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Synthesis of the optically active key intermediate of FR901483

Shigeru Ieda [a,†], Toshiyuki Kan [b,‡], Tohru Fukuyama [a,*]

[a] Graduate School of Pharmaceutical Science, University of Tokyo 7-3-1 Hongo, Bunkyo-ku 113-0033, Japan
[b] School of Pharmaceutical Sciences, University of Shizuoka and Global COE Program, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

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ABSTRACT

Efficient synthesis of the tricyclic key intermediate **2** for (−)-FR901483 **1** was accomplished. The precursor of the intramolecular aldol reaction **4b** is constructed by the Ugi 4CC reaction and subsequent intramolecular Dieckmann condensation. This approach allows a fully stereocontrolled total synthesis of (−)-FR901483, which would provide various derivatives.

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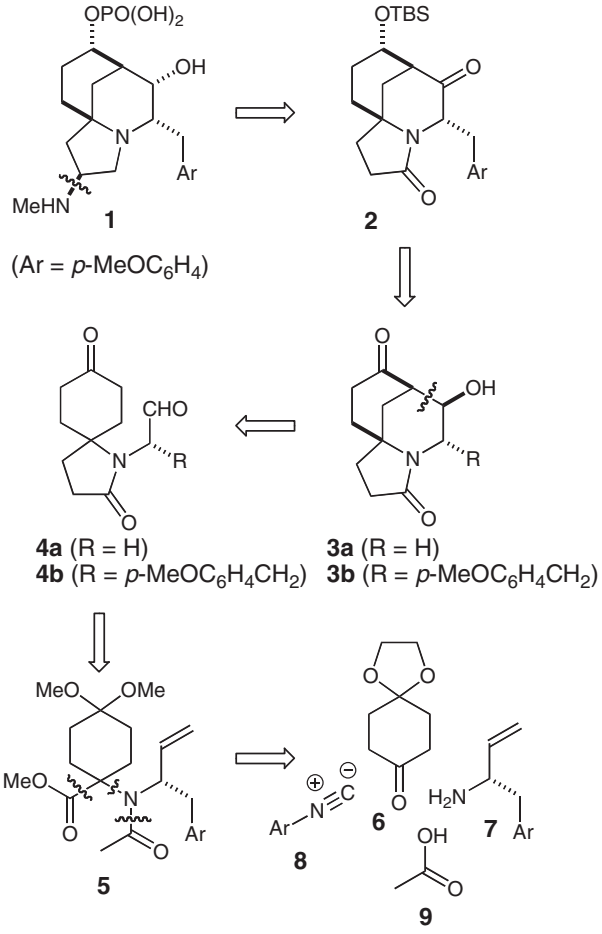
(−)-FR901483 **1** is an immunosuppressant isolated from the fermentation broth of *Cladobotryum* sp. No. 11231.[1] Because its unique tricyclic structure is an attractive target for the total synthesis, several synthetic studies[2] and total syntheses[3] have been reported. Since we reported a stereoselective total synthesis of racemic **1** in 2004,[3e] our next challenge has been to devise a synthetic route to the optically active form of **1**. Herein, we report a short-step and stereocontrolled synthesis of optically active tricyclic **2**, a key intermediate of our racemic total synthesis of **1**.

Our retrosynthetic analysis of **1** is illustrated in Scheme 1. In view of the fact that the crucial step in our racemic synthesis was an intramolecular aldol reaction of the keto-aldehyde **4a** to provide the tricycle intermediate **3a**, our first attempt was to perform an enantioselective intramolecular aldol reaction of **4a** by means of chiral catalysts. Since desymmetrical aldol reactions of **4a** with several types of chiral catalysts did not give satisfactory results,[4] we decided to examine a diastereoselective aldol reaction of **4b** to construct the tricycle intermediate **3b**, which could easily be converted to intermediate **2** according to our racemic synthesis. The crucial step of our synthesis, therefore, should be the facile construction of the optically pure spiro intermediate **4b**. While numerous procedures have been reported on the synthesis of α-trisubstituted amines, we opted to employ the Ugi 4CC reaction[5] to construct **5** because of its powerfulness in assembling complex molecules from simple components.[6]

As shown in Scheme 2, a mixture of commercially available cyclohexanedione monoethyene acetal **6**, optically active amine **7** (Scheme 4),[7] *p*-methoxyphenyl isocyanide **8**,[8] and acetic acid **9** in



Scheme 1. Structure and synthetic strategy of (−)-FR901483.

