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Total Synthesis of FR901483

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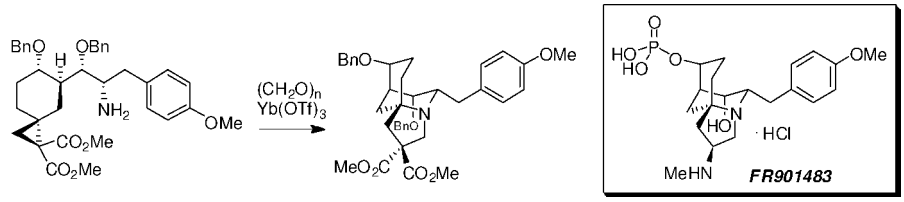
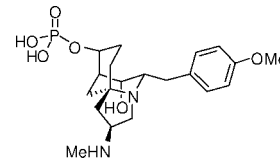
ABSTRACT



The architecturally sophisticated skeleton of the immunosuppressive alkaloid FR901483 was assembled via a process relying on the reaction of an in situ generated imine with a suitably disposed donor−acceptor cyclopropane. A short sequence of functional group transformations provided the natural product in an efficient manner.

FR901483 (**1**, Figure 1) is a potent immunosuppressive alkaloid isolated from the fermentation broth of *Cladobotryum* sp.[1] As an inhibitor of purine biosynthesis with a novel mode of action compared to leading immunosuppressive agents cyclosporin A and FK-506 (both of which display significant toxicity at high doses), FR901483 has garnered significant attention from the synthetic community due to its biological activity and unique aza-tricyclic structure. This has resulted in the publication of a number of inventive total syntheses[2] and ongoing synthetic efforts.[3]



FR901483 (1)

Figure 1. Structure of FR901483.

Our interest in FR901483 was piqued as part of our research program aimed at the synthesis of complex pyrrolidine ring systems via ring-opening/annulation reactions of cyclopropanes.[4] At the outset, we envisioned two potential deconstructive routes (Scheme 1). Retrosynthetic route A would have as a late-stage step an intramolecular aldol reaction where the substrate would be spiroheterocycle **2**, in turn assembled via an intermolecular imine/cyclopropane formal cycloaddition between substrates such as **3** and **4**.[4b,5] Route B, on the other hand, would reverse the order of the

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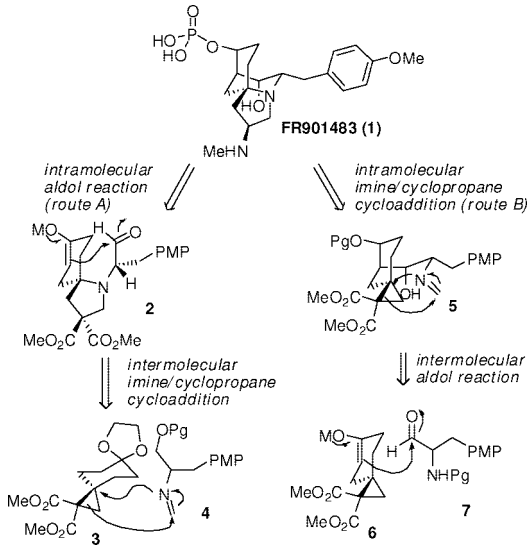
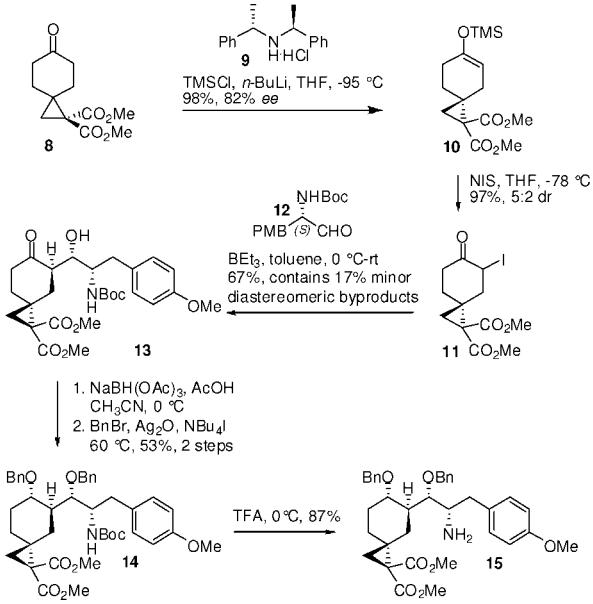
Scheme 1. Retrosynthetic Analysis of FR901483



two key steps. In other words, an intermolecular aldol reaction of **6** with **7** would set the stage for an intramolecular imine/cyclopropane cycloaddition involving substrate **5**. Retrosynthetic route A, to put it succinctly, did not prove viable as most Lewis acids promoted an eliminative cyclopropane ring opening. Route A was therefore abandoned in favor of the ultimately successful intramolecular formal cycloaddition strategy (route B).

