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An efficient synthesis of the orally-active GpIIb/IIIa antagonist FR184764

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Abstract—An efficient synthesis of the orally-active GpIIb/IIIa antagonist FR184764 was achieved. The key intermediate, an optically active ethynyl β-amino ester, was synthesized efficiently by utilizing a lipase catalyzed kinetic resolution step.

Platelet aggregation is an important component in the thrombotic process and is present in a wide variety of pathological circumstances. Fibrinogen receptor antagonists disrupt the platelet–fibrinogen interaction involved in white thrombus formation, and peptides containing the sequence Arg-Gly-Asp (RGD) antagonize binding of fibrinogen to the GpIIb/IIIa receptor, thereby inhibiting platelet aggregation. Many peptido-mimetics based on the RGD sequence of fibrinogen have been reported,[1] and tirofiban has been developed by Merck as an injectable drug. However an orally-active GpIIb/IIIa antagonist has not been marketed, despite many efforts. In our search for new orally-active GpIIb/IIIa antagonists, we have succeeded in the discovery of FR184764 (Fig. 1) as an analog with good oral bioavailability.

FR184764 inhibits ADP induced platelet aggregation effectively, with an IC_{50} for ADP induced human platelet aggregation of 0.033 μM. This contrasts with an IC_{50} of 50 μM for RGD-NH_2, and this compound displays good oral absorption as shown by ex vivo assay in rat oral administration. During the course of development of this compound, we required a route to produce large amounts of FR184764 for further studies, and our retro-synthetic analysis is outlined in Scheme 1.

Compound **1** can be synthesized by condensation of acids **2**, **3**, and amine **4**, where **3** and **4** are optically active. Compound **3** can be obtained via optical resolution with L-tartaric acid, but there are few effective synthetic methods to obtain **4**.[2] As a result, we needed to establish a new synthetic method to obtain **4**, and opted to utilize a lipase-catalyzed kinetic resolution of a β-lactam derivative. Acid **2** was readily synthesized from commercially available ethyl isonipecotate (**5**). Amine **5** was N-protected with a Boc group and the ester group was reduced to an aldehyde with DIBAL at −78 °C. Subsequent Horner–Emmons reaction with triethyl phosphonoacetate and sodium hydride as base gave α,β-unsaturated ester with an *E*/*Z* ratio of 95:5. The *E*/*Z* mixture of the ester was hydrolyzed by sodium hydroxide to give **2** in 45% yield over four steps (Scheme

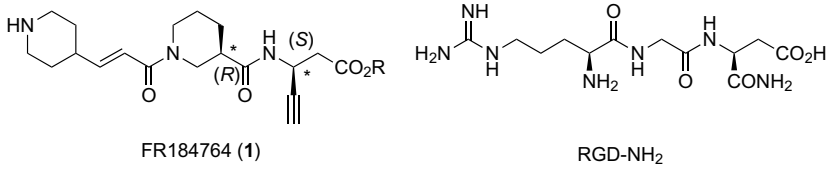

Figure 1.

Keywords: GpIIb/IIIa antagonist; Orally-active; FR184764; Lipase catalyzed kinetic resolution.
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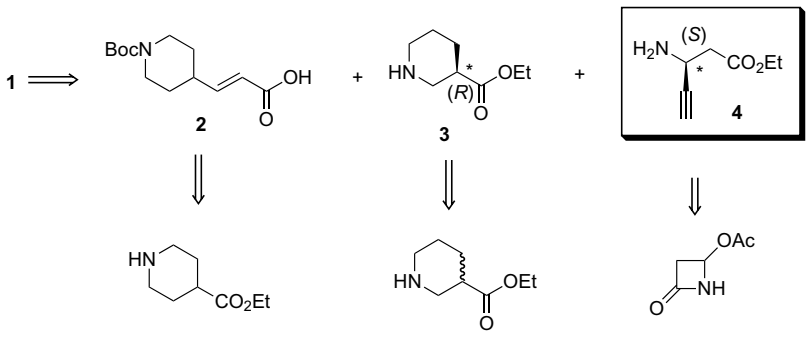
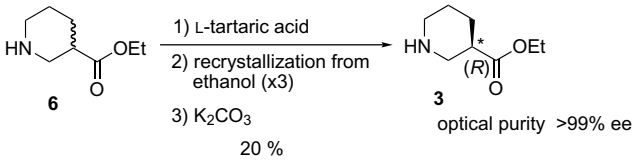


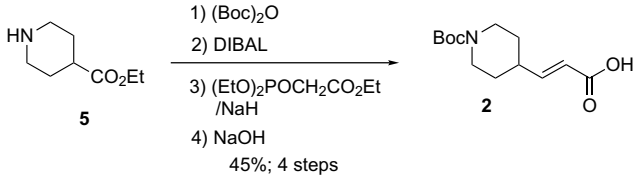
Scheme 1.

