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Total Synthesis of FR901483

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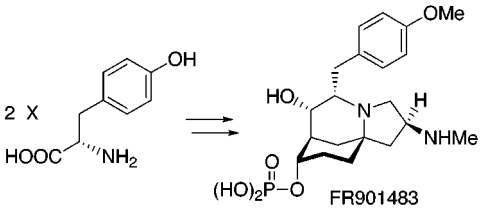
ABSTRACT



The total synthesis of FR901483, a structurally novel immunosuppressant, has been accomplished by the use of technology recently developed in this laboratory for the oxidative cyclization of phenolic oxazolines to spirolactams. Our approach may reflect the biosynthetic pathway leading to the natural product.

FR901483, **1**, is an immunosuppressant produced by a *Cladobotryum* species. The compound was described in 1996 by a research team at the Fujisawa Pharmaceutical Company.[1] Its highly novel structure is reminiscent of a family of muscarinic antagonists reported by Takeda Industries and known as TAN1251A−D.[2] The unique architecture of these natural products has elicited substantial synthetic activity.[3] In particular, important work by Snider has recently led the first synthesis of **1** and to the elucidation of its absolute configuration.[3c] Our own involvement in this area began with the perception of **1** as being formally derived from two molecules of tyrosine. This surmise may well reflect the biogenetic origin of the molecule. Regardless, an especially concise synthesis might result if a suitably blocked *N*-tyrosinyl tyrosine dipeptide might be induced to undergo the bond-forming processes depicted in Figure 1. One of these

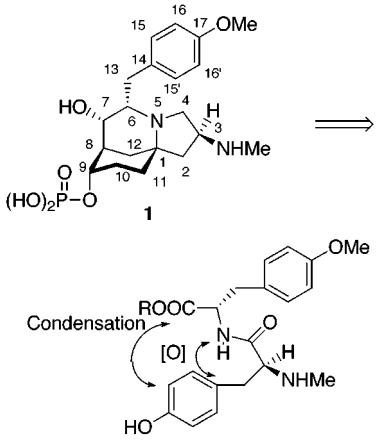


Figure 1. Structure of FR901483 and restrosynthetic logic for the construction of its ring system.

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

(2) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. Int. Patent PCT, 1991, WO91/13887.

(3) FR901483. (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280 (synthetic studies). (b) Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaría, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891 (analogues). (c) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (d) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (e) Funk, R. L.; Maeng, J.-H. *Abstracts of Papers*, 220th National Meeting of the American Chemical Society, Washington, DC, August 20−24, 2000; American Chemical Society: Washington, DC, 2000; Abstract ORGN 264 (total synthesis). TAN1251A−D: (f) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493. (g) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643 (total synthesis).

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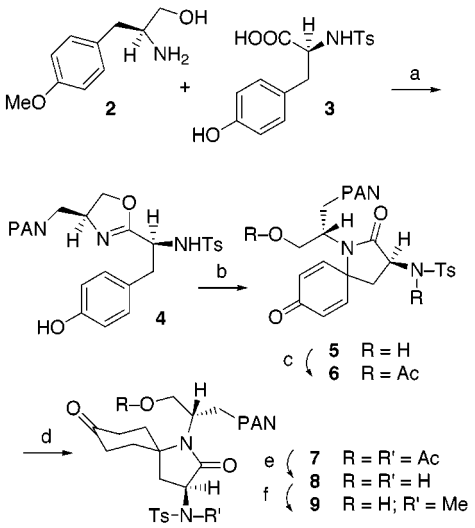
transformations, the oxidative cyclization of a phenolic amide to a spirolactam, was regarded as being unfeasible until 1998, when we demonstrated that spirolactam formation may be achieved by oxidation of appropriate phenolic oxazolines.[4] At the end of 2000, Sorensen reported a variant of this chemistry that involves a free secondary amine, instead of an oxazoline, as a nucleophile for oxidative azaspirocyclization and utilized this transformation in a brilliant total synthesis of **1**.[3d] We now wish to describe the total synthesis of FR901483 by the use of our oxazoline-based methodology.

