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Total Synthesis of the Immunosuppressant FR901483 via an Amidoacrolein Cycloaddition

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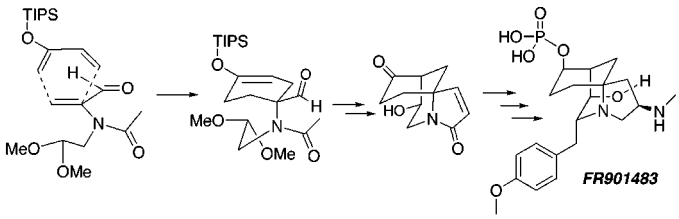
ABSTRACT



The total synthesis of the potent immunosuppressant FR901483 is described. In a key step, the intermolecular Diels−Alder cycloaddition of an amidoacrolein with 2-(triisopropylsilyloxy)-1,3-butadiene produced the desired 3-cyclohexene-1-carboxaldehyde. This compound was subjected to basic followed by acidic conditions which effected two sequential aldol cyclizations to deliver the tricyclic ring system of the natural product, suitably functionalized for completion of the total synthesis.

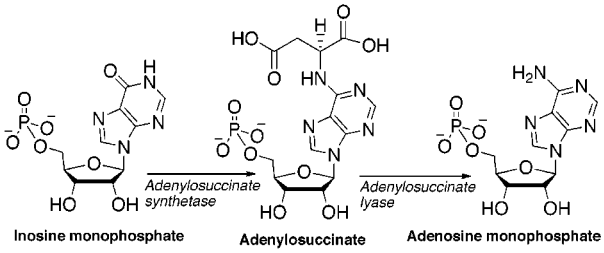
Organ transplant recipients can attribute their survival, in part, to the discovery of the immunosuppressive agents cyclosporin A and FK-506 (tacrolimus). However, these compounds are toxic at high doses[1] and, consequently, the identification of additional immunosuppressants which function by mechanisms of actions different from these two drugs[2] remains an ongoing concern. To that end, the Fujisawa company screened a number of microbial culture broths for the inhibition of 12-*O*-tetradecanoylphorbol 13-acetate stimulated T-cell proliferation in the presence of *exogenous* IL-2, conditions which suppress the antiproliferative activity of tacrolimus.[3] An active compound, FR901483 (**1**), was isolated from the fermentation broth of a fungal strain, *Cladobotryum* sp. No. 11231, that was retrieved from litter collected at Iwaki, Japan.[3] It was further demonstrated that FR901483 significantly prolongs graft survival time in the rat skin allograft model, and moreover, evidence was obtained which is suggestive of a different mechanism of action, namely, inhibition of purine nucleotide biosynthesis.[4,5]

(1) Fujita, T.; Hirose, R.; Yoneta, M.; Sasaki, S.; Inoue, K.; Kiuchi, M.; Hirase, S.; Chiba, K.; Sakamoto, H.; Arita, M. *J. Med. Chem.* **1996**, *39*, 4451 and references therein.

(2) These drugs function by inhibiting the phosphatase activity of calcineurin which, in turn, prevents the activation of T-cell-specific transcription factors that are involved in the expression of the lymphokine interleukin-2 (IL-2), see: Schreiber, S. L. *Cell* **1992**, *70*, 365 and references therein.

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

(4) Addition of adenosine or deoxyadenosine (but not deoxyguanosine, deoxycytidine, uridine or thymidine) resulted in elimination of the immunosuppressive activity by FR901483.[3] Moreover, the desphosphoryl compound is not biologically active.[3] Thus, FR901483 may inhibit one of the key steps (shown below) for adenosine biosynthesis. Indeed, certain structural similarities between these metabolites and FR901483 are intriguing.



(5) Inhibitors of purine biosynthesis are selectively cytotoxic toward lymphocytes vis-à-vis other cells since the former lack the purine salvage pathway and must rely on de novo purine biosynthesis, see: Robinson, C. J. *Drugs Future* **1995**, *20*, 356 and references therein.

