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Tetrahedron Letters 45 (2004) 8103–8105
Tetrahedron Letters

An efficient and tunable route to AG7088, a rhinovirus protease inhibitor

Dawei Ma,[a,*] Weiqing Xie,[a] Bin Zou,[a] Qiong Lei[a] and Duanqing Pei[b]

[a]*State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*
[b]*Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455, USA*

Received 16 June 2004; revised 18 August 2004; accepted 24 August 2004
Available online 21 September 2004

Abstract—Aldol reaction of *N*,*N*-dibenzyl valinal with propiolic acid ethyl ester derived lithium reagent provides *anti*-aminoalcohol **8** and *syn*-aminoalcohol **9**, which are converted into the lactone **6** via two different routes. Alkylation of **6** followed by lactone ring opening afford the acid **2a**, which is coupled with the amine **3** and 5-methylisoxazole-3-carboxylate acid **1**, respectively, to deliver AG7088.

AG7088 is a potent 3C protease inhibitor with an EC_{90} of less than 0.1 μM against 48 different serotypes of human rhinovirus (HRV).[1,2] This compound was discovered by Agouron researchers and is currently in human clinical trials to treat the common cold.[1,2] This inhibitor was received more attention recently because it was proposed as a promising inhibitor to viral main proteinase (M^{pro}, also called $3Cl^{pro}$), a key enzyme for controlling the activities of the coronvirus replication complex.[3] Since the coronvirus is the causative agent of severe acute respiratory syndrome (SARS), development of potent inhibitors for this enzyme would be of benefit for SARS therapy.

By computer modeling, Hilgenfeld and co-workers indicated that the *p*-fluorobenzyl side chain at the P2 position of AG7088 might be too big for fitting into the S2 pocket of coronvirus M^{pro} and those AG7088 analogues with smaller groups at this site might have more favored interaction with this enzyme thereby serving as more potent inhibitors.[3] In order to prove this hypothesis, as well as to discover potent coronvirus M^{pro} inhibitors based on this hypothesis, we initiated a program to synthesize AG7088 analogues.

As the retrosynthetic analysis outlined in Figure 1, AG7088 was prepared initially by Agouron researchers

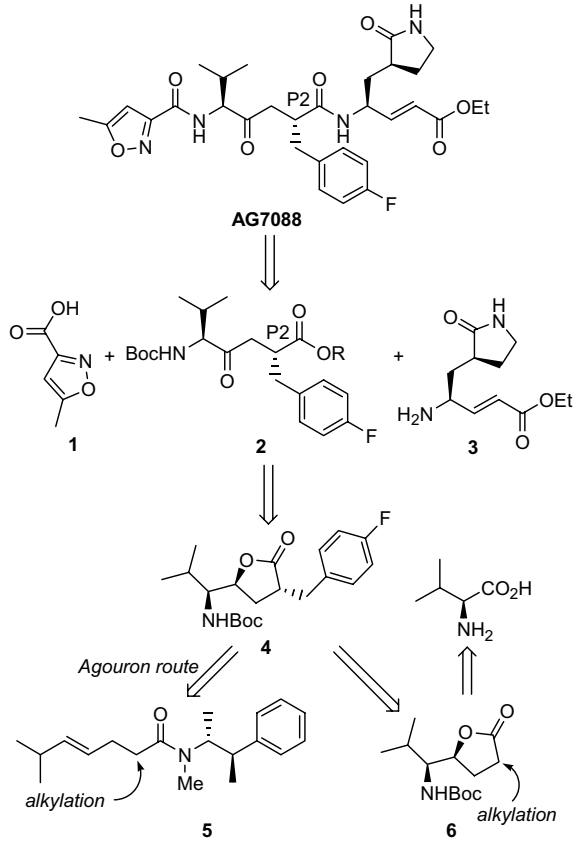

Figure 1. Structure of AG7088 and its retrosynthetic analysis.