Commercial L-tyrosine was converted to building blocks **2**[5] and **3**[6] (Scheme 1). The union of **2** and **3** to furnish

Scheme 1[a]

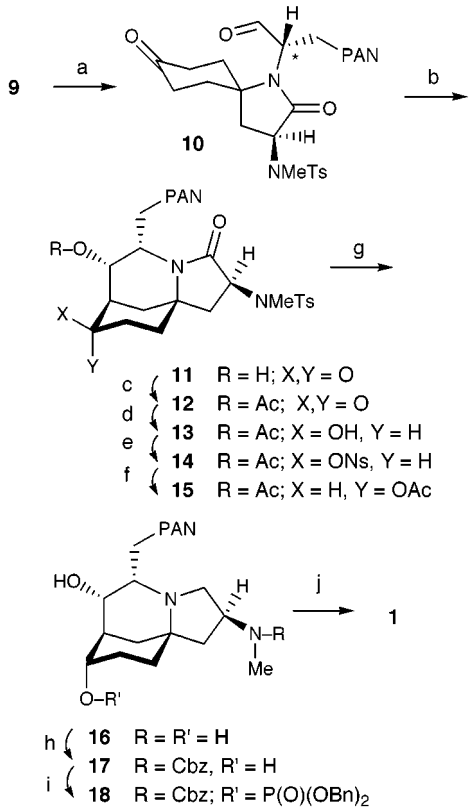


[a] Key: (a) PPh_3, CCl_4, Et_3N, pyridine, MeCN, 73%; (b) $PhI(OAc)_2$, CF_3CH_2OH, then solid $NaHCO_3$; (c) Ac_2O, pyridine, 4-DMAP, 41% b−c; (d) H_2, PtO_2, AcOEt, 96%; (e) K_2CO_3, MeOH, 79%; (f) MeI, K_2CO_3, Me_2CO, 93%. PAN = *p*-anisyl.

oxazoline **4** was achieved in a single step, and without erosion of stereochemical integrity, by the Vorbrüggen method.[7] An advantage of this technique is that no protection of the phenol in **3** is required. Reaction of **4** with iodobenzene diacetate (DIB) in trifluoroethanol induced spirocyclization to **5**, which was immediately acetylated to furnish **6**. The reasons for (i) the use of an *N*-tosyl protecting group in **3** and (ii) the acetylation of **5** have been detailed elsewhere.[4] Briefly, the oxygen atom of carbonyl-type *N*-blocking agents (carbamates, etc.) tends to react with the electrophilic intermediate produced by DIB activation of the phenol. No such interference is observed with *N*-sulfonamido units. Second, the primary alcohol in **5** readily adds in a 1,4 sense to the dienone, complicating subsequent manipulations. Acetylation suppresses this inconvenience. Notice that exposure of **5** to Ac_2O/pyridine results in acetylation of both primary alcohol and tosylamide, but this is inconsequential. Hydrogenation of the dienone was effected with PtO_2 as the catalyst, to prevent reductive aromatization back to a phenol.[4] Deacetylation and selective *N*-methylation converted **7** to **9**.

The primary alcohol in **9** was oxidized to aldehyde **10** (Scheme 2) with TPAP/NMO.[8] Compound **10** appeared to

Scheme 2[a]



[a] Key: (a) TPAP, NMO, CH_2Cl_2, 77%; (b) NaOMe, 9:1 MeOH−H_2O, 44% of **11**; other diastereomers also formed; (c) Ac_2O, pyridine, CH_2Cl_2, 94%; (d) L-Selectride, THF, −78 °C, 94%; (e) NsCl, Et_3N, 4-DMAP, CH_2Cl_2, 72%; (f) CsOAc, 18-cr-6, PhH, 80 °C, 72%; (g) LAH, THF, −78 °C to reflux, 6 h; (h) Cbz-Cl, Et_3N, CH_2Cl_2, 74% g−h; (i) $iPr_2NP(OBn)_2$, tetrazole, CH_2Cl_2, then tBuOOH; (j) 3 N HCl, MeOH, then H_2, Pd(C), MeOH, 29% i−j. PAN = *p*-anisyl.

be fairly resistant to epimerization at the starred center, as first described by Snider.[3c] Indeed, configurational stability has been observed in several amino acid-derived aldehydes.[9] Stereochemical stability facilitated a subsequent aldol-type cyclization of **10** to **11** by minimizing the probability of formation of aldol diastereomers epimeric at C-6.

