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Stereocontrolled Total Synthesis of Potent Immunosuppressant FR901483

Toshiyuki Kan, Teppei Fujimoto, Shigeru Ieda, Yusuke Asoh, Haruka Kitaoka, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

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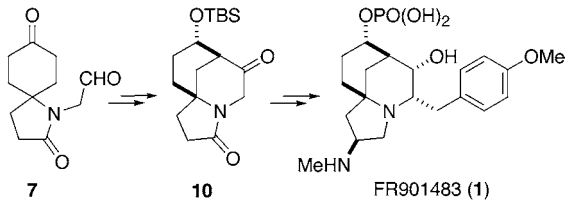
ABSTRACT

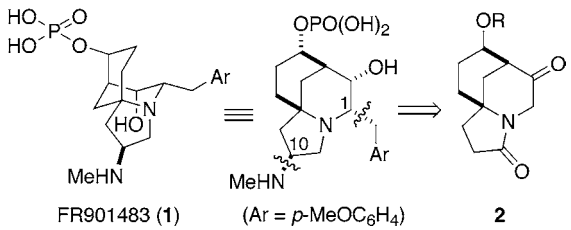


A total synthesis of the potent immunosuppressant FR901483 (1) has been accomplished. The key feature of our convergent synthesis is the stereoselective incorporation of the *p*-methoxybenzyl and methylamino groups within the core moiety 10. Tricycle 10 was itself constructed by an intramolecular aldol reaction of the symmetrical keto-aldehyde 7.

FR901483 (**1**) is a novel immunosuppressant isolated from the fermentation broth of the *Cladobotryum* species by researchers at the Fujisawa Pharmaceutical Company.[1] The promising biological activity and intriguing structure of this compound has made it an attractive target for total synthesis.[2,3] Although four total syntheses of **1** have been reported to date, none are completely stereoselective.[4] Herein, we describe a stereocontrolled total synthesis of racemic **1** that could potentially lead to a range of diverse analogues. The heart of our synthetic plan is illustrated in Scheme 1; it would involve the intermediacy of tricycle **2** and use its multiple carbonyl groups to append the requisite *p*-methoxybenzyl and methylamino groups at C(1) and C(10), respectively. The synthesis of **2** would be accomplished using an intramolecular aldol reaction on the symmetrical keto-aldehyde **7** as a key step.

As shown in Scheme 2, the cyclization precursor **7** was readily prepared by an eight-step sequence from inexpensive nitromethane (**3**) and methyl acrylate (**4**). Upon treatment of **3** and 3 equiv of **4** with 5 mol % DBU, the desired Michael reaction proceeded smoothly to afford the triester. Subsequent reduction of the nitro group and concomitant ester-amide exchange proceeded to provide **5**, which possessed the required quaternary carbon. After Dieckmann condensation

Scheme 1. Structure and Synthetic Strategy of **1**



(1) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.

(2) For a review of biomimetic synthesis of this family compounds, see: Takayama, H. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 350.

(3) For the synthetic studies, see: (a) Fujimoto, T.; Kitaoka, H.; Ieda, S.; Kan, T.; Fukuyama, T. *Abstract of papers, 79th Symposium on Organic Synthesis, Japan*; The Society of Synthetic Organic Chemistry, Japan: Tokyo, June 2001; p 17. (b) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013. (c) Brummond, K. M.; Lu, J. L. *Org. Lett.* **2001**, *3*, 1347. (d) Wardrop, D. J.; Zhang, W. M. *Org. Lett.* **2001**, *3*, 2001. (e) Puigbo, G.; Diaba, F.; Bonjoch, J. *Tetrahedron* **2003**, *59*, 2657. (f) Bonjoch, J.; Diaba, F.; Puigbo, G.; Peidro, E.; Sole, D. *Tetrahedron Lett.* **2003**, *44*, 8387.

(4) For total syntheses, see: (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (b) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (c) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7543. (d) Maeng, J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125.