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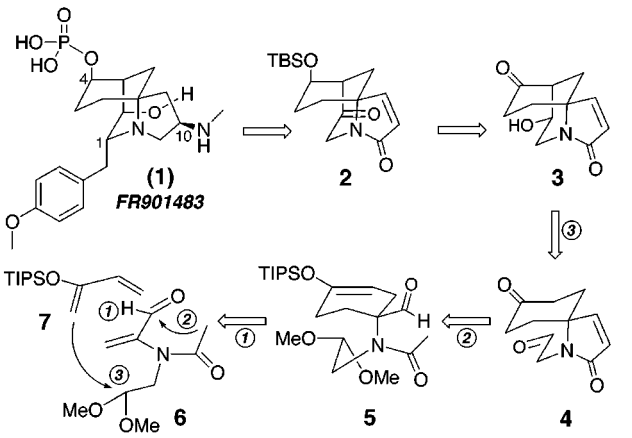
This promising biological activity coupled with an intriguing structure, secured by X-ray crystallographic analysis,[3] elicited our interest in FR901483 as a target for total synthesis.[6] In particular, the relatively uncommon 1-alkyl-1-aminocyclohexane substructure embodied in **1** might be assembled by application of cycloaddition reactions of 2-amidoacroleins, recently developed in our group.[7] A retrosynthetic analysis which outlines the implementation of this synthetic protocol is shown in Scheme 1. Thus, it was

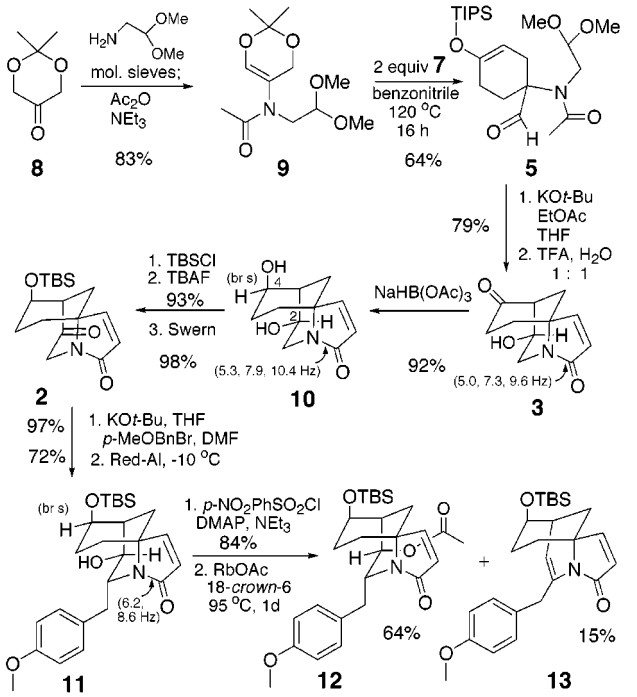
Scheme 1



envisaged that lactam **2** possessed the necessary functionality for the introduction of the C(1) *p*-methoxybenzyl and C(10) methylamino substituents via enolate alkylation and amination reactions, respectively. A number of scenarios, albeit multistep, are conceivable for the transposition of the *β*-hydroxy ketone functionality present in lactam **3** to the isomeric version in lactam **2**. Lactam **3** could be constructed by a "biomimetic" aldol ring closure of **4**,[8] which in turn could be fashioned by another aldol-type cyclization within aldehyde **5**. Finally, a Diels−Alder cycloaddition of silyloxydiene **7** with the 2-amidoacrolein **6** was expected to furnish **5**. It should be noted that this intermolecular cycloaddition was expected to install not only the central 1-alkyl-1-aminocyclohexane substructure of FR901483 but also both of the electrophilic and nucleophilic components, appropriately tuned, for the pending sequential aldol cyclizations. We report herein the realization of this plan in a total synthesis of racemic FR901483.

The precursor to amidoacrolein **6**, 1,3-dioxin **9**, was prepared using our standard procedure.[7] Thus, the imine derived from the condensation of 2,2-dimethyl-1,3-dioxan-5-one (**8**)[9] with aminoacetaldehyde dimethyl acetal was acetylated with acetic anhydride/triethylamine to afford dioxin **9** in 83% yield (Scheme 2). Retro Diels−Alder

Scheme 2



reaction of dioxin **9**[10] in warm benzonitrile (120 °C, 16 h) generated the amidoacrolein **6** which was trapped in situ with the silyloxydiene **7**[11] to afford the desired cycloadduct **5** (64%).[12] An aldol cyclization between the acetamide and proximate aldehyde functionalities within **5** proceeded smoothly (2 equiv of KOt-Bu, 10 equiv of EtOAc, THF, 0

(6) For previous synthetic work, see: (a) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391. (b) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280. (c) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (d) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (e) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (f) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (g) Bonjoch, J.; Diaba, F.; Puigbo, G.; Sole, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891. (h) Sole, D.; Peidro, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225.

(7) The preliminary account of this work will be reported separately.