* Corresponding author.
E-mail addresses: kant@u-shizuoka-ken.ac.jp (T. Kan), fukuyama@mol.f.u-tokyo.ac.jp (T. Fukuyama).
† Present address: Process Chemistry Labs, Astellas Pharma Inc. 160-2, Akahama, Takahagi, Ibaraki 318-0001, Japan.
‡ Fax: +81 54 264 5745.

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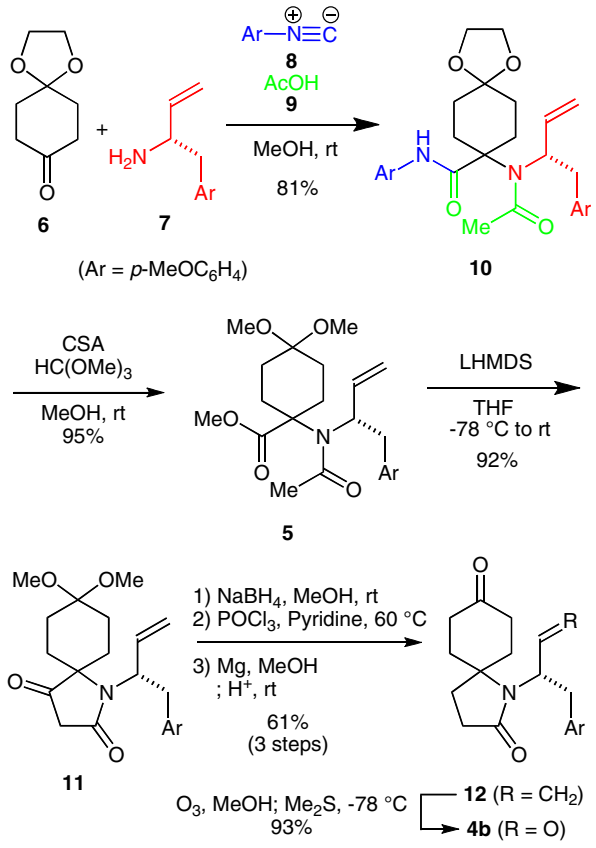
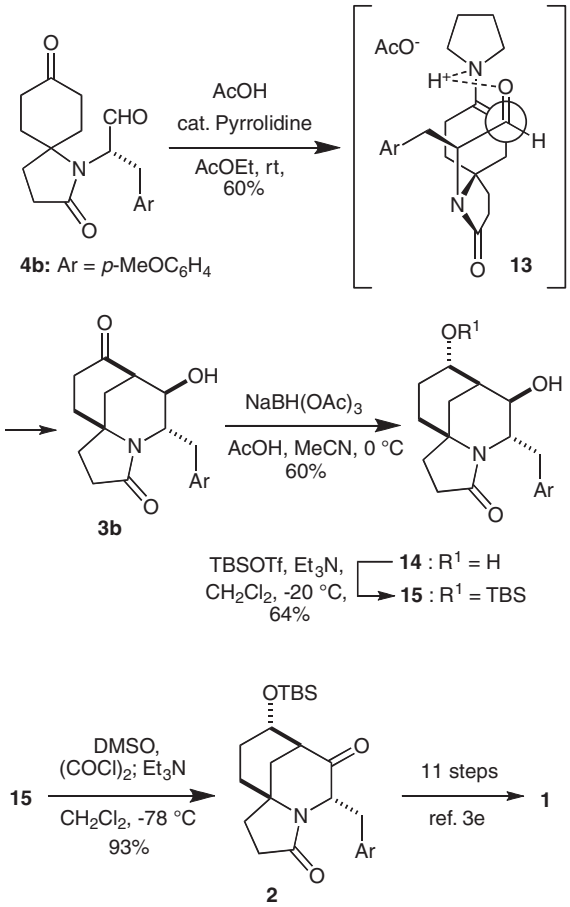


Scheme 2. Synthesis of cyclization precursor **4b** for an intramolecular aldol reaction.

