phase III for the prevention of secondary thrombotic events such as heart attack and stroke.



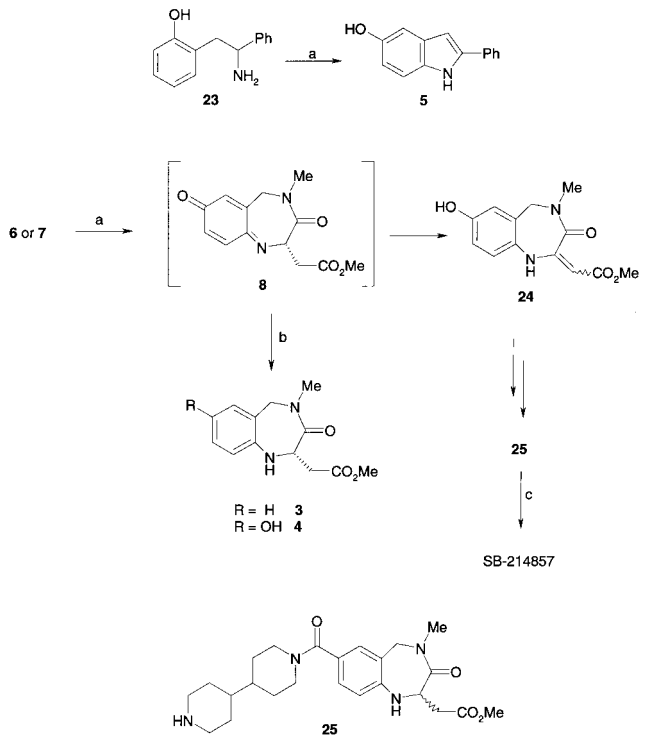
For the oncoming phase III clinical trials we required several hundreds of kilograms of SB-214857 and therefore an efficient and robust route of synthesis. The medicinal chemistry route[2] that was used to prepare the initial supplies of SB-214857 was not suitable for the quantities we now required. This was due in part, to the facile β-elimination of ammonia to form fumarate **1** during the fluoride displacement reaction. This resulted in low yields (30–40%) of the key intermediate **2** (Scheme 1). We therefore engaged ourselves in a program of research to discover alternative, novel and efficient synthetic routes to SB-214857. Our initial targets were benzodiazepines **3** or **4** (Scheme 2) since we had an efficient method to convert these intermediates to SB-214857 using an inventive palladium catalysed aminocarbonylation process.[3,4]

The unusual structure of SB-214857 with regards to the chiral *2S*-acetic acid side chain limited our scope to apply known procedures for the preparation of the 1,4-benzodiazepine nucleus.[5,6] Notwithstanding one potential route we considered involved exploitation of Teuber's oxidative cyclisation reaction using Fremy's salt[7] to prepare 2-phenyl-5-hydroxy indole **5**.[8] Using this methodology we hoped to convert phenol **6** or hydroquinone **7** to iminoquinone **8**. Subsequent hydrogenation of this would give us the required benzodiazepine **4** (Scheme 2).



Scheme 1

Reagents and conditions: (a) DMSO, toluene, 3Å molecular sieves, 128-130 °C, 22h.



Scheme 2

Reagents and conditions: (a) potassium nitrosodisulfonate (Fremy's salt), 2.2 equiv., HCl conc., 1.0 equiv., $CHCl_3$, AcOH, H_2O (b) catalytic hydrogenation (c) resolution.[11]

The phenol **6** and hydroquinone **7** were readily prepared (Scheme 3). Condensation of aldehydes **9**, **10** and **11** with methylamine in ethanol gave the Schiffs bases **12**, **13** and **14** and these were hydrogenated over 10% palladium on charcoal to afford amines **15**, **16** and **17** respectively in