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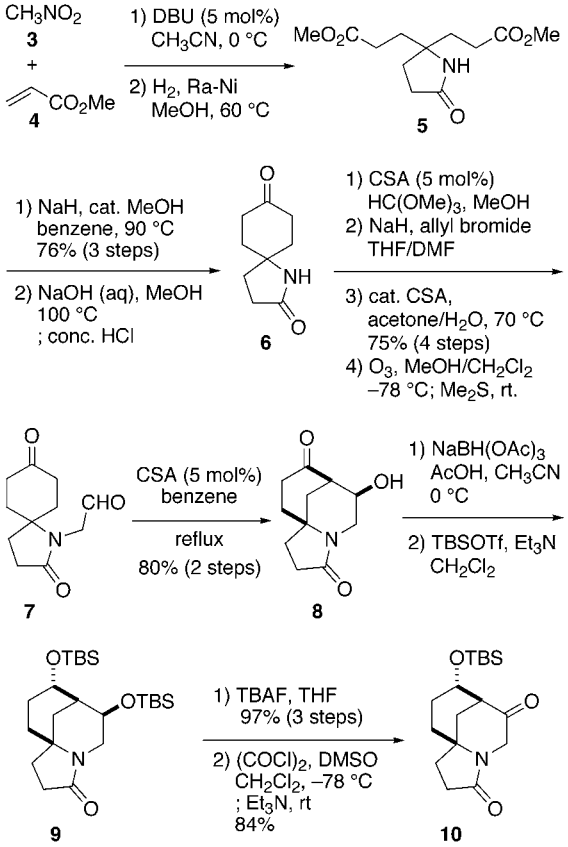
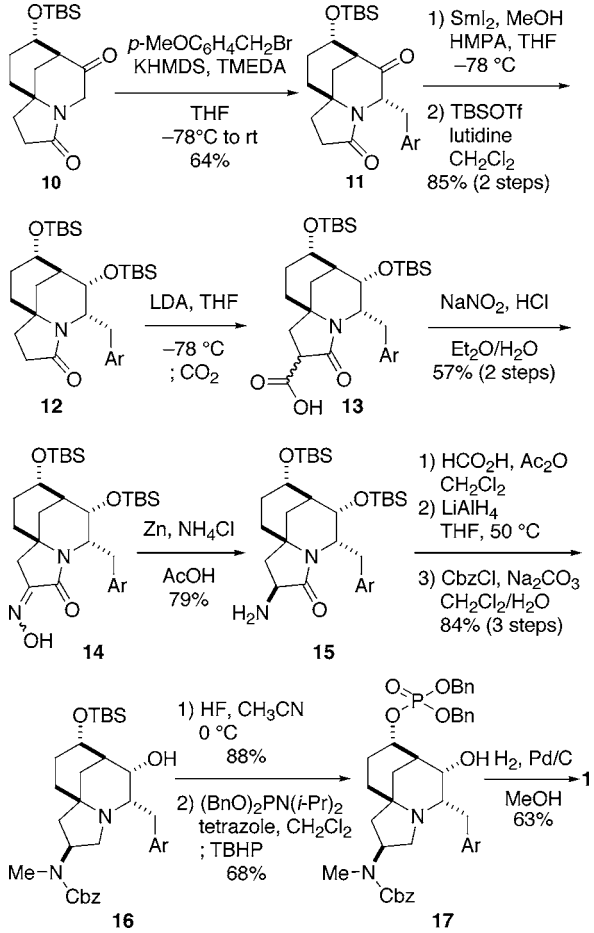
Scheme 2. Synthesis of Key Intermediate **10**



Scheme 3. Total Synthesis of FR901483 (**1**)



of the diester **5**, basic hydrolysis of the corresponding methyl ester and neutralization with acid caused decarboxylation of the β-keto acid to afford the spiro-lactam **6** in high yield.

