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Total Synthesis of (−)-FR901483†

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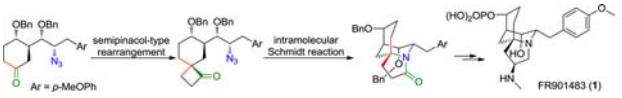
ABSTRACT



A total synthesis of the immunosuppressive alkaloid (−)-FR901483 (1) has been described. The intriguingly azatricyclic structure of 1 was constructed by the semipinacol-type rearrangement and intramolecular Schmidt reaction of an azido cyclohexanone derivative. This strategy provides a distinctive and competitive approach to the natural product 1.

FR901483 (**1**, Figure 1), a metabolite, was isolated from the fermentation broth of the fungal stain *Cladobotryum* sp. NO. 11231 by scientists at the Fujisawa Pharmaceutical Co. in 1996.[1] Its structure and relative configuration were determined by X-ray crystallography, and the absolute configuration was ascertained by total synthesis.[2a] It was demonstrated that FR901483 exhibits potent immunosuppressive activity in vitro and significantly prolongs graft survival time in the rat skin allograft model, which probably resulted from the interference with de novo purine nucleotide biosynthesis via inhibition of key enzymes involved in the pathway.[1] This alkaloid contains a unique and highly strained 5-azatricyclo[6.3.1.0^{1,5}]dodecane skeleton, which was unprecedented in nature. Its potential medicinal value and intriguingly azatricyclic structure are very attractive to a number of synthetic chemists. Several elegant total syntheses[2] and numerous synthetic approaches[3] toward **1** have been disclosed in the past few years. However, developing an enantioselective total synthesis of **1** is still necessary.

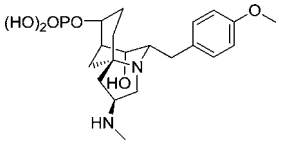


Figure 1. Structure of (−)-FR901483 (**1**).

In light of Aubé's report of the improved intramolecular Schmidt reaction,[4] many important relevant reactions have been designed and widely applied in the total syntheses of alkaloids.[5] However, construction of the bridged azapolycyclic system still remains an under-explored

† Patent pending, Chinese Patent Application (No. 201210130574.1).

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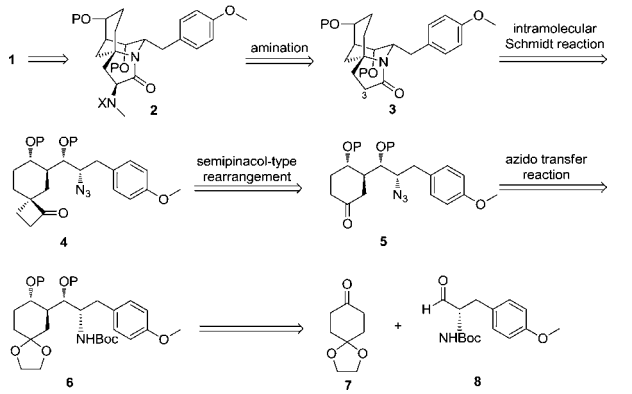
project by utilizing these reactions. As a result, only a few examples were reported.[4a,6] In connection with our longstanding interest in the semipinacol rearrangement reaction,[7] the intramolecular Schmidt reaction[8] and relative alkaloid syntheses,[9] herein, we wish to present our total synthesis of (−)-FR901483 (**1**) by these reactions of an azido cyclohexanone derivative and subsequent elaboration of the resulting aza-tricyclic skeleton.

Our retrosynthetic analysis is outlined in Scheme 1. FR901483 (**1**) could be easily obtained from the precursor **2** by means of transformation of functional groups. Compound **2** might be accessed via introduction of an amino group at C3 in **3**. The aza-tricyclic structure of key intermediate **3** was conceived via an intramolecular Schmidt reaction of azido spirocyclobutanone **4**, which will be derived from carbonyl compound **5** through a semipinacol-type rearrangement reaction. The azide **5** might be synthesized by azido transfer reaction from amide **6**, which can be easily obtained from commercially available ketone **7** and Boc-protected chiral amino aldehyde **8**.

