Synthesis of Desmethylamino FR901483

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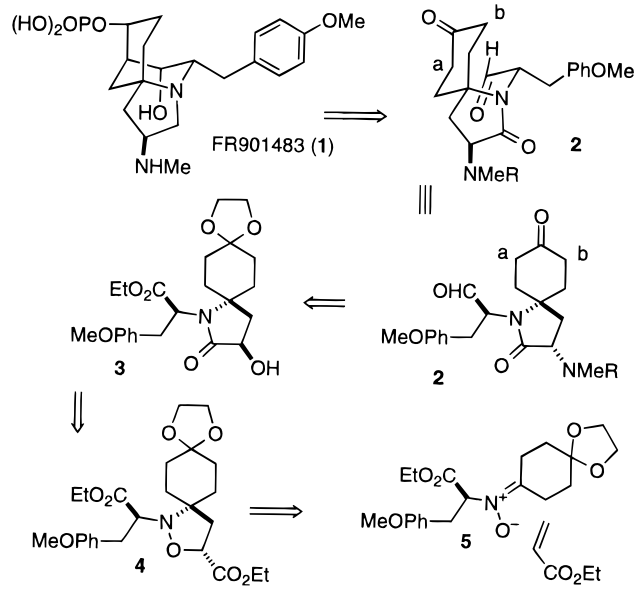
FR901483 (**1**), a novel immunosuppressant, has been isolated from the fermentation broth of *Cladobotrym* sp. No. 11231 by a Fujisawa group.[1] The structure has been determined X-ray crystallographically. FR901483 exerts potent immunosuppressive activity in vitro and significantly prolongs graft survival time in the rat skin allograft model, apparently by inhibition of purine nucleotide biosynthesis. The azatricyclic structure with a phosphate ester is structurally novel and is probably derived biosynthetically from a tyrosine dimer by oxidative coupling to close the pyrrolidine ring and an aldol reaction to form the tricyclic skeleton.

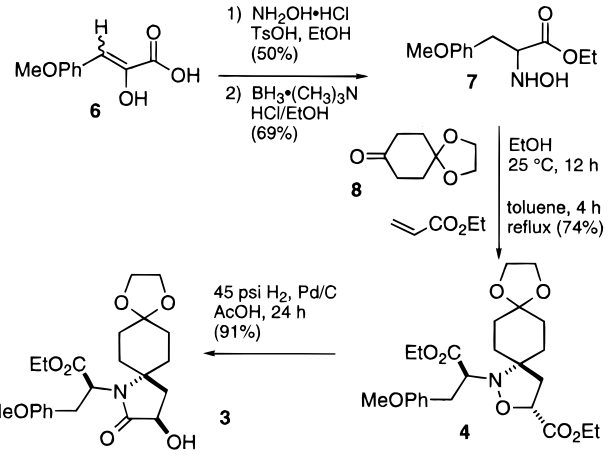
This analysis suggested that **1** could be prepared by an aldol reaction of keto aldehyde **2**. While this should provide



efficient access to the ring system, there were stereochemical concerns since the aldol reaction of **2** could give eight products. Enolization of the ketone can occur at carbons a or b, addition to the aldehyde can occur to give either the equatorial or axial alcohol, and enolization of the aldehyde will convert **2** to a diastereomer that would give four additional aldol products. Keto aldehyde **2** should be easily formed from lactam acetal ester **3**, which should be readily available from isoxazolidine **4**, which will be constructed by 1,3-dipolar cycloaddition of nitrone **5** with ethyl acrylate. Although this route to spirocyclic lactams is well-precedented with simple nitrones,[2] there are stereochemical questions in the cycloaddition with **5**,[3] which will give two diastereomers. Despite concerns about stereochemical control in the aldol and cycloaddition steps, the brevity of this route makes it an attractive approach to FR901483.[4]

p-Methoxybenzaldehyde and hydantoin were converted to (*p*-methoxyphenyl)pyruvic acid (**6**).[5] Reaction of **6** with hydroxylamine hydrochloride and TsOH in EtOH[6] afforded 50% of the oxime ester, which was reduced with $BH_3{\cdot}NMe_3$ in acidic ethanol[7] to give 69% of hydroxylamine **7**.

