Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4455-4458, 1996

Published by Elsevier Science Ltd
Printed in Great Britain

PII: S0040-4039(96)00694-6

0040-4039/96 $15.00 + 0.00

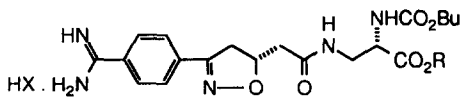
The Chiral Specific Synthesis of DMP 754, a Platelet GP IIb/IIIa Antagonist

Lin-hua Zhang*, L. Anzalone, P. Ma, G.S. Kauffman, L. Storace, R. Ward

Chemical Process R&D, PRF(S1), The DuPont Merck Pharmaceutical Company, Deepwater, NJ 08023-0999, USA

Abstract: An effective and chiral specific synthesis of DMP 754 (**1**), a non-peptide platelet GP IIb/IIIa antagonist, is reported.

The research of platelet glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists as antithrombotic agents has been an active area in recent years.[1] The GPIIb/IIIa complex was identified as the final common pathway for all platelet agonists. The binding of adhesive proteins such as fibrinogen to GPIIb/IIIa causes platelets to aggregate. This binding is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence. A number of peptides containing Arg-Gly-Asp sequence (RGD) have been discovered as platelet GP IIb/IIIa antagonists.[2] However, development of peptides into therapeutic agents has been hindered by their poor oral bioavailability and rapid degradation by peptidases in biological system.[3] In an effort to search for and develop non-peptide GPIIb/IIIa antagonists, a number of isoxazoline compounds have been discovered as potent GPIIb/IIIa antagonists.[4] The preparation of isoxazoline compounds in optically pure form poses synthetic challenges, especially on large scale. Furthermore, most isoxazolines such as **2** and **3** are not fully crystalline compounds, increasing the difficulties of purification. As a part of our clinical study program on these potent antithrombotic agents, an effective synthesis of optically pure isoxazolines was required. In addition, one needs find a stable and pharmaceutically suitable drug substance as a development candidate. Described on this paper are successful efforts in this area, which led to the discovery and development of DMP 754 (**1**), a crystalline pro-drug as an orally active non-peptide platelet GPIIb/IIIa antagonist.



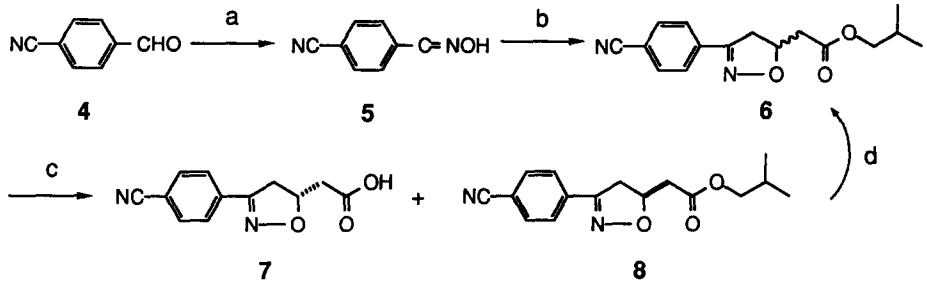
1, X = CH_3CO_2, R = CH_3

2, X = Cl, R = CH_3

3, X = $PhSO_3$, R = H

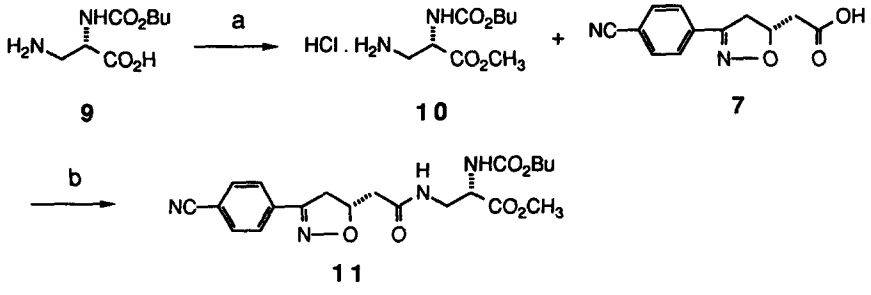
The synthesis of DMP 754 (**1**) started from 4-cyanobenzaldehyde (**4**). Reaction of **4** with hydroxyamine sulfate in methanol gave 4-cyanobenzaldoxime (**5**) in 95% yield. A 1,3-dipolar cycloaddition of nitrile oxide to alkene was utilized to construct the racemic isoxazoline **6**.[5] Reaction of oxime **5** with N-chlorosuccinimide in the presence of triethylamine generated the active nitrile oxide intermediate, which further condensed with