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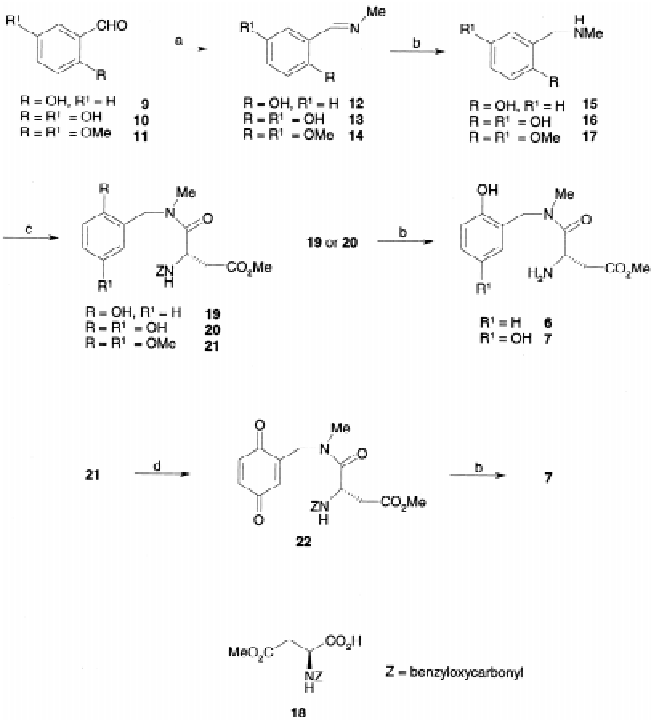
quantitative yield. The amines were then coupled with *N*-*Z*-L-aspartic acid-β-methyl ester **18** using DCC to give amides **19**, **20** and **21** in 81%, 46% and 100% yields respectively. Hydrogenation of **19** and **20** over 10% palladium on charcoal produced the required substrates **6** and **7** in 91% and 70% yields respectively after purification by chromatography on silica gel. Hydroquinone **7** was also prepared from **21** via the quinone **22**. Oxidative demethylation of **21** with ammonium cerium(IV) nitrate furnished the quinone **22** and hydrogenation of this over 10% palladium on charcoal gave **7** in 50% yield.



Scheme 3

Reagents and conditions: (a) $MeNH_2$ (8.03M solution in EtOH), 1.5 equiv., toluene (b) 10% Pd-C, EtOH, H_2 (c) **18**, 1.1 equiv., DCC, 1.1 equiv., (HOBT for the preparation of **15** only, 1.1 equiv.), (d) Ammonium cerium(IV) nitrate, 2.5 equiv., MeCN, H_2O, -10 – 10 °C, 3h.

With the required amines in hand, they were treated with Fremy's salt under the acidic conditions described by Teuber for the conversion of **23** to 5-hydroxyindole **5**.[8,9] Interestingly compound **24** was formed in 18% yield from the phenol **6** and in 56% yield from the hydroquinone **7**. Oxidation of **7** with potassium ferricyanide also gave **24** but in only 14% yield. It appears that the required iminoquinone **8** does form but it readily tautomerizes to the aromatic benzodiazepine. Although the chirality was lost, the application of this oxidative cyclization methodology to the synthesis of a 3-oxo-1,4-benzodiazepine derivative is completely novel.[10] The product **24** can be successfully converted to SB-214857 in good yield and with high optical purity (Scheme 2); precise details for this conversion will be published in due course.

In conclusion SB-214857 can be prepared from cheap and readily available starting materials. The key oxidative cyclisation of **7** is novel for the preparation of 2-substituted 1,4-benzodiazepines and should be applicable to the preparation of several analogous benzazepine systems.

References and Notes

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(9) Experimental procedure for the reaction of **7** with Fremy's salt. To a solution of (3*S*) methyl-3-amino-4-{*N*-methyl-*N*-(2,5-dihydroxybenzyl) carbamoyl} butanoate **7** (30.30g at ca 45% purity, 0.048mol) in water (2.08 L) and acetic acid (233 ml) and chloroform (5.0 L) was added HCl (9.7 ml of an 11.0M aqueous solution, 0.107mol) followed by Fremy's salt (63.4g, 0.237 mol) in water (3.0 L) at room temperature. The reaction mixture was stirred for 3h after which time the chloroform layer was separated, was washed with water (1.0 L) and then was concentrated to dryness. The resultant dark foamy residue was chromatographed on silica gel using AcOEt : hexane - 3:1 as eluant. The title compound was obtained as a white solid (7.29g, 56%); HRMS, Found M^++H 263.1016. $C_{13}H_{15}N_2O_4$ requires 263.1032. δ_H ($CDCl_3$, 270 MHz) 3.00 (3H, s), 3.75 (3H, s), 4.25 (2H, s br), 5.40 (1H, s), 5.80 (1H, s), 6.70 - 6.80 2H, m), 6.85 (1H, d) and 10.50 (1H, s).

(10) Cyclization of an amide group onto a hydroquininone in the presence of silver (I) oxide to give a 3,4-dihydro-1,4-benzodiazepine-2,5-dione has been recently published. However, precise details concerning conditions and yields were not disclosed; Kraus, G.A.; Melekhov, A. *Tetrahedron Lett*., **1998**, *39*, 3957.

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