Condensation of hydroxylamine **7** with ketone **8** in EtOH gave nitrone **5**, which was treated with ethyl acrylate in toluene at reflux for 4 h to give 74% of a 9:1 mixture of isoxazolidine **4** and the diastereomer. This mixture was



reduced over 10% Pd/C under 45 psi H_2 in AcOH for 24 h to give 91% of a 9:1 mixture of lactam **3** and the diastereomer. Recrystallization in a mixture of CH_2Cl_2, hexane, and EtOAc gave the pure major diastereomer **3**. The stereochemistry was determined to be that needed for elaboration to FR901483 by X-ray crystallographic structure determination.[8]

The methylamino group was easily introduced by tosylation of **3** (TsCl, DMAP, Et_3N in CH_2Cl_2, 12 h) to give 99% of tosylate **9**, which was treated with NaN_3 in DMF to give 89% of the azide. Hydrogenation of the azide over Pd/C gave the amine, which was treated with BOC_2O to give carbamate **10** quantitatively. Methylation of **10** with NaH and MeI gave 86% of *N*-methylcarbamate **11**. Because of concerns about the possible stereochemical complexity of the aldol reaction of **2**, we decided to investigate this step first on model **13** lacking the protected *N*-methylamino substituent.

Reaction of tosylate **9** with NaI in acetone at reflux gave 99% of the iodide, which was reduced with $SnBu_3H$ and AIBN in toluene at reflux to give 97% of lactam **12**. Reduction of the ester with $LiBH_4$ in ether/THF afforded the primary alcohol, which was treated with HCl, AcOH, and water to cleave the ketal, affording 79% of the keto alcohol from **12**. Oxidation of the primary alcohol with Dess−Martin reagent provided 82% of the requisite keto aldehyde **13**, which can only give four aldol products, rather than the eight possible from **2**. Keto aldehyde **13** has a single chiral center, so that enolization of the aldehyde will have no effect in the racemic series.

We were delighted to find that the aldol reaction[9] occurred readily with acceptable stereocontrol. Cyclization of **13** with

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

(2) (a) Funk, R. L.; Daggett, J. U. *Heterocycles* **1987**, *26*, 2175. (b) Blum, C.; Hutchison, A. US Pat. US005286860A; *Chem. Abstr.* **1994**, *120*, 245160b.

(3) For a review of asymmetric 1,3-dipolar cycloadditions, see: Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(4) For other approaches to this ring system, 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.

(5) Billek, G. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 627.

(6) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

(7) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309.

(8) X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

(9) For the synthesis of azabicyclo[3.3.1]nonanes or bicyclo[3.3.1]nonanes by aldol reactions, see: (a) Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986. (b) Patir, S.; Rosenmund, P.; Götz, P. H. *Heterocycles* **1996**, *43*, 15.

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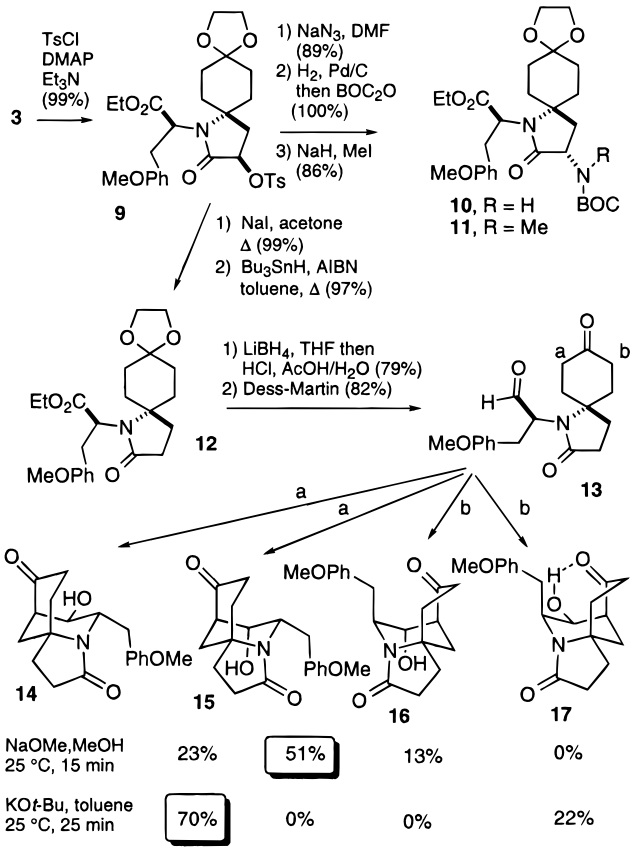
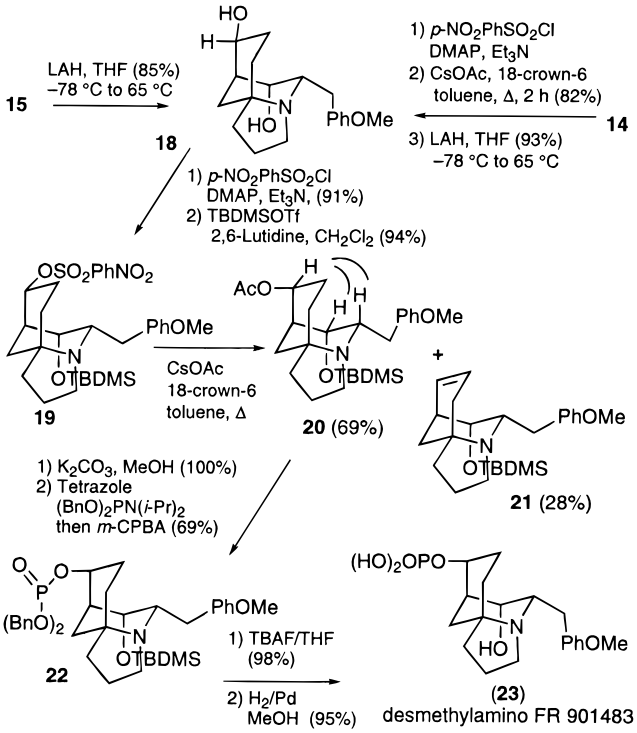