Scheme 1. Retrosynthetic Analysis of (−)-FR901483 (**1**)



With the above synthetic strategy in mind, we began with construction of the key precursor **17** of the intramolecular Schmidt reaction (Scheme 2). The known diol **9** was prepared from **7** and **8** through an aldol reaction and a reduction reaction according to the protocol of Brummond.[2g] Under our modified conditions,[10] benzyl protection of **9** afforded 71% yield of **10**, whose configuration was confirmed by X-ray crystallography analysis.[11] After removal of the Boc protecting group,[2g] treatment of the amine with shelf-stable imidazole-1-sulfonyl azide hydrochloride (**11**)[12] gave the azido compound **12** in 82% yield over two steps. The ketal protecting group was removed from **12** using TsOH to produce the carbonyl compound **13** in excellent yield. We synthesized **17** using a semipinacol-type rearrangement reported by Trost,[13] which utilized selenoxide as a leaving group to promote the formation of stereoreversed cyclobutanone (Scheme 2). Accordingly, ketone **13** was treated with cyclopropyldiphenyl-sulphonium tetrafluoroborate (**14**) and KOH in DMSO at room temperature to produce **15**. Then the epoxy moiety of **15** was opened with phenylselenide in ethanol to give the hydroxysenide **16**. After oxidation of **16** with *m*-CPBA at −30 °C in *n*-hexane and CH_2Cl_2, rearrangement in the presence of pyridine from −30 °C to room temperature afforded the azido spirocyclobutanone **17** in 57% yield over three steps and its diastereoisomer **17′** in 14% yield. The structures of two compounds were confirmed by X-ray analysis, respectively[11] (see Figure 2). It should be noted that no purification was needed for compound **15** and **16** during this procedure.

Scheme 2. Preparation of Azido Ketone **17**

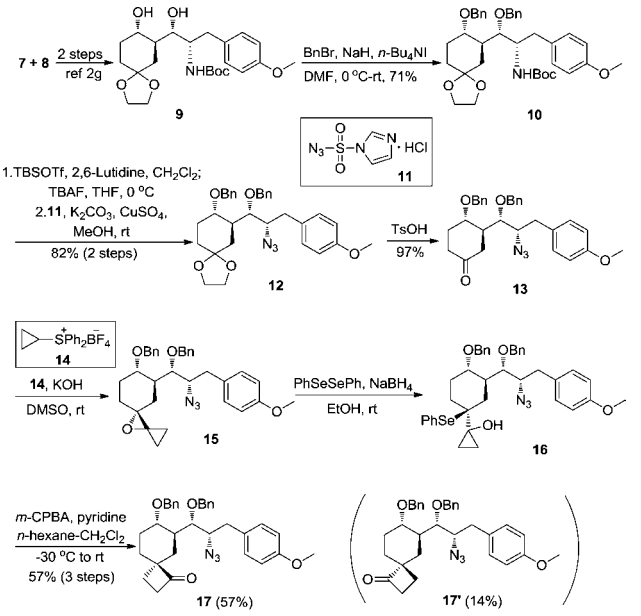


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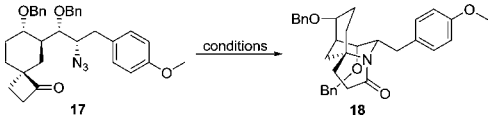
Table 1. Intramolecular Schmidt Reaction of Azido Ketone **17**



17 **18**

entry	conditions	yield (%)
1	TFA (neat), 60 °C	0[a]
2	$MeAlCl_2$ (2 or 10 equiv), CH_2Cl_2, −78 °C→rt	0[a]
3	$BF_3\cdot Et_2O$ (2 equiv), CH_2Cl_2, −78 °C→rt	0[a]
4	$SnCl_4$ (2 equiv), CH_2Cl_2, −78 °C→rt	0[a]
5	$HBF_4\cdot Et_2O$ (2 equiv), Et_2O, −78 °C→rt	0[a]
6[14]	$TiCl_4$ (2 equiv), CH_2Cl_2, −78 °C→rt	0[b]
7	TfOH (2 equiv), CH_2Cl_2, 0 °C, 2 h	36
8	TfOH (2 equiv), CH_2Cl_2, −10 °C, 24 h	41
9	NfOH (2 equiv), CH_2Cl_2, 0 °C, 24 h	40
10	$ClSO_3H$ (2 equiv), CH_2Cl_2, 0 °C, 5 min	40
11	**$ClSO_3H$** (2 equiv), **CH_2Cl_2**, **−30 °C, 6 h**	67
12	$ClSO_3H$ (2 equiv), CH_2Cl_2, −40 °C, 24 h	60
13	FSO_3H (2 equiv), CH_2Cl_2, 0 °C	0[b]
14	FSO_3H (2 equiv), CH_2Cl_2, −30 °C, 2 h	35
15	FSO_3H (2 equiv), CH_2Cl_2, −40 °C, 24 h	25

