Pergamon

Tetrahedron Letters 42 (2001) 6807–6809

TETRAHEDRON LETTERS

An efficient synthesis of a key intermediate for the preparation of the rhinovirus protease inhibitor AG7088 via asymmetric dianionic cyanomethylation of *N*-Boc-L-(+)-glutamic acid dimethyl ester

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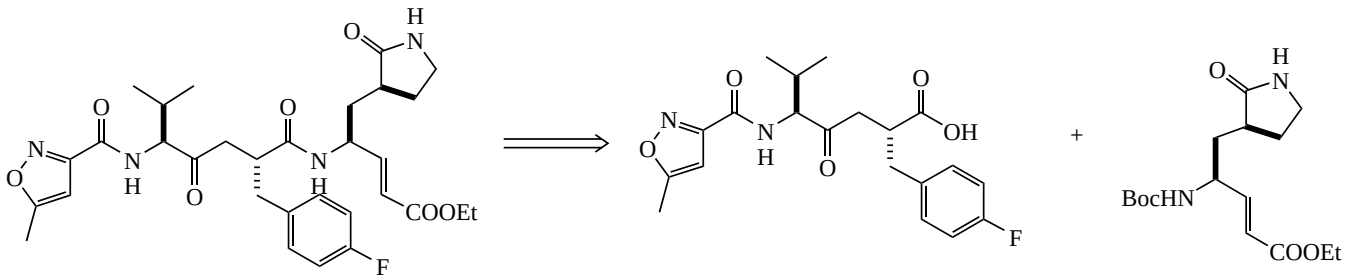
Received 14 June 2001; accepted 27 July 2001

Abstract—An efficient synthetic route to a key intermediate for the preparation of the rhinovirus protease inhibitor **AG7088** has been developed employing a key asymmetric dianionic cyanomethylation of *N*-Boc-L-(+)-glutamic acid dimethyl ester. This methodology enables the preparation of this compound in kilogram quantities with an overall yield of 30%. © 2001 Elsevier Science Ltd. All rights reserved.

As part of our ongoing efforts to develop rhinovirus protease inhibitors for treatment of the common cold, large quantities of the drug candidate **AG7088** were required. This necessitated the development of a new, efficient and cost-effective synthetic approach to the drug substance. One general synthetic strategy is based on a convergent union of subunits **1** and **2** (Scheme 1). The medicinal chemistry synthesis of **2** employed 13 steps and was prohibitively lengthy for scale-up.[1] Therefore, our efforts have been focused on developing a new and efficient synthetic route to **2** which is more practical and viable for scale-up. In this communication, we report the realization of this goal.

A retrosynthetic analysis indicated that lactam ester **3** could be converted to **2** via a sequence of reduction, oxidation and Wittig olefination reactions. A synthesis of the *tert*-butyl ester analogue of **3** from lactam ester **4** has been reported in the literature,[2] although the key step (cyanomethylation of lactam ester **4**) yielded the desired product as a 2:1 mixture of diastereomers (Eq. (1)). Obviously, a more stereoselective approach to **3** is



Scheme 1.

Keywords: asymmetric synthesis; lactams; alkylation.

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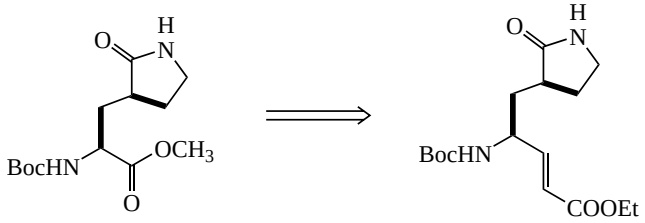
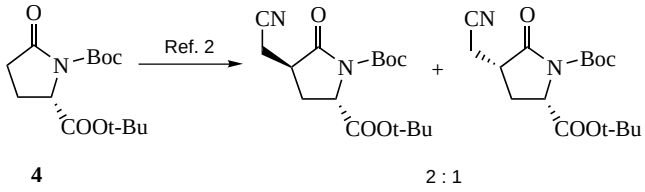
PII: S0040-4039(01)01416-2

highly desirable. Recently, Hanessian has studied the 1,3-asymmetric induction in dianionic alkylation of the commercially available *N*-Boc-L-(+)-glutamic acid dimethyl ester **5** and reported high stereoselectivities.[3] For example, alkylation of the dianion of **5** with allyl bromide afforded the desired *anti* isomer **6** in 92% yield and >98% *de* (Eq. (2)). We reasoned that this type of alkylation could be employed in an approach to lactam ester **3**.