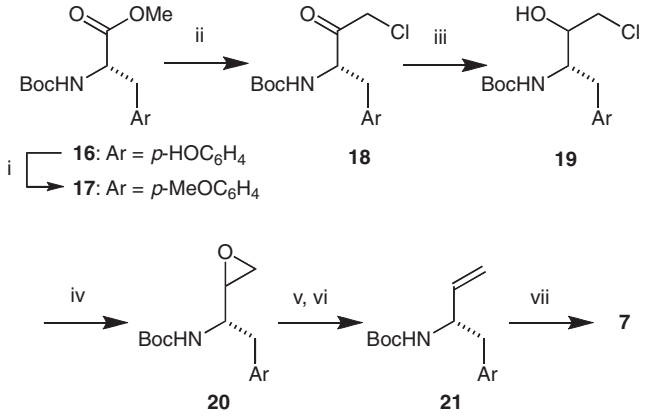
MeOH was allowed to stand at room temperature to afford **10**,[9] in which all the carbon atoms necessary to construct the tricyclic key intermediate **2** were efficiently assembled in a single step. Although hydrolysis of the *C*-terminal amide bond in the Ugi adducts is often troublesome,[10] methanolysis of the *p*-methoxyphenyl amide in **10** proceeded (Scheme 5)[11] unusually smoothly with a concomitant acetal exchange to provide **5**. Subsequent intramolecular Dieckmann condensation proved to be quite effective in constructing the spiro-lactam ring. Thus, upon treatment with LHMDS, **5** underwent a cyclization to give **11**. The ensuing deoxygenation of the carbonyl group in **11** was carried out in a three-step sequence involving a reduction of the ketone with $NaBH_4$, dehydration with phosphoryl chloride, and a chemoselective one-electron reduction of the resultant unsaturated lactam, giving the desired amide **12**. In addition, simultaneous hydrolysis of the dimethyl acetal occurred during the acidic work-up of the last step.[12] At this stage, oxidative cleavage of terminal olefin in **12** was performed by ozonolysis to afford **4b**.

With the desired optically active keto-aldehyde **4b** in hand, we then focused on the diasteroselective intramolecular aldol reaction. The similar intramolecular cyclization of **4b** was reported by Snider.[13] Although we have tested the same reactions, the reproducibility was not enough. Therefore we selected acidic conditions at room temperature. After several attempts, upon treatment of keto-aldehyde **4b** with acetic acid and a catalytic amount of pyrrolidine,[14] the desired cyclization proceeded smoothly to afford **3b**. The advantage of this transformation is that the two chiral centers were distinctively generated in one step. While the stereochemistry of the hydroxy group in **3b** is the opposite of the natural product,[15] it was needed in controlling the endo-reduction of the ketone of **3b**. Thermodynamic control might presumably be operating for the stereochemistry of the diequatorial aldol product **3b**. Following the route established for racemic **3a**, **3b** was converted uneventfully to **2**. Thus, stereoselective reduction of **3b** was carried out by $NaBH(OAc)_3$ via chelation with the hydroxyl group to give **14** (Scheme 3).

