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Tandem Cationic *aza*-Cope Rearrangement–Mannich Cyclization Approach to the Core Structure of FR901483 via a Bridgehead Iminium Ion

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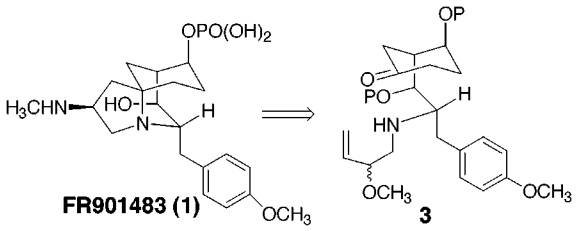
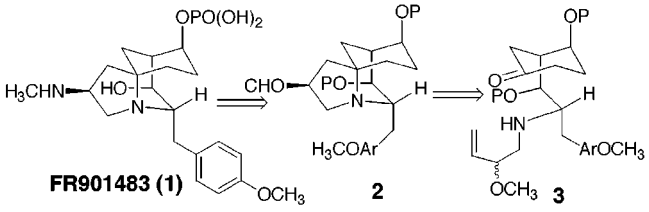
ABSTRACT



An approach to the potent immunosuppressant FR901483 is described. This route utilizes a tandem cationic *aza*-Cope rearrangement–Mannich cyclization to generate the core structure of this compound. In addition, this is the first demonstration of this tandem reaction passing through a bridgehead iminium ion.

Researchers at Fujisawa Pharmaceutical Co. Ltd. recently reported the isolation of FR901483 (**1**), an immunosuppressant possessing a novel tricyclic structure and a phosphate residue (Scheme 1).[1] This compound is likely to function by a mechanism that is different from that of cyclosporin A or tacrolimus (FK 506), an important feature given the drug-associated side effects of either of these drugs. It is thought that the role of FR901483 in suppressing the immune system results from an antimetabolite activity whereby adenylosuccinate synthetase and/or adenylosuccinase lyase are inhibited. These enzymes function as key catalysts in the de novo purine nucleotide biosynthetic pathway.

Scheme 1



FR901483 is also an exciting target in that it possesses a unique substructure that has not been heretofore observed in nature. This unprecedented structure has already resulted in a flurry of interest from the synthetic community.[2] Consequently, the biological activity, novel structure, and the potential for rapid access to FR901483 was the impetus

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

(2) For the total synthesis of (−)-FR901483, see: (a) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765. (b) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (c) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. For the total synthesis of (±)-FR901483, see: (d) Funk, R. L.; Maeng, J.-H. 220th ACS National Meeting, Washington, DC, Abstract 264; for other approaches to FR901483, see: (e) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (f) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280. (g) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (h) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391.

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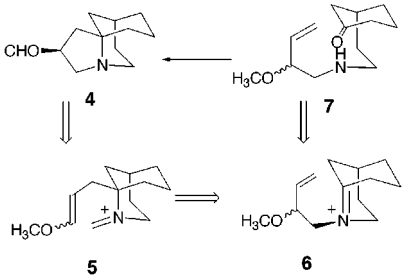
for our group initiating a synthetic approach to this compound. Our first retrosynthetic disassembly of the target leads to the functionalized 3-formyl pyrrolidine **2**. Formyl pyrrolidines have been accessed in a very efficient manner by Overman using a tandem cationic *aza*-Cope rearrangement−Mannich cyclization strategy.[3] Thus, on the basis of elegant precedents provided by Overman, the formyl pyrrolidine moiety of **2** can in principle be obtained from the amino ketone **3** via the tandem reaction, through a bridgehead iminium ion. This retrosynthetic analysis represents a facile entry to the synthesis of FR901483 with the potential to set all the stereochemistry of this target by starting with an amino aldehyde derived from L-tyrosine.

In an effort to quickly establish the feasibility of this route, we targeted a precursor **4** possessing only the functionality necessary for the tandem rearrangement−cyclization process (Scheme 2). The functionally barren precursor, amino

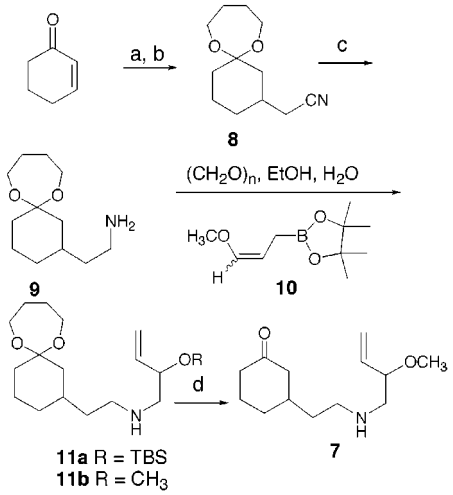
Scheme 2



aldehyde **4**, possesses the core structure of **1** with an aldehyde handle that provides access to the amino methyl group via a Curtius rearrangement. Amino aldehyde **4** is the product of a Mannich cyclization of iminium ion **5**, which in turn can be obtained via an *aza*-Cope rearrangement of the iminium ion **6**. This bridged bicyclic substructure is particularly interesting, in that it is in violation of Bredt's rule as applied to bridging carbocycles. Bridgehead imines have been prepared, and in fact, Kibayashi has shown that bridgehead imines can be alkylated.[2e,4] Finally, bridgehead iminium ion **6** arises from the intramolecular condensation reaction of the secondary amine and ketone moieties of **7**.