* Corresponding author. Tel.: +86 21 6416 3300; fax: +86 21 6416 6128; e-mail: madw@pub.sioc.ac.cn

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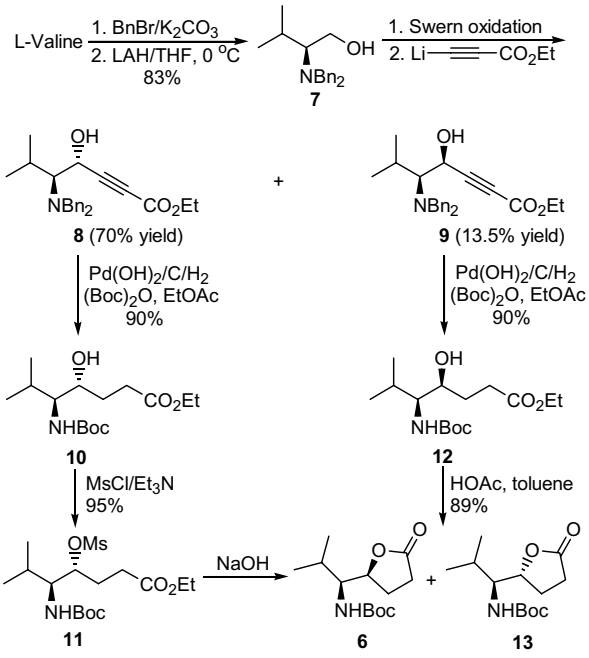
doi:10.1016/j.tetlet.2004.08.179

by coupling the ketomethylene dipeptide isostere **2** with 5-methylisoxazole-3-carboxylate acid **1** at its left hand and **3** at its right hand.[1] The ketoester **2** was obtained through a lactone **4** using diastereoselective alkylation of (−)-pseudoephedrine-derived amide **5** with *p*-fluorobenzyl bromide and subsequent lactonization promoted by NBS as the key steps.[4] Obviously, this protocol is not so efficient for quickly assembling AG7088 analogues with different side chains at the P2 site because installation of this side chain was set up at the early stage. This drawback, together with the requirement of (−)-pseudoephedrine as the chiral auxiliary, promoted us to develop a new route to the lactone **4** by direct alkylation of lactone **6**. This lactone could be prepared using L-valine as the starting material.

Our synthesis for the lactone **6** was illustrated in Scheme 1. After L-valine was treated with benzyl bromide under the assistance of potassium carbonate, the resultant ester was reduced with LAH to provide *N*,*N*-dibenzyl valinol **7**. Swern oxidation of **7** followed by nucleophilic attack by a lithium reagent derived from propiolic acid ethyl ester provided *anti*-aminoalcohol **8** in 70% yield, together with *syn*-aminoalcohol **9** in 13.5% yield. The stereochemistry of **8** was assigned by transformation of it to known lactone **16** as described below. Since the diastereoselectivity (**8**:**9** = 5.2) was not good at the aldol reaction step, we attempted to improve it using suitable additives. It was found low diastereoselectivity was still encountered when $TiCl_4$,[5] $Al(OPr\text{-}i)_3$,[5] or $MgCl_2$[6] was used. However, the ratio of **8** to **9** jumped to 9:1 when 2 equiv of HMPA[6] was added. Unfortunately, the yield was only 58% in this case. Consequently we still employed the initial condition to get aldol products when the reaction was scaled up.



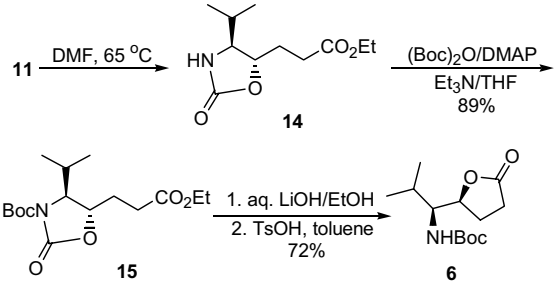
Scheme 1.

After hydrogenation of the *syn*-aminoalcohol **9** catalyzed by $Pd(OH)_2/C$ along with in situ protection with di-*tert*-butyl dicarbonate, alcohol **12** was obtained. Treatment of **12** with acetic acid in toluene delivered the lactone **6**[7] in 89% yield. In order to convert the *anti*-aminoalcohol **8** to **6**, its C4 stereochemistry should be reversed. Accordingly, hydrogenolysis of **8** followed by in situ protection produced alcohol **10**, which was transformed into its mesylate **11** with mesyl chloride. It was expected to obtain the lactone **6** by simple lactonization of **11** through an intramolecular S_N2 reaction. However, we found that a mixture of **6** and its 5-epimer **13** were isolated under various conditions such as exposure of **11** to NaOH in ethanol or DMF. The ratio of **6** and **13** was about 2:1–1:1, which implied that S_N1 reaction might also take place. Thus, we had to give up this protocol for assembling **6** from the alcohol **10**.