[a] All of the azido ketone **17** was recovered. [b] **17** disappeared, but no desired product was present.

With the key precursor **17** in hand, our effort was focused on the construction of challenging complex lactam **18** by the intramolecular Schmidt reaction. As shown in Table 1, treatment of **17** with neat trifluoroacetic acid (TFA) at 60 °C did not afford the desired product **18** (Table 1, entry 1). Lewis acids used frequently in Schmidt reaction also gave the same results (Table 1, entries 2−5). In particular, using $TiCl_4$ as the promotor, **18** was not obtained but **17** disappeared (Table 1, entry 6).[14] Encouragingly, when applying trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 at 0 °C (Table 1, entry 7), we obtained the desired product **18** albeit a low yield of 36%. When the reaction was carried out at −10 °C for about one day, the yield slightly increased to 41% (Table 1, entry 8). Futher lowering the temperature had no effect on the yield, but longer reaction time. Nonafluoro-1-butanesulfonic acid gave similar results as TfOH (Table 1, entry 9). To our delight, treatment of **17** with chlorosulfonic acid ($ClSO_3H$) in CH_2Cl_2 at 0 °C for only 5 min led to **18** in 40% yield (Table 1, entry 10). After a series of experiments, we found that treatment of **17** with $ClSO_3H$ in CH_2Cl_2 at −30 °C for 6 h gave the best result (Table 1, entry 11). To the best of our knowledge, it was the first time that $ClSO_3H$ was used as a promotor of the Schmidt reaction. Additionally, the use of more acidic fluorosulfonic acid (FSO_3H) resulted in lower yield (Table 1, entries 13, 14 and 15). $ClSO_3H$, therefore, was selected as the promoter of the intramolecular Schmidt reaction for **17** leading to **18**. However, diastereoisomer **17′** had no corresponding product under the optimized conditions and most of **17′** was consumed.

As illustrated in Scheme 3, the X-ray crystal structures of compound **17** and **17′** unambiguously reveal that the carbonyl group is distant from the azido group in both stable conformations in which the side substituents are at an equatorial position (Figure 2). For compound **17**, a conformational inversion facilitates the intramolecular Schmidt reaction successfully since azido group is close to carbonyl group (see conformation II). However, conformational inversion is ineffective to **17′**, because both of two conformations have unsuitable distance between the two reactive groups for the expected intramolecular Schmidt reaction under the optimized conditions (Scheme 3). This information explains well with our experimental results. Furthermore, coordination of the Lewis acids to the two ether oxygen atoms of **17** more or less prevents the conformational inversion, which probably explains the failed results during the optimization of the reaction conditions (Table 1, entries 2−4 and 6).

With the main skeleton of FR901483 (**1**) constructed, subsequent introduction of the amino group and transformation of functional groups would complete the total synthesis of **1** (Scheme 4). Compound **18** was treated with LDA in THF at −78 °C, followed by DPPA and Boc_2O at the same temperature gave **19** and its epimer in 85% yield (dr = 2:1).[15] Despite its modest dr value, this methodology provides a good method for the synthesis of α-amino lactam. Removal of the benzyl protecting group of 2-Boc-aminolactam **19** was completed with catalytic hydrogenolysis over $Pd(OH)_2/C$ to give **20** in 95% yield. Both of Boc and the lactam group were reduced in one step through $LiAlH_4$ in refluxing THF, and then the resulting secondary amine was protected with a Cbz group to afford diol **21**.[2c] Compound **21** was converted to **1** under mild conditions in two steps.[2e] Selective phosphitylation of the C-9 hydroxy gave the corresponding phosphite ester intermediate, which was then oxidized with *m*-CPBA in the presence of Et_3N to give the dibenzyl phosphate **22**.