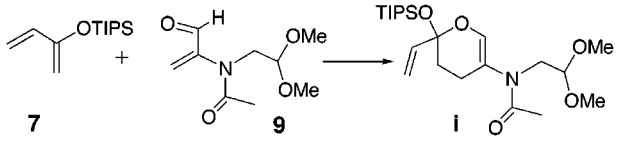
(8) The biosynthetic pathway to FR901483 most likely involves oxidative cyclization of a tyrosyltyrosine derivative to a spirocyclic lactam and subsequent aldol or Dieckman cylization to afford the tricyclic ring system. For the preparation of spirolactams from tyrosine amides, see refs 6c and 6d. For the preparation of desmethylamino FR901483 and FR901483 via a related internal aldol reaction, see refs 6e and 6f, respectively.

(9) Commercially available from Acros Organics or prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride. Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687.

(10) (a) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 1290. (b) Funk, R. L.; Bolton, G. L. *Tetrahedron Lett.* **1988**, *29*, 1111. (c) Funk, R. L.; Yost, K. J., III. *J. Org. Chem.* **1996**, *61*, 2598.

(11) Prepared following the procedure used for the preparation of 2-(*tert*-butyldimethylsilyloxy)butadiene. Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, D. A.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

(12) The heterocycloadduct **i** was also isolated in 12% yield and was the major product when 2-(trimethylsilyloxy)-1,3-butadiene was employed, most likely a reflection of the relative steric bulk of the two silyl substituents. For other examples of this steric effect, see: Rucker, C. *Chem. Rev.* **1995**, *95*, 1009.

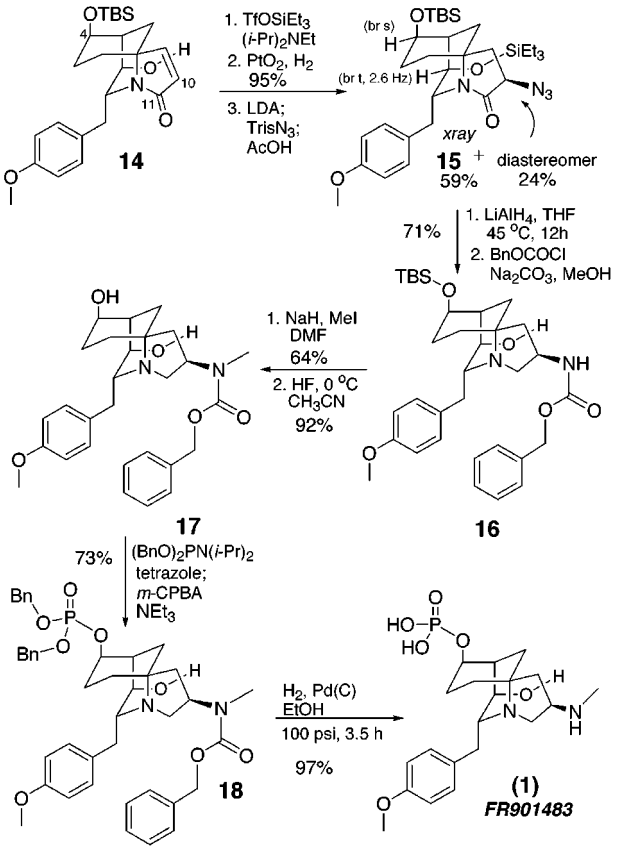


°C, 40 min) and directly afforded the corresponding conjugated lactam.[13] This product was of sufficient purity for the second aldol reaction, which was best accomplished under acidic conditions (1:1 TFA, H_2O, 0 °C → rt, 4 h), presumably proceeding through the keto aldehyde intermediate **4** en route to the desired β-hydroxy ketone in 79% yield for the two steps. Thus, the potential of amidoacrolein cycloaddition reactions in polycycle synthesis is validated by the assembly of tricycle **3** in just four steps from dioxanone **8**.

The next phase of the synthesis involved the transposition of aldol adduct **3** to the protected "aldol" adduct **2**. Accordingly, β-hydroxyketone **3** was subjected to conditions (2.5 equiv of $NaBH_4$, AcOH, rt, 30 min) which effected a directed reduction[14] of the carbonyl moiety of **3** and thereby introduced the axial C(4) hydroxyl functionality of **10** (92%) with complete stereocontrol. All attempts to either selectively oxidize or protect the C(2) hydroxyl of **10** were unsuccessful. However, the C(2) equatorial silyl ether of the bis-*tert*-butyldimethylsilyl ether derivative of **10** could be selectively cleaved (1 equiv of TBAF, rt, 1 h, 93% for the two steps) and the resulting hydroxyl oxidized to afford ketone **2** and thereby complete the aldol switch transformation. The enolate derivative of **10** (1 equiv of KO*t*-Bu, THF, 0 °C, 20 min) could be stereoselectively *p*-methoxybenzylated, provided that an inverse addition protocol was employed (addition of the enolate to 3 equiv of *p*-MeOBnBr, DMF, 0 °C, 20 min, 97%) in order to suppress dialkylation. A number of reducing agents were examined (e.g., L-Selectride, DIBAL-H, AlH_3, $NaBH_4$) in an attempt to stereoselectively reduce the resulting ketone to the desired C(2) axial alcohol **14** (Scheme 3). However, only the equatorial alcohol **11** was observed and, consequently, the C(4) stereogenic center was inverted by treatment of the nosylate derivative of **11** with rubidium acetate (5 equiv) in the presence of 18-crown-6 (5 equiv) to afford the desired acetate (64%) accompanied by, surprisingly, the *syn* elimination product, alkene **13** (15%), and recovered nosylate (16%).