Our synthetic route (Scheme 2) commenced with the addition of an enolate derived from ketone **8** (readily prepared in three steps from 1,4-cyclohexanedione monoethylene ketal) to homochiral aldehyde **12**. This union requires

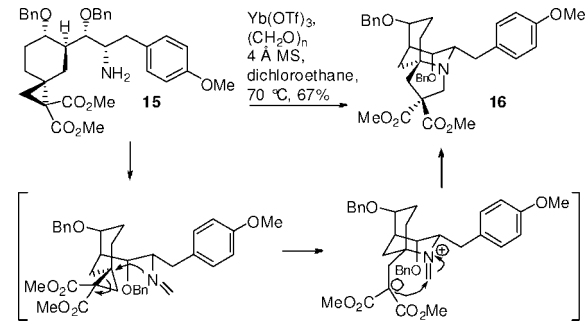
Scheme 2. Preparation of Compound **15**



an asymmetric deprotonation event to generate the chiral center of spirocyclopropane **13** in a selective fashion.[6] This was best achieved by treatment of ketone **8** with the chiral lithium amide derived from **9**[7] in the presence of chlorotrimethylsilane (Scheme 2). Under these conditions, enol ether **10** was prepared in enantiomeric excesses ranging from 74−82%. While internal quench conditions[8] were generally used for this transformation, external quench conditions in the presence of lithium chloride provided similar results.[9] Crystallization of the crude material from pentane at −78 °C could provide **10** in ≥95% ee; however, because the undesired enantiomer of **10** can be eliminated as minor diastereomeric byproducts after reaction with chiral aldehyde **12**, this was not usually performed. Iodide **11** was prepared in high yield as an inconsequential 5:2 mixture of diastereomers by treatment of **10** with *N*-iodosuccinimide. Exposure of iodide **11** to aldehyde **12** and triethylborane in toluene promoted a Reformatsky-type reaction[10] to form compound **13** with an acceptable degree of selectivity considering the complicated stereochemical aspects of the transformation. As observed for similar compounds, ketone **13** is prone to *N*-Boc pyrrole formation on standing and should be used immediately in subsequent transformations or stored in solution.[2f,11] Reduction of ketone **13** provided the crude *cis*-diol[12] which was directly protected as the bis-benzyl ether **14** using conditions reported by Brummond.[2f] Finally, removal of the nitrogen protecting group provided amine **15**, a suitable substrate for the imine/cyclopropane cyclization event.

The key pyrrolidine-forming reaction was performed by adding **15** to a dilute solution of paraformaldehyde and ytterbium(III) triflate in dichloroethane at 70 °C (scheme 3).

Scheme 3. Intramolecular Imine/Cyclopropane Annulation



Notably, no products resulting from direct cyclopropane ring-opening by the pendant amine moiety were evident, even when the reaction was performed in the absence of paraform-

(6) For a recent review of the use of chiral lithium amides in organic synthesis, see: O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439–1457.

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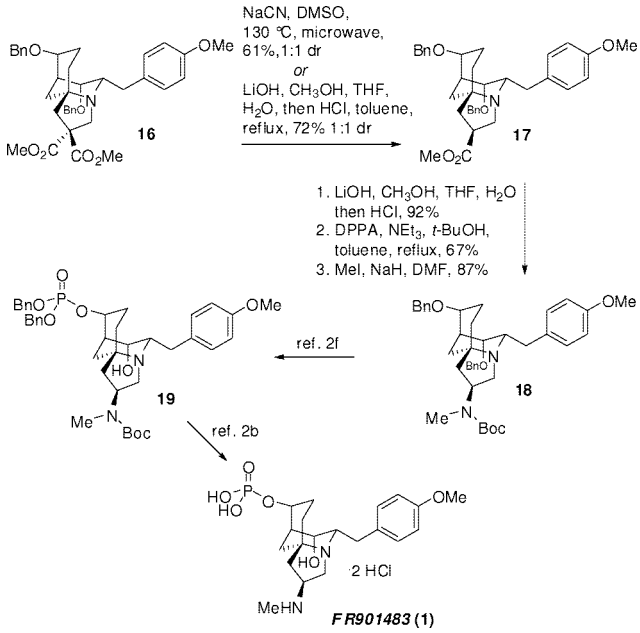
Scheme 4. Completion of the Synthesis of FR901483



aldehyde.[13] Preheating the solution served to minimize eliminative ring-opening of the cyclopropyl moiety.

With the tricyclic core of the natural product constructed, the task of incorporating the amine and phosphate moieties of FR901483 was undertaken. Krapcho dealkoxycarbonylation[14] of **16** successfully removed the superfluous ester function forming **17** as a separable 1:1 mixture of diastereomers; however, monosaponification followed by heating in refluxing toluene resulted in a slightly better yield. Exposure of *epi*-**17** to potassium bis(trimethylsilyl)amide in THF at −35 °C resulted in epimerization to a 1:1 mixture of diastereomers which could again be separated.[15] Hydrolysis of the ester of **17** provided an amino acid which readily underwent a Curtius rearrangement[16] to garner the *N*-Boc-protected amine. Alkylation proceeded smoothly yielding compound **18**, which matched the data provided by Brummond in their formal synthesis of FR901483 in all respects.[2f] Removal of the benzyl protecting groups and incorporation of the phosphate moiety provided pyrrolidine **19**, prepared previously by the Sorenson group.[2b] Removal of the remaining protecting groups proceeded uneventfully, thus completing our synthesis of FR901483.

In summary, a total synthesis of FR901483 has been accomplished by relying on a previously unreported intramolecular reaction on an imine and a 1,1-cyclopropanediester. This work also highlights the successful desymmetrization of a prochiral spirofused cyclopropane and the triethylborane mediated coupling of a chiral α-aminoaldehyde and α-iodocyclohexanone derivative. The entire synthetic sequence requires 18 linear steps and is competitive with previously reported syntheses 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.

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