isobutyl vinylacetate to furnish the desired framework of **6**. This one-pot reaction provided isoxazoline (**6**) in 90% yield from oxime **5**. An enzymatic resolution[6] of isobutyl ester (**6**) with lipase PS30 in phosphate buffer (pH 7.5) provided optically pure acid (**7**) with the R configuration, and a chiral ester **8** possessing the S configuration. A similar reaction with methyl ester of **6** failed to produce optically pure material on large scale due to the presence of chemical hydrolysis. This optically active ester (**8**) was racemized to its raceme **6** with a catalytic amount of potassium t-butoxide in toluene at 40 °C. The racemization took about 1 h to go to completion. This enzymatic resolution - base epimerization process provided the optically pure isoxazoline acid (**7**) in 70% yield from raceme **6** (**Scheme 1**).



Scheme 1. a) Hydroxyamine sulfate, 95%; b) NCS, Et_3N, isobutyl vinylacetate, 90%; c) lipase PS30, 70%; d) $KOBu^t$, 85%.

The synthesis of right hand segment of DMP 754 began from a commercially available amino acid, N-α-butoxycarbonyl-1,2-diaminopropionic acid (**9**). Esterification of amino acid (**9**) with methanol in the presence of thionyl chloride gave the methyl ester (**10**). Coupling of amine (**10**) with acid (**7**) provided optically pure intermediate **11**, a precusor to the final products **1**, **2**, and **3** (**Scheme 2**).

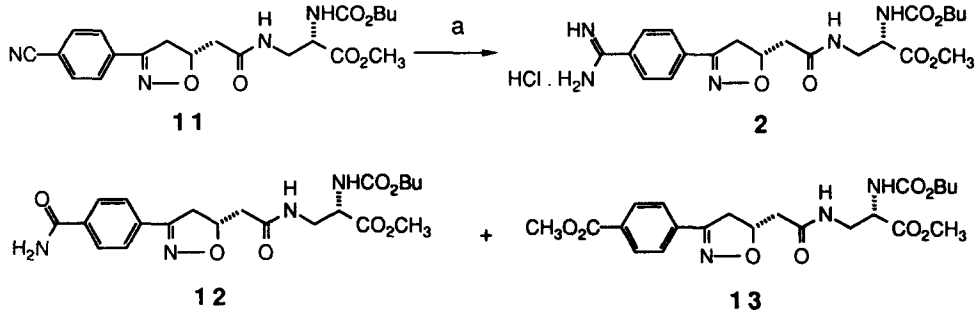


Scheme 2. a) $SOCl_2$, MeOH, 98%; b) Py-Bop[7] 85%.

With a large quantity of intermediate (**11**) in hand, the stage was set to study the amidine formation. There are a number of reports which detail the synthesis of the amidine functional group.[8] However, the most effective way to synthesize the amidine function from cyanophenyl isoxazoline (**11**) was through the imidate

intermediate (**14**). The Pinner reaction is a classical method to prepare imidates from cyano compounds.[9] Reaction of cyanophenyl isoxazoline (**11**) with saturated methanolic hydrogen chloride provided imidate (**14**) in good yield. However, the imidate was not stable under strongly acidic conditions and gradually decomposed during work-up. Reaction of **11** in other solvents such as ethanol and isopropanol effected transesterification as well as decomposition. Finally, reaction of cyanophenyl isoxazoline (**11**) with methanol/HCl in methyl acetate gave imidate (**14**) in 90% yield.

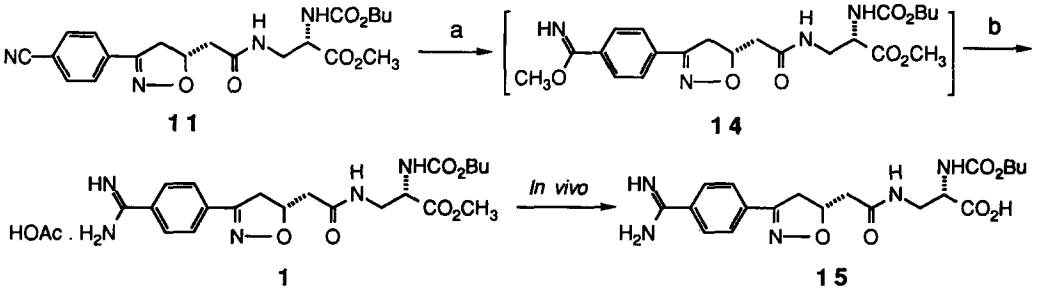
Typically, imidates can convert into amidines by reaction with ammonia or ammonium carbonate. However, reaction of imidate (**14**) with ammonia in methanol provided a mixture of diastereomers. We soon found that these isoxazoline compounds are very sensitive to base, and epimerize easily under alkaline conditions (pH > 10.5). Presumably, the epimerization of the isoxazoline is through a reversible Michael addition. When ammonium carbonate was used in the reaction, the same phenomena was observed even though the epimerization was not as severe as in the former case. Furthermore, large quantities of side products, amide (**12**) and diester (**13**), were generated in the reaction. It was very difficult to purify isoxazoline (**2**) from the reaction mixture because it was an amorphous solid and could not be crystallized. In earlier SAR studies product (**2**), an HCl salt of amidinephenyl isoxazoline, was isolated by tedious chromatographic purifications.[4] Isoxazoline (**2**) was converted into its salt form of free acid (**3**) in 2 steps, a partially crystalline compound under X-ray analysis. The overall yield from **11** to **3** was <5% (**Scheme 3**). One had to find a better synthesis to convert cyano intermediate (**11**) into an amidine.