The final stage of the synthesis (Scheme 3) required three major operations: introduction of the C(10) nitrogen atom, reduction of the C(11) carbonyl, and substitution of the C(4) phosphate moiety for the silyl ether functionality of alcohol **14**, in turn prepared by straightforward saponification of acetate **12** (7 equiv of KOH, MeOH, rt, 12 h, 74%). The first of these objectives was accomplished by protection of the hydroxyl group of **14** as the corresponding triethylsilyl ether, reduction of the unsaturated lactam (PtO_2, H_2, EtOH, 12 h, 95% for two steps), and azidification of the enolate derivative of the saturated lactam following Evans' protocol[15]

Scheme 3



(3 equiv of LDA, 3 equiv of trisyl azide, −78 °C, 5 min; 12 equiv of AcOH, −78 °C to rt, 1 h) to afford a diastereomeric mixture of azides. Although the diastereomers were easily separated by column chromatography ($\Delta R_f = 0.3$), stereochemical assignments derived from ^{1}H NMR spectroscopic analysis were not straightforward. Fortunately, X-ray crystallographic analysis of the major isomer showed that it possessed the desired stereochemistry at C(10) and, in addition, that the other stereogenic centers had been correctly assigned on the basis of the anticipated equatorial/axial cyclohexane proton coupling patterns for the diagnostic resonances.

Simultaneous reduction of the lactam and azide functional groups[16] with concomitant removal of the triethylsilyl protecting group was accomplished by subjecting lactam **15** to $LiAlH_4$ (5 equiv) to afford a diamino alcohol whose primary amine functionality was selectively acylated with benzyl chloroformate to deliver carbamate **16** (71% yield for two steps). The remaining carbon atom of the natural product was introduced by methylation of carbamate **16**, and deprotection of the TBS ether gave diol **17**. The selective phosphorylation of the less encumbered hydroxyl was capricious when tetrabenzyl pyrophosphate was employed but was reproducible if diol **17** was first converted to the

(13) The β-hydroxylactam was obtained when the cyclization was performed in the absence of ethyl acetate and could be dehydrated by standard procedures (MesCl, NEt_3). However, we serendipitously discovered in one experiment that ethyl acetate (a contaminant from the column chromatography of amide **5**) remarkably facilitated the in situ dehydration, presumably via transesterification to a β-acetoxylactam. The generality of this procedure is under investigation.

(14) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287. (c) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449. (d) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.

(15) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(16) For additional examples of the preparation of vicinal diamines by reduction of α-azido lactams/amides, see: (a) Hu, J.; Jagdmann, G. E. *Tetrahedron Lett.* **1995**, *36*, 3659. (b) Lopez-Herrera, F. J.; Sarabia-Garcia, F.; Heras-Lopez, A.; Pino-Gonzalez, M. S. *J. Org. Chem.* **1997**, *62*, 6056.

corresponding phosphite ester[6d] and then oxidized with *m*-CPBA in the presence of triethylamine to produce the dibenzyl phosphate **18**. Finally, hydrogenolysis of the dibenzyl phosphate and benzyl carbamate functionalities provided (±) FR901483 which was characterized as the hydrochloride salt. The ^{1}H and ^{13}C NMR and IR spectra were identical in all respects with the previously published spectra as well as more detailed spectra provided by the Fujisawa company.

In conclusion, we have completed the total synthesis of the potent immunosuppressant FR901483 in 22 steps and 2.4% overall yield from dioxanone **8**. In addition, we have demonstrated that the easily accessible trifunctional arrays of 2-amidoacroleins can be exploited in the rapid assembly of tricyclic ring systems. Additional applications of this methodology in natural product synthesis are now warranted and will be reported in due course.

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Supporting Information Available: Characterization data, detailed experimental procedures, and ^{1}H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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