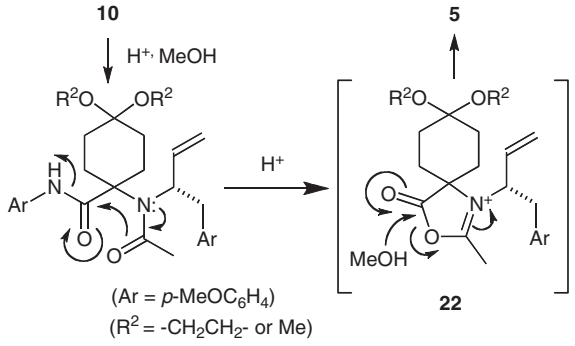
Selective protection of the *exo*-oriented hydroxy group of **14** as the TBS ether followed by Swern oxidation of the remaining alcohol provided the key intermediate **2**. All spectral data (^1H NMR, ^{13}C NMR, IR, and HRMS) of **2** are in agreement with our intermediate in the racemic synthesis, except for an optical rotation. The



Scheme 3. Synthesis of optically active key intermediate **2**.



Scheme 4. Preparation of optically active amine **7**. (i) MeI, K_2CO_3, DMF, rt, 99%; (ii) sodium chloroacetate, Et_3N, *t*-BuMgCl, THF, 0 °C to rt, 71%; (iii) $NaBH_4$, MeOH, rt; (iv) NaOH, THF–H_2O, rt, 97% (two steps); (v) KSCN, THF–H_2O, 60 °C; (vi) Ph_3P, toluene, 80 °C, 47% (two steps); (vii) 6 N HCl, MeOH, rt, 98%.



Scheme 5. Neighboring group participation in the methanolysis of **10**.

enantiomeric excess of **2** (96% ee) was determined by a chiral HPLC.

In conclusion, we have achieved an efficient synthesis of the key intermediate **2** for the total synthesis of (−)-FR901483 **1**, utilizing the Ugi 4CC reaction and a diastereoselective intramolecular aldol reaction. We are currently improving our racemic route[16] for the total synthesis of (−)-FR901483 and its analogs, and the results will be published in due course.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.089.

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4. For example: L-proline, DMF, 24% yield, 0% ee and L-phenylalanine, DMF, 10% yield, 18% ee; unpublished results.
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7. Optically active amine **7** was prepared in seven steps from commercially available *N*-Boc-tyrosine methyl ester **16**. Epoxide **20** was prepared in accordance with US Patent 59,29,284, 1997.
8. Synthesis of isocyanide **8**: Gokel, G. W.; Widera, R. P.; Weber, W. P. *Org. Synth. Coll. Vol. VI* **1988**, 232.
9. In this Ugi 4CC reaction, the reaction rate depends on the structure of the amine moiety **7**. The vinyl group facilitated the reaction considerably as compared with the other aldehyde equivalents.
10. (a) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. *Heterocycles* **2007**, *73*, 403; (b) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. *Synlett* **2004**, 44.
11. Presumably, this reaction proceeds via oxazolonium intermediate **22** through neighboring group participation. As shown in Scheme 5, the acetamide moiety plays a key role in this transformation. This speculation is supported by the fact that the amide of the Passerini compound, which has an acetate instead of the acetamide moiety, was unaffected under the same methanolysis conditions. Trimethyl orthoformate played an important role for dehydration as well as trapping *p*-anisidine.
12. During the dehydration reaction with phophoryl chloride, concomitant formation of methyl enol ethers was observed. After the mixture was reduced with magnesium in methanol without purification, both enol ether and dimethyl ketal were subjected to acidic hydrolysis to give ketone **12**.
13. Snider, B. B.; Lin, H.; Foxman, B. H. *J. Org. Chem.* **1998**, *63*, 6442. Their reaction conditions could not be applied in our study because we have found that the cyclization reaction proceeded with significant racemization under the basic conditions.
14. Spencer, T. A.; Schmiegel, K. K.; Williamson, K. L. *J. Am. Chem. Soc.* **1963**, *85*, 3785. This well-known classic condition was rediscovered in the Solensen's work[3b] although it exclusively gave the 'undesired' stereoisomer for their synthetic studies.
15. Similar stereochemistry of the aldol product was observed with **4a**. Both hydroxy groups of **3a** and **3b** are equatorially oriented and syn to the carbonyl groups.
16. In our racemic synthesis, conversion of **2** to **1** was accomplished in 11 steps and 12% overall yield.[3e]