2). Recrystallization from hexane gave the *E* form of **2** exclusively. Optically active (*R*)-nipecotic ester **3** was obtained by optical resolution of racemic nipecotic acid ethyl ester (**6**) with L-tartaric acid according to the literature procedure.[3] The resulting salt was recrystallized from ethanol three times and treated with aqueous potassium carbonate and extracted with ethyl acetate to give the free form of **3** in 20% yield. The optical purity of **3** was >99% ee, as determined by HPLC analysis after urea formation by treatment with (*S*)-1-(1-naphthyl)ethyl isocyanate (Scheme 3).



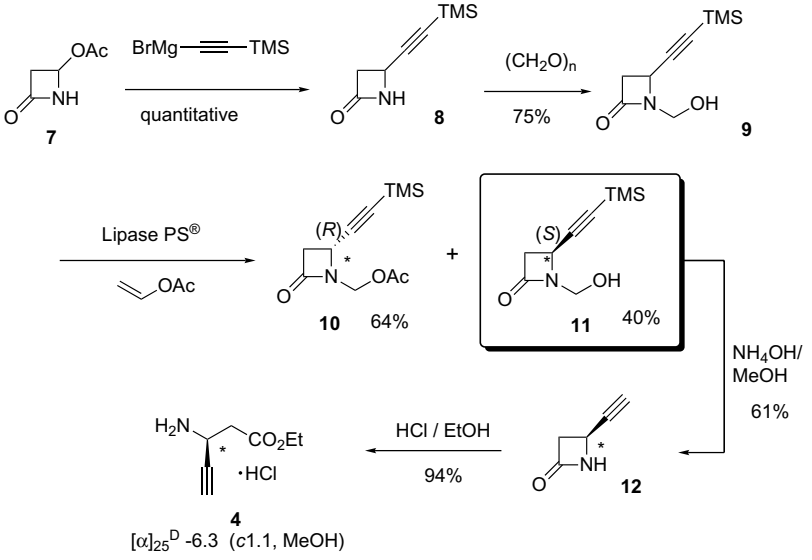
Scheme 3.

Amine **4** was synthesized from commercially available 4-acetoxy-2-azetidinone (**7**) in five steps as shown in Scheme 4. Reaction of **7** from −30 °C to 10 °C for 2 h with 5 equiv of 2-trimethylsilylethynylmagnesium bromide, generated from ethylmagnesium bromide and ethynyltrimethylsilane in situ at −30 °C, gave **8** in quantitative yield. Compound **8** was then heated with 3 equiv of paraformaldehyde at 120 °C for 1 h without solvent. After short column chromatography, pure **9** was obtained in 75% yield as a white solid.

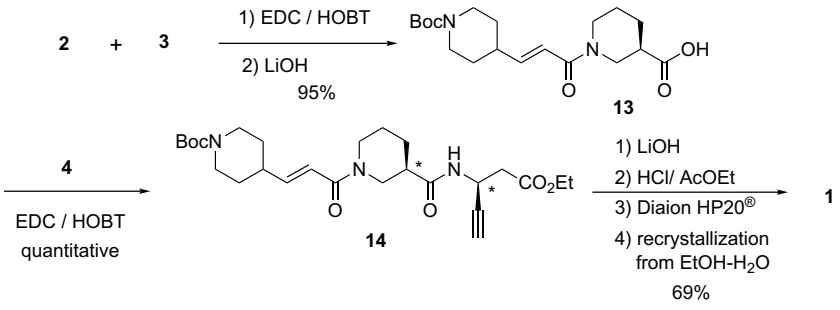


Scheme 2.

Terao and co-workers reported[4] lipase catalyzed enantioselective transesterifications of a 1-hydroxymethyl-2-azetidinone derivative with vinyl acetate. We applied this method to **9** using Lipase PS®[5] and vinyl acetate. Though it was reported that transesterification of 1-hydroxymethyl-2-azetidinone derivatives were performed only in methylene chloride, we investigated



Scheme 4.



Scheme 5.

various kinds of solvent. As a result, in a mixed solvent system of 1:2 methylene chloride and diisopropyl ether, the reaction rate was more than two and a half times faster than that with other solvents (1,4-dioxane or methylene chloride). Although the enantioselection was not perfect, when reaction conversion was about 60%, the enantiomeric excess of **11** was up to 97% ee, as determined by HPLC analysis. From the reaction mixture, **10** and **11** were separated by silica gel column chromatography easily and **11** was isolated in 40% yield as a white solid.[6] The configuration of **11** was determined to be (*S*) by optical rotation in comparison with an authentic sample synthesized from L-aspartic acid dibenzyl ester.[7] Optically active **11** was deprotected in one step by treatment with 5 equiv of aqueous ammonia in methanol in 71% yield. The deprotected β-lactam **12** was ring-opened and esterified by treatment with 5.8 N hydrogen chloride solution in ethanol to give ethynyl β-amino ester **4** in 94% yield. The enantiopurity of **4** was 98% ee, as determined by HPLC analysis.