3 **2**

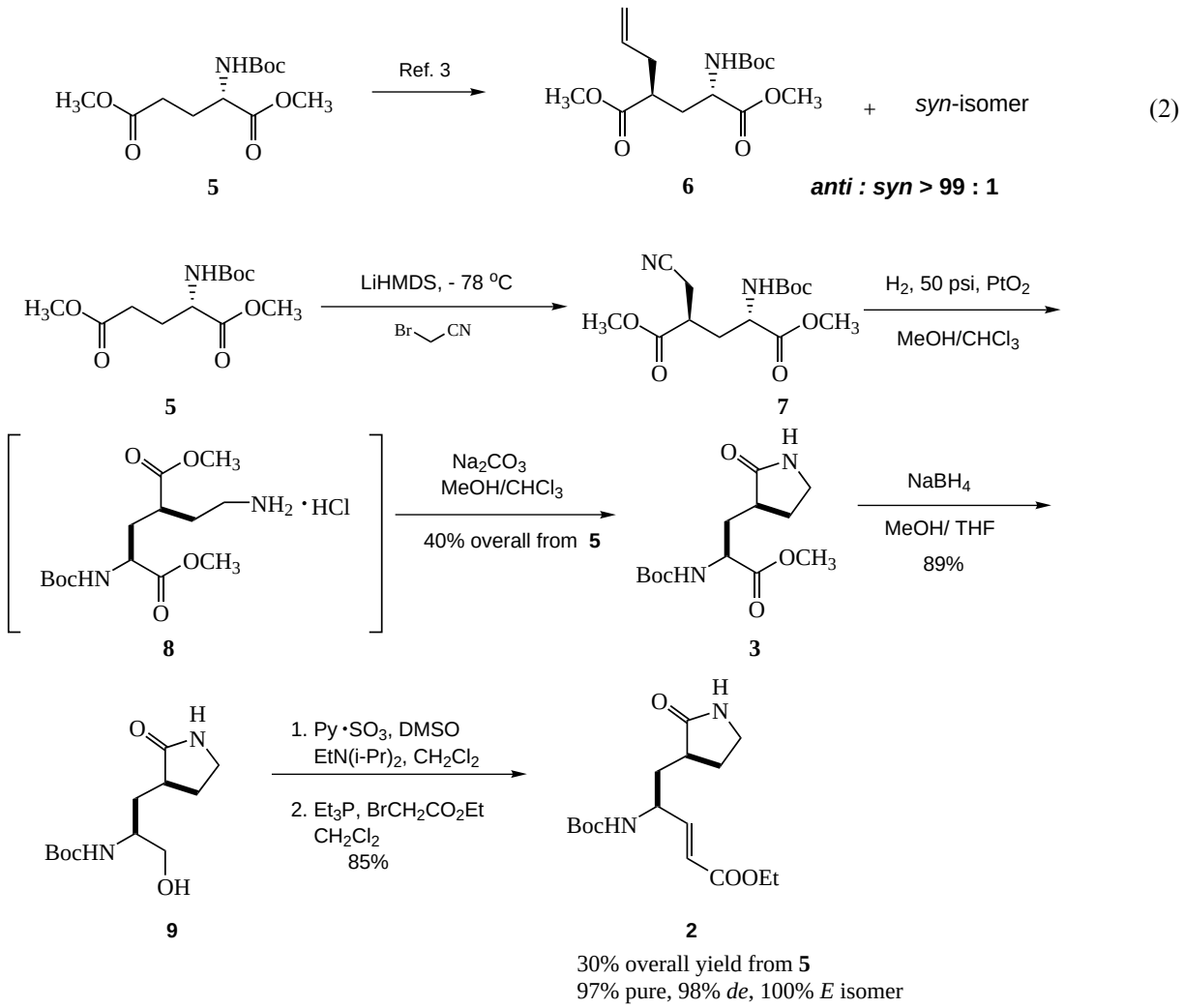
Our synthesis commenced with dianionic alkylation of **5** using 2.16 equiv. of LiHMDS and 1.07 equiv. of bromoacetonitrile (Scheme 2). As expected, this alkylation reaction was highly stereoselective and afforded **7**



4 2 : 1 (1)

almost exclusively with the desired stereochemistry in high yield.[4] This was an additional example of the novel stereochemistry which was first developed by Hanessian.[3] According to the original report, the chemistry was limited to allylic halides.[3] Our results demonstrated that this type of dianionic asymmetric alkylation could be extended to other activated halides.