Scheme 3. a) HCl, MeOH; ammonium carbonate; chromatographic purification; 18% of **2** from **11**.

In order to prevent the epimerization of chiral centers during the amidination, a slightly acidic media would be an ideal condition for this step. We chose to use ammonium acetate, a salt of a weak acid and a weak base, as the reagent to solve the problem of epimerization. Since the amidine formed in the reaction is a stronger base than ammonia, it is possible to form the acetate salt (**1**) *in situ* from isoxazoline (**11**). Indeed, reaction of imidate isoxazoline (**14**) with ammonium acetate under slightly acidic conditions (pH 6 - 7) furnished product (**1**). This desired compound (**1**) precipitated from the medium in optically pure form in 75% yield from **11**

(Scheme 4). Compound (**1**) is a crystalline prodrug, converts quantitatively and rapidly into the potent active moiety (**15**) *in vivo*.



Scheme 4. a) HCl, MeOH, methyl acetate; b) ammonium acetate, 75% of **1** from **11**.

It is known that the zwitterionic nature of amidine acids such as (**3**) or (**15**) could display poor aqueous solubility and liposolubility in the physiological pH range.[3] This would reduce the bioavailability of the drug substance after oral administration due to poor permeability. Furthermore, synthesis of (**3**) will increase the drug development cost and make the product less competitive on the market. On the basis of the above considerations DMP 754 (**1**), an amidine acetate prodrug, was selected for clinical investigation. Indeed the clinical results have shown that DMP 754 (**1**) is an orally active and extremely potent platelet GPIIb/IIIa antagonist.

References and Notes

1. a) Gould, R. J.; Polokoff, M. A.; Friedman, P. A.; Huang, T-F.; Holt, J. C.; Cook, J.J. Niewiarowski, S. *Proc. Soc. Exp. Biol. Med.* **1990**, *195*, 168; b) Semanen, J.; Ali, F.; Romoff, T.; Calvo, R.; Sorenson, E.; Vasko, J.; Storer, B.; Berry, D.; Bennett, D.; Strohsacker, M.; Powers, D.; Stadel, J.; Nichols, A. *J. Med. Chem.* **1991**, *34*, 3114.
2. Bach, A.C.; Eyermann, C.J.; Gross, J.D.; Bower, M.J.; Harlow, R.L.; Weber, P.C.; Degrado, W.F. *J. Am. Chem. Soc.* **1994**, *116*, 3207.
3. Wolff, M. E. *Burger's Medicinal Chemistry and Drug Discovery*, 5th edition, **1995**.
4. Olson, R. E.; Wityak, J.; Xue, C.; Sielecki, T.; Cain, G.; Mousa, S.; Thoolen, M.; Racanelli, A.; Hausner, E.; Reilly, T.; Degrado, W.; Wexler, R. *The 211th ACS National Meeting, #250,* **March 24-28, 1996**.
5. a) Pedwa, A. *Comp. Org. Synth.* **1991**, *4*, 1069; b) Wade, P. A. *Comp. Org. Synth.* **1991**, *4*, 1111; c) Kim, Y.; Kim, S.; Park, D. *Tetrahedron Lett.* **1993**, *34* , 6063.
6. Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*, VCH, **1995**.
7. Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205.
8. Rousselet, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34* , 6395.
9. Allen, R.; Schumann, E.; Day, W.; Campen, M. *J. Am. Chem. Soc.* **1958**, *80*, 591.

(*Received in USA* 14 *March* 1996; *revised* 8 *April* 1996; *accepted* 9 *April* 1996)