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(10) For a modified preparation of the literature procedure, see the Supporting Information.

(11) CCDC 877989 (**10**), CCDC 877990 (**17**), and CCDC 877991 (**17′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(14) When we were preparing this paper, it was reported that the $TiCl_4$ could promote the semipinacol−Schmidt reaction of the simple substance in reference 6b. However, our previous experiment indicated that this condition did not work for **17**, which contains the necessary functional groups for synthesis of FR901483.

(15) The relative stereochemistry of product **19** was confirmed by later synthesis. For the reaction with DPPA for synthesis of α-amino lactam, see: (a) Villalgordo, J. M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1996**, *79*, 213–219. (b) Bentz, E. L.; Goswami, R.; Moloney, M. G.; Westway, S. M. *Org. Biomol. Chem.* **2005**, *3*, 2872–2882.

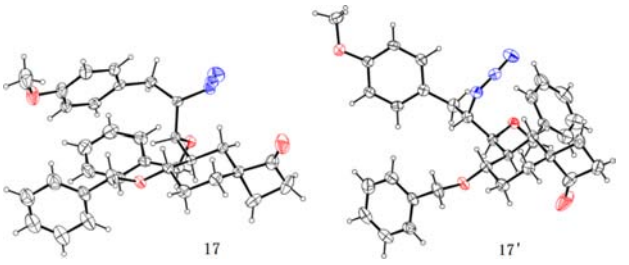
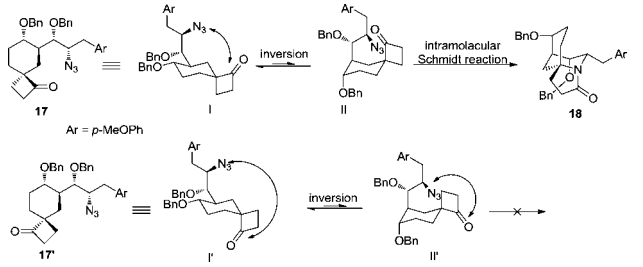


Figure 2. X-ray crystal structure of **17** and **17′**.

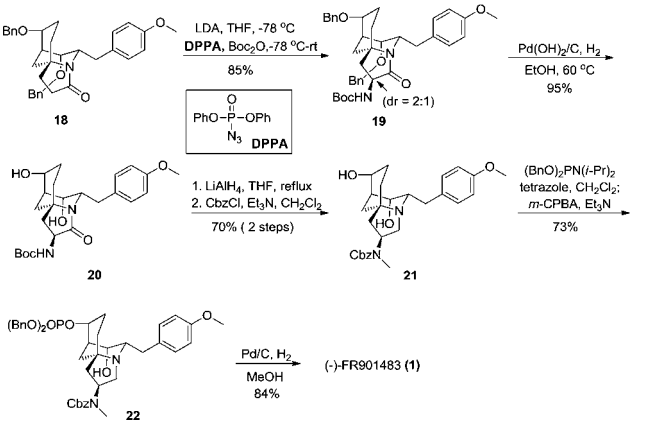
Scheme 3. Probable Process of the Intramolecular Schmidt Reaction



Simultaneous hydrogenolysis of the dibenzyl phosphate ester and benzyl carbamate of **22** over Pd/C proceeded smoothly to afford FR901483 (**1**), of which the spectral data were identified with those of the natural product.[1,2f]

In conclusion, we have completed a total synthesis of the potent immunosuppressant (−)-FR901483 in 3.5% overall yield and 16 steps from commercially available ketone **7** by utilizing the semipinacol-type rearrangement and intramolecular Schmidt reaction of an azido cyclohexanone derivative as the key steps.

Scheme 4. Completion of the Total Synthesis of (−)-FR901483



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Supporting Information Available. Experimental procedures and compound characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This manuscript was published ASAP on June 26, 2012. Scheme 4 has been updated. The corrected version was reposted on June 29, 2012.

The authors declare the following competing financial interest(s): A related patent is pending for the Chinese Patent Application (No. 201210130574.1).