In the following step, **7** was subjected to hydrogenation in the presence of PtO_2 and chloroform.[5] The reaction went smoothly to furnish the corresponding amine HCl salt **8**. It is interesting to note that the widely used Boc group is not affected by the hydrogenation in the presence of chloroform, although it has been reported that the reaction could tolerate some acid-labile functional groups.[5] The salt **8** was then treated with



5 **6** ***anti* : *syn* > 99 : 1** (2)

5 **7**

8 **3**

9 **2**

30% overall yield from **5**
97% pure, 98% *de*, 100% *E* isomer

Scheme 2.

Na_2CO_3 at 60°C for 4–5 h to produce the lactam ester **3** in an overall yield of 40% from **5**. In an alternative procedure, **7** was converted to **3** in a yield of 80% by employing the combination of $NaBH_4$ and $CoCl_2$.[6]

The next step was to reduce the ester group selectively to the corresponding alcohol **9** in the presence of the lactam. We examined both $NaBH_4$ and $LiBH_4$ for this transformation and both reagents proved equally effective.[7] In the case of $NaBH_4$, the reaction afforded **9** in an 89% yield versus an 81% yield for $LiBH_4$. Since $NaBH_4$ is easier to handle during scale-up, we chose $NaBH_4$ over $LiBH_4$ as the reducing agent.

Completion of the synthesis required lactam alcohol **9** to be oxidized to the corresponding aldehyde followed by Wittig olefination. Initial studies indicated that the α-amino aldehyde intermediate resulting from the oxidation of **9** was highly water soluble and prone to epimerization. With this in mind, and also to make the process efficient and simple, we combined these two reactions (oxidation/olefination) in a single reaction vessel.[8] Thus, **9** was oxidized with pyridine·SO_3 in DMSO and then treated with the Wittig reagent (generated from triethylphosphine and ethyl bromoacetate) to afford crude **2** which was further purified through a trituration procedure. According to chiral HPLC analysis, compound **2** from this new route had a purity of 97% and a *de* of 98%. More importantly, this product is exclusively the *E* isomer as indicated by HPLC and proton NMR spectral analyses. The yield of **2** from **9** was 85%.

In summary, a new synthetic route to the key intermediate **2** via asymmetric dianionic cyanomethylation has been developed and could be scaled up to the multikilogram level. This route is highly efficient (4 steps and 30% overall yield), highly stereoselective (98% *de* and 100% *E* isomer), utilizes inexpensive starting materials and requires no chromatographic purification.

Acknowledgements

We are grateful for many helpful discussions throughout the course of this work with Dr. Kim Albizati, Dr. Ben Borer and Dr. David Kucera. We also thank Ms. Laura Kuhn, Mr. Michael Mohajeri and Mr. Jason Ewanicki for providing HPLC data.

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4. Representative procedure: To a solution of *N*-Boc-L-(+)-glutamic acid dimethyl ester (**5**, 600 g, 2.18 mol, 1 equiv.) in THF (6.0 L) was added dropwise a solution of LiHMDS in THF (4.7 L, 1 M, 4.7 mol, 2.16 equiv.) at −78°C under an argon atmosphere. The resulting dark mixture was stirred at −78°C for 1 h. At the same time, bromoacetonitrile (400 g) was stirred with basic aluminum oxide (70 g) for 2 h and then filtered. The freshly filtered bromoacetonitrile (280 g, 2.33 mol, 1.07 equiv.) was added dropwise to the dianion solution over a period of 1 h while maintaining the temperature below −70°C. The reaction mixture was stirred at −78°C for additional 1–2 h and the disappearance of the starting material (**5**) was confirmed by TLC analysis. The reaction was quenched with pre-cooled methanol (300 ml) in one portion and stirred for 30 min. The resulting methoxide was then quenched with a pre-cooled acetic acid in THF solution (270 ml HOAc/2 L THF) in one portion. After stirring for 30 min, the cooling bath was removed and replaced with water bath. The reaction mixture was allowed to warm up to 0±5°C and then poured into a brine solution (250 g of NaCl in 4 L of water) in a 50 L extractor. The layers were separated, and the organic layer was concentrated to afford a dark brown oil (~850 g). Silica gel (800 g), activated carbon (200 g) and methylene chloride (2 L) were added to the Rotovap flask and spun on a Rotovap for 1 h without heat and vacuum. The slurry was then filtered and washed with another 2 L of methylene chloride. The light brown filtrate was concentrated to afford a light brown oil (**7**, 620 g, 90% crude yield). The crude product **7** was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.12–2.24 (m, 2H), 2.77–2.82 (m, 2H), 2.85–2.91 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.32–4.49 (m, 1H), 5.13 (d, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 28.6, 34.3, 38.6, 49.8, 53.1, 80.9, 117.5, 155.9, 172.4, 172.8; HRMS: m/z 314.1481 (calcd for $C_{12}H_{22}N_2O_4$: 314.1486).
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