The synthesis was completed as shown in Scheme 5. Compound **2** was coupled with amine **3** in the presence of EDC and HOBT, followed by hydrolysis of the ethyl ester by aqueous lithium hydroxide solution under ice cooling to give **13** in 95% yield as a solid. Compound **13** was coupled with **4** with EDC and HOBT to give **14** in quantitative yield. The ester and Boc groups were cleaved by treatment with aqueous lithium hydroxide solution followed by hydrogen chloride in ethyl acetate, respectively, to give crude **1** as the hydrogen chloride salt, which was passed through HP-20®, freeze-dried, and recrystallized from H_2O–EtOH to give pure **1**.[8]

In conclusion, we have established a simple procedure to prepare the new GpIIb/IIIa antagonist FR184764. All synthetic reactions are straightforward, so we have been able to prepare 180 g (515 mmol) of **1** easily in one batch with laboratory apparatus. The structure–activity relationships of FR184764 and other related compounds will be reported in due course.

Acknowledgements

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References and notes

1. For reviews, see; (a) Agah, R.; Plow, E. F.; Topol, E. J. *Platelets* **2002**, 769; (b) Mousa, S. A. *Drug Discovery Today* **1999**, *4*, 552, and references cited therein.
2. (a) Zablocki, J. A.; Rico, J. G.; Garland, R. B.; Rogers, T. E.; Williams, K.; Schretzman, L. A.; Rao, S. A.; Bovy, P. R.; Tjoeng, F. S.; Lindmark, R. J.; Toth, M. V.; Zupec, M. E.; McMackins, D. E.; Adams, S. P.; Miyano, M.; Markos, C. S.; Milton, M. N.; Paulson, S.; Herin, M.; Jacqmin, P.; Nicholson, N. S.; Panzer-Knodle, S. G.; Haas, N. F.; Page, J. D.; Szalony, J. A.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem.* **1995**, *38*, 2378; (b) Cossy, J.; Schmitt, A.; Cinquin, C.; Buisson, D.; Belotti, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1699; (c) Topgi, R. S.; Ng, J. S.; Landis, B.; Wang, P.; Behling, J. R. *Bioorg. Med. Chem.* **1999**, *7*, 2221.
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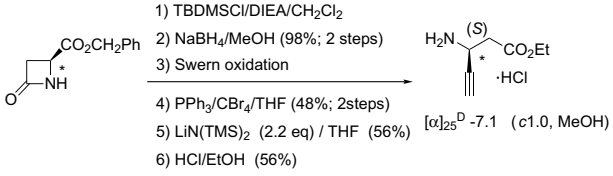
5. Purchased from Amano Enzyme Inc.
6. The experimental method to obtain **11** was as follows. To a solution of **9** (200 g, 1.01 mol) in methylene chloride (2.0 L) and diisopropyl ether (4.0 L) were added Lipase PS® (152 g) and vinyl acetate (280 mL, 3.03 mol). This suspension was stirred vigorously at 37 °C for 12–15 h. After the reaction conversion was 60%, as confirmed by HPLC analysis, the lipase was filtered off and washed with methylene chloride. The filtrate was evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel to give pure **10**. $[\alpha]_D^{28}$ −134.6 (*c* 1.03, $CHCl_3$).
7. (a) Ohkubo, M; Takahashi, F.; Yamanaka, T.; Sakai, H.; Kato, M. International Patent WO 9508536;



(b) Related synthesis was reported. Boys, M. L. *Tetrahedron Lett.* **1998**, *39*, 3449.
8. Spectral data of **1**: $[\alpha]_D^{19}$ −69.5 (*c* 1.00, CH_3OH). IR (KBr) 2361, 1726, 1655, 1601, 1277, 1255, 1223, 1194 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.19–1.41 (m, 2H), 1.59–1.88 (m, 5H), 2.14–2.32 (m, 4H), 2.51–2.76 (m, 4H), 2.89–3.17 (m, 4H), 3.89–4.42 (m, 2H), 3.89–4.42 (m, 2H), 4.60–4.71 (m, 1H), 6.36 (d, J = 15.1 Hz, 1H), 6.57 (dd, J = 15.1, 6.4 Hz, 1H), 8.85 (m, 1H). Mass (m/z) 352 ($M+H^+$). Anal. Calcd for $C_{19}H_{27}N_3O_4 \cdot 1.1H_2O$: C, 59.58; H, 7.74; N, 10.77. Found: C, 59.59; H, 7.78; N, 10.89.