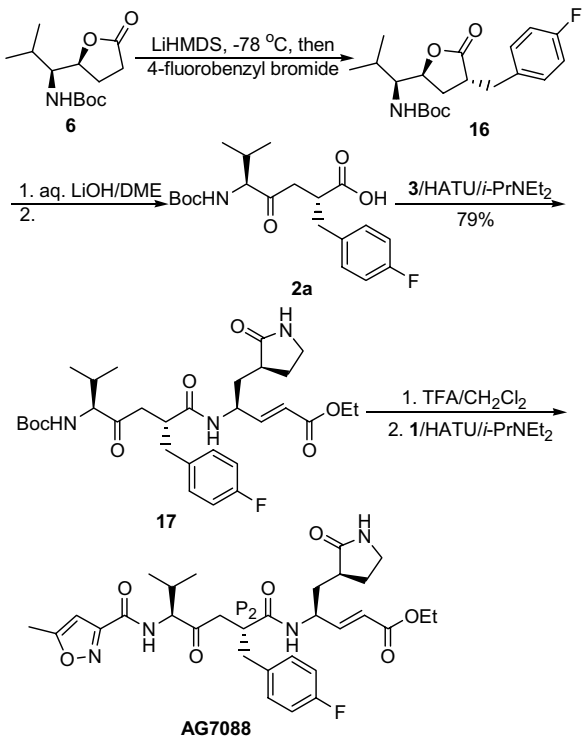
Occasionally, we found that **11** was spontaneously transformed into oxazolidone **14** by standing at room temperature, which indicated that an intramolecular S_N2 reaction between mesylate unit and carbonyl moiety of Boc group occurred. Based on this observation, we developed a route from **11** to **6** as depicted in Scheme 2. Heating **11** in DMF at 65 °C produced **14** quantitatively, which was treated with di-*tert*-butyl dicarbonate to afford **15** in 89% yield. After hydrolysis to cleavage the ester group and the oxazolidone ring, the resultant γ-hydroxy acid was converted into the lactone **6** mediated with TsOH.

With the lactone **6** in hand, we finished the total synthesis of AG7088 starting from its alkylation. As depicted in Scheme 3, treatment of **6** with LiHMDS followed by trapping the anion with 4-fluorobenzyl bromide provided lactone **16** in 63% yield, together with its 2-epimer in 4.5% yield. Next, the lactone ring was opened with aqueous LiOH in DME, the liberated hydroxy group was oxidated with PCC to afford **2a** in 61% yield. Finally, coupling of **2a** with the amine **3**[8] mediated with HATU produced **17** in 80% yield, which was exposed to trifluoroacetic acid to remove the Boc protecting group. The liberated amine was connected with 5-methylisoxazole-3-carboxylic acid **1** assisted by HATU to furnish AG7088[9] in 73% yield. Its analytical data were all identical with those reported.

As a conclusion, we have developed a novel protocol to construct AG7088 using L-valine as the chiral starting material. The key elements include a diastereoselective



Scheme 2.



Scheme 3.

aldol reaction of N-protected valinal, transformation of the alcohol **8** into the lactone **6**, and subsequent alkylation. This route is obviously efficient for tuning the substituents at the P2 position to obtain AG7088 analogues. Further synthetic work, as well as the biological evaluation of the resultant compounds, are underway and will be reported in due course.

Acknowledgements

The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (Grant 20132030 and 20342002), and Science and Technology Commission of Shanghai Municipality (Grants 02JC14032 and 03XD14001) for their financial support.

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7. Selected data: $[\alpha]_D^{15}$ −48.3 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.74 (t, J = 6.9 Hz, 1H), 4.56 (d, J = 9.9 Hz, 1H), 3.45 (t, J = 9.6 Hz, 1H), 2.53 (dd, J = 9.6, 5.7 Hz, 2H), 2.29–2.04 (m, 2H), 1.90–1.79 (m, 1H), 1.45 (s, 9H), 1.02 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ESI-MS *m*/*z* 275 $(M + NH_4)^+$.
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9. Selected data: $[\alpha]_D^{26}$ +32.8 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.11 (m, 4H), 7.00–6.94 (m, 2H), 6.63 (dd, J = 15.3, 4.8 Hz, 1H), 6.40 (s, 1H), 5.92 (s, 1H), 5.50 (d, J = 15.6 Hz, 1H), 4.71–4.61 (m, 1H), 4.51–4.41 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.42–3.30 (m, 2H), 3.24–3.13 (m, 1H), 2.98–2.84 (m, 2H), 2.73–2.52 (m, 3H), 2.48 (s, 3H), 2.43–2.26 (m, 2H), 1.93–1.70 (m, 2H), 1.61–1.51 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ESI-MS *m*/*z* 599 $(M + H)^+$.