(4) (a) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (b) Braun, N. A.; Bray, J. D.; Ciufolini, M. A. *Tetrahedron Lett.* **1999**, *40*, 4985. (c) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397.

(5) The preparation of **2** has been described: Abarbri, M.; Guignard, A.; Lamant, M. *Helv. Chim. Acta* **1995**, *78*, 109. Jung, M. E.; Jachiet, D.; Rohloff, J. R. *Tetrahedron Lett.* **1989**, *30*, 4211. Unfortunately, the product thus obtained is not optically pure. A short route to **2** that safeguards optical integrity was developed via (i) double methylation of phenolic and carboxy units of the *N*-carbomethoxy-L-tyrosine; (ii) LAH reduction of the ester; and (iii) carbamate cleavage. Details are provided as Supporting Information.

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The product distribution observed in the aldol step proved to be sensitive to the nature of the solvent employed.[3c] Thus, protic solvents favored formation of the aldol diastereomer displaying the correct C-7-(*S*) configuration, while conduct of the reaction in aprotic media, e.g., DBU/CH_2Cl_2, promoted formation of the incorrect C-7-(*R*) diastereomer as the major product. Optimal conditions for the production of the desired **11** entailed treatment of **10** with NaOMe in 10% aqueous methanol, but other diastereomers were also obtained.

The secondary alcohol in **11** was acetylated prior to L-Selectride reduction of the cyclohexanone, which occurred highly stereoselectively from the *Si* face, thereby affording exclusively the equatorial alcohol **13**.[10] While this result may seem to be in conflict with principles governing the reactivity of selectride agents,[11] it is apparent that the shape of the molecule precludes approach from the *Re* face of the carbonyl. Inversion of C-9 configuration à la Snider[3c] afforded **15**.[10] LAH reduction of **15** engendered release of the acetyl groups, deoxygenation of the amide, and cleavage of the sulfonamide to afford diol **16**. This substance amounts to the dephosphorylated form of **1**. As of yet, compound **16** is not a known natural product, but it is reported to be a biologically inactive metabolite of **1**.[1] The secondary amine was blocked as a Cbz derivative, setting the stage for phosphorylation of the C-9 alcohol. This transformation was achieved by phosphitylation−oxidation.[12] Significant differences in steric environment between C-7 and C-9 permitted selective phosphitylation of the C-9 alcohol in **17** without protection of the C-7 OH group. The presumed phosphite intermediate was oxidized in situ to **18**, which was treated with excess 3 N aqueous HCl prior to hydrogenolysis of all benzyl groups. The emerging, fully synthetic bis-hydrochloride salt of **1** was identical in all respects (^{1}H, ^{13}C, MS, TLC, $[\alpha]_D$) to a sample of natural material, prepared from the monohydrochloride of **1**, kindly provided by the Fujisawa Co., by treatment with excess 3 N aqueous HCl.

The key step in the present synthesis of FR901483, the transformation of **4** to **5**, amounts to an oxidative dearomatization leading to the formation of a C−N bond. Analogous reactions involving formation of C−O bonds have enjoyed widespread use in organic chemistry.[13] We thus feel that the "aza" variant of this process holds considerable potential for the chemical synthesis of many complex nitrogenous substances. Work in the area continues, and additional results will be disclosed in due course.

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

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(10) Structure confirmed by X-ray crystallography. Compound **13**: Ousmer, M.; Braun, N. A.; Ciufolini, M. A.; Perrin, M. *Z. Kristallogr. NCS* **2000**, *215*, 597. Compound **15**: Ousmer, M.; Braun, N. A.; Ciufolini, M. A.; Perrin, M.; Bavoux, C. *Z. Kristallogr. NCS*. Submitted.

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