The synthesis of the key cyclization precursor **7** was initiated (Scheme 3) by addition of the lithium anion of trimethylsilylacetonitrile to cyclohexenone to give the protodesilylated 1,4-addition product directly after column chromatography in good yield (82%).[5] Protection of the

Scheme 3[a]



[a] (a) TMSCHLiCN, THF, 82%; (b) butanediol, PPTS, benzene, reflux, 92%; (c) $LiAlH_4$, THF, 80%; (d) 1M HCl, acetone, H_2O, 95%.

ketone was then effected (PPTS, butanediol)[6] to afford compound **8** in 92% yield. Reduction of the nitrile using LAH gives the primary amine **9** (80%).

Initial attempts to effect the monoalkylation of the primary amine **9** (in excess) with 4-bromo-3-methoxy-1-butene[3c] gave poor yields of the desired product **11b**. Moreover, a recently published method for the monoalkylation of primary amines with alkyl bromides utilizing $CsOH{\cdot}H_2O$ did not prove to be successful either.[7] Other attempts to improve the amine alkylation using a reductive amination[8] reaction involving 2-(*tert*-butyldimethylsilyloxy)-but-3-enal[9] did afford a 76% yield of **11a**. However, this compound proved unsuitable for the subsequent tandem *aza*-Cope/Mannich reaction. Fortunately, Petasis has developed a three-component coupling method involving amines, aldehydes and organoboronates.[10] On the basis of this precedent, amine **9** was treated with paraformaldehyde and excess allylboronate **10**[11] in EtOH and H_2O to give amine **11b** in 58% isolated yield. Removal of the ketal of **11b** with 1M HCl in acetone furnished the tandem cyclization precursor, amino ketone **7** in 95% yield.

We were delighted to find that treatment of compound **7** to *p*-toluenesulfonic acid (PTSA) in refluxing benzene afforded the amino aldehyde **4** (*dr*, 2/1) via the tandem cationic *aza*-Cope rearrangement-Mannich cyclization sequence (Scheme 4). The diastereomeric ratio was determined by ^1H NMR intregration of the corresponding formyl peaks. The resulting amino aldehyde was then protected as ketal

(3) For reviews, see: (a) Overman, L. E.; Ricca, D. J. *Comp. Org. Synth.* **1991**, *2*, 1007. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (c) Overman, L. E.; Kakimoto, M.-a.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

(4) Yamazaki, N.; Ito, T.; Kibayashi, C. *Synlett* **1999**, 37. For references concerning bridgehead imines, see: Braje, W. M.; Wartchow, R.; Hoffman, M. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 2540. Wayne, G. S.; Snyder, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 9860. Radziszewski, J. G.; Downing, J. W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 2799. Sheridan, R. S.; Ganzer, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6158. Toda, M.; Hirata, Y. Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1597.

(5) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 1599.

(6) The choice of butanediol as the reagent for protection is based on the facile removal of the resulting dioxepane ketal. Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643 and references therein.

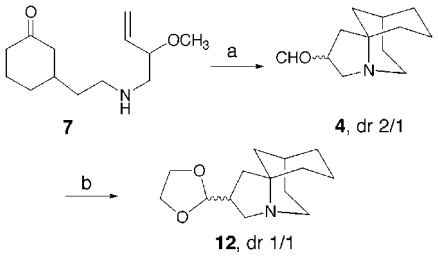
(7) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K.-W. *Org. Lett.* **1999**, *1*, 1893.

(8) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552

(9) Hayashi, M.; Yoshiga, T.; Nakatani, K.; Ono, K.; Oguni, N. *Tetrahedron* **1994**, *50*, 2821.

(10) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

Scheme 4[a]



[a] (a) PTSA, benzene, reflux; (b) $(CH_2OH)_2$, PTSA, benzene.

12 for the purpose of isolation and characterization. The yield for this two-step process (**7** → **12**) is 72%.

The structural assignments of the azatricycles **4** and **12** is worth further discussion. Because of the instability of the aminoaldehyde **4**, isolation and characterization was difficult. In our hands, ketal **12** is the only derivative in which diastereomers can be separated by HPLC.[12] After separation of the diastereomeric ketals, the structural assignment was made on the basis of APT and DEPT experiments. The presence of one quaternary and three tertiary carbons in both diastereomers clearly matches the structure of **12**, the core structure of FR901483 (**1**).

(11) (a) Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett.* **1999**, 1069. (b) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246.

In conclusion, we have demonstrated an unprecedented tandem cationic *aza*-Cope rearrangement−Mannich cyclization passing through an *anti*-Bredt iminium ion intermediate. This sequence of transformations gives rise to a marked increase in molecular complexity as evidenced by the conversion of the monosubstituted cyclohexanone **7** to the azatricycle **4**. In addition, this natural product contains a particularly well suited structure to serve as a scaffold for a diversity-based synthesis. Efforts are currently being made to synthesize FR901483 via the appropriately functionalized precursor **3** and to prepare a library of analogues.

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Supporting Information Available: Characterization data and full experimental procedures are provided for compounds **7**, **8**, **9**, **11b**, **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We have also shown that treatment of aldehyde **4** with Ag_2O affords the carboxylic acid in a 76% overall yield for the tandem rearrangement and oxidation steps. We have performed the Curtius rearrangement on this carboxylic acid using diphenylphosphoryl azide (DPPA), NEt_3, and *t*-BuOH to afford the desired Boc protected amine in 21% yield. While the yield is low, this reaction sequence provides support for the successful application of this approach to FR901483 and will be optimized.