2.4 equiv of NaOMe in MeOH for 15−30 min at 25 °C provided 51% of the needed stereoisomer **15**, 23% of **14** with the required equatorial *p*-methoxybenzyl group but with the undesired equatorial hydroxyl group, and 13% of **16** with an axial *p*-methoxybenzyl group. On the other hand, aldol reaction with excess KO-*t*-Bu in toluene for 25 min at 25 °C afforded 70% of **14** and 22% of the fourth diastereomer **17**. The stereochemistry of the aldol adducts was assigned by analysis of the COSY and NOESY spectra.

These results indicate that the aldol reaction occurs mainly from carbon a, presumably because this leads to more stable products with an equatorial *p*-methoxybenzyl group. The required axial alcohol **15** is the major product (51%) with NaOMe in MeOH, while the undesired equatorial alcohol **14** is isolated in 70% yield as one of only two stereoisomers with KO-*t*-Bu in toluene. Fortunately, both **14** and **15** can be elaborated to desmethylamino FR901483 (**23**).

Reaction of **15** with LAH in THF at −78 °C to reflux reduced the ketone and the amide to give 85% of **18** stereospecifically. Reaction of **14** with *p*-nitrobenzenesulfonyl chloride, DMAP, and Et_3N in CH_2Cl_2 afforded the nosylate, which was inverted with CsOAc and 18-crown-6 in toluene at reflux[10] for 2 h to give the acetate of **15** in 82% yield from **14**. Reaction of this acetate with LAH reduced the acetate, ketone, and amide, providing 93% of **18**. Not surprisingly, LAH reduced the ketone of **15** from the less hindered exo face to give **18** with the undesired endo alcohol.

Inversion of the stereochemistry of the hydroxyl group was accomplished by reaction of **18** with *p*-nitrobenzenesulfonyl chloride, DMAP, and Et_3N in CH_2Cl_2 to selectively nosylate the less hindered equatorial alcohol in 91% yield. The axial alcohol was protected as the TBDMS ether with TBDMSOTf and 2,6-lutidine in CH_2Cl_2, providing **19** in 94% yield. Reaction of **19** with CsOAc and 18-crown-6 in toluene at



reflux[10] afforded 69% of the desired acetate **20** and 28% of the readily separable elimination product **21**. The stereochemistry of **20** was unambiguously established by the large NOEs between the three methine hydrogens, which are all on the endo face of the azabicyclo[3.3.1]nonane.

Elaboration of **20** to desmethylamino FR901483 (**23**) was accomplished by hydrolysis of the acetate with K_2CO_3 to give the alcohol quantitatively, which was treated with tetrazole and $(BnO)_2PN(i\text{-}Pr)_2$ to give the dibenzyl phosphite ester,[11] which was oxidized to give 69% of the dibenzyl phosphate with *m*-CPBA. Hydrolysis of the TBDMS group with TBAF in THF (98%), followed by hydrogenolysis of the dibenzyl phosphate (95%), afforded **23**. To our surprise, the ^1H NMR spectrum of **23** in CD_3OD indicated that a mixture of two compounds was present. We speculated that protonation of the tertiary amine by the phosphoric acid can occur on either face to give a mixture of diastereomers.[12] Treatment of **23** with K_2CO_3 gave the dipotassium salt of **23** as a single compound, whose spectral data correspond to those of **1**, except for the expected differences in the pyrrolidine ring.

In conclusion, we have developed an efficient approach to FR901483 and shown that the 1,3-dipolar cycloaddition proceeds with 9:1 selectivity and that the model aldol reaction of **13** gives either **14** or **15** with reasonable selectivity, depending on the reaction conditions. Both of these aldol adducts can be elaborated to desmethylamino FR901483, which has been prepared in 3.3% overall yield from **6** in 18 steps.

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Supporting Information Available: Experimental procedures, X-ray data for **3**, and ^1H and ^{13}C NMR spectral data for selected compounds (61 pages).

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