The cyclization precursor **7** was prepared from **6** by a four-step sequence involving protection of the ketone as the dimethyl ketal, allylation of the amide, acidic hydrolysis of the dimethyl ketal, and oxidative cleavage of the double bond. Upon treatment of **7** in the presence of 5 mol % CSA, the crucial intramolecular aldol reaction furnished the desired tricycle **8** as a single isomer. The synthesis of **8** from **3** and **4** could be readily scaled up because no chromatographic purifications were required during the synthetic process, which produced **8** as white crystals. A desymmetrizing aldol reaction of **7** could also potentially be used for the preparation of the optically active compound.[5] Upon treatment with $NaBH(OAc)_3$,[6,7] the ketone **8** underwent hydroxyl group directed reduction to give the diol, which without purification was protected as the TBS ether to afford **9**. Selective cleavage of the equatorial TBS ether and oxidation of the resultant alcohol under Swern conditions provided the key intermediate **10**.[8]

The next challenge in the synthesis was stereoselective incorporation of the *p*-methoxybenzyl and methylamino groups into the tricyclic ketone **10** (Scheme 3). Diastereoselective alkylation of **10** with *p*-methoxybenzyl bromide was accomplished by treatment with KHMDS and TMEDA; it gave the desired ketone **11** as a single isomer.[9] Conversion of the ketone **11** into the *exo*-oriented alcohol was performed by a one-electron reduction. Thus, upon treatment with samarium(II) diiodide (SmI_2)[10] in the presence of HMPA, ketone **11** underwent smooth reduction at −78 °C. Subsequent protection as the TBS ether gave **12**. In the SmI_2-mediated reaction of **11**, the addition of HMPA played a key role in its high selectivity.[11] Diastereoselective incorporation of the nitrogen atom in **12** was also achieved utilizing a one-electron reduction as the key step. Because

(5) For a review on enantioselective desymmetrization, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, *13*, 1765.

(6) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(7) For a similar reaction, see ref 4d.

(8) The synthetic protocol based on the $NaBH(OAc)_3$ reduction and selective deprotection of the TBS ether has already been reported in ref 4d. However, the transformation of **8** to **10** has been developed independently in our laboratory; see ref 3a.

(9) Since the alkylation of **10** without TMEDA provided concomitantly the dialkylated product, TMEDA presumably plays a key role in this reaction. Similar enhancement of the mono-alkylation reaction by the addition of alkylamine derivatives was reported; see: Goto, M.; Akimoto, K.; Aoki, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1999**, *40*, 8129.

(10) For a recent review of SmI_2, see: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(11) The similar reduction of **11** without HMPA did not proceed at −78 °C, and the selectivity was approximately 5:1 to 7:1. The enhancement of the reduction potency of SmI_2 by addition of HMPA has been reported; see: Inanaga, J.; Yamaguchi, M. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 200.

the direct alkylation of amide **12** with several electrophiles was unsuccessful as a result of its low selectivity, we decided to investigate its conversion to the α-oxime amide **14**. Thus, treatment of the lactam **12** with LDA followed by the addition of solid CO_2 provided the carboxylic acid **13**. Subsequent treatment of **13** with sodium nitrite under acidic conditions, followed by a sequential nitrosation and decarboxylation, provided the oxime **14**. The crucial reduction of **14** was accomplished by treatment with zinc in acetic acid; the desired amine **15** was obtained as a single isomer.

Mono-N-methylation of the primary amine **15** was achieved in a stepwise manner. After conversion of **15** into the formamide, treatment with lithium aluminum hydride allowed simultaneous reduction of both the lactam and the formamide and concomitant deprotection of one of the TBS groups to provide the corresponding a methylamine derivative, which was protected with a Cbz group to afford **16**. After deprotection of the TBS ether, regioselective incorporation of the phosphate ester was achieved via the phosphoramidite method,[12] which gave **17**.[13] Finally, simultaneous cleavage of the Cbz and the benzyl ester groups by hydrogenolysis conditions yielded racemic FR901483 (**1**), the spectral data of which (^{1}H NMR, ^{13}C NMR, IR, and HRMS) were in full agreement with those of the natural product.[1]

In conclusion, a highly stereoselective total synthesis of FR901483 (**1**) has been accomplished by alkylation of the key intermediate **10**, which itself was obtained by an intramolecular aldol reaction. Our synthesis featured a stereoselective construction of the *exo*-oriented alcohol by SmI_2-mediated reduction. Finally, the amine stereochemistry at C(10) was set by a one-electron reduction.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a review of the phosphoramidite method, see: Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223.

(13) For a similar regioselective phosphitylation, see ref 4a.