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Synthetic studies toward the immunosuppressant FR901483. Facile construction of the azatricyclic skeleton

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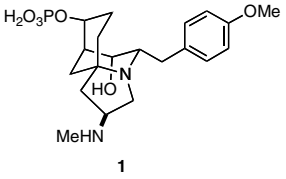
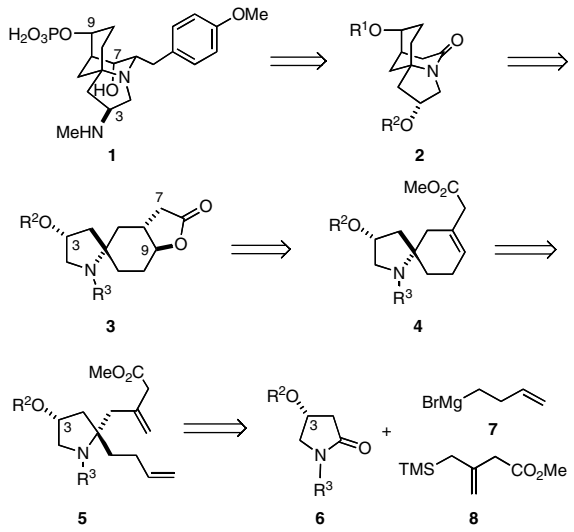
Abstract—A concise synthesis of the azatricyclic core structure of FR901483, a potent immunosuppressant, has been accomplished. The key elements of the approach involve a nucleophilic addition to an acyl iminium ion, a ring closing metathesis and a lactone–lactam rearrangement to provide the tricyclic structure.

A potent immunosuppressant, FR901483 (**1**), was isolated in 1996 from the fermentation broth of the fungal strain *Cladobotryum* sp. No. 11231 by Fujisawa Pharmaceutical Company in Japan.[1] The structure of **1** was initially determined by ^{1}H NMR and ^{13}C NMR spectroscopy, and the absolute configuration was elucidated by Snider and Lin,[2] who reported the first total synthesis of **1**. From a medicinal perspective, FR901483 is of interest because it prolongs graft survival time in the rat skin allograft model by inhibiting purine nucleotide synthesis, a mechanism of action that differs from that of common immunosuppressants like cyclosporin A and tacrolimus (FK-506).[1] Five other total syntheses of **1** have since been reported,[3] most of which were inspired by the postulated biosynthesis and feature an intramolecular aldol reaction to provide the azatricyclic core. We were attracted to the synthesis of FR901483 (**1**) as a means of developing new chemistry that may be of more general utility. Herein we describe our strategy for the synthesis of **1**, which differs from all of the previously described approaches, and the successful application of the underlying chemistry to the facile construction of the tricyclic core.



1

Our approach, which is outlined in Scheme 1, requires the stereoselective elaboration of the advanced intermediate **2** via α-hydroxylation of an amide enolate, introduction of the *p*-methoxybenzyl group, and refunctionalization of the protected hydroxyl group at C(3) to give the requisite methylamino moiety. We envisioned



1 **2** **3** **4** **5** **6** **7** **8**

Scheme 1.

Keywords: Additions to *N*-acyl iminium ions; Ring closing metathesis; Lactone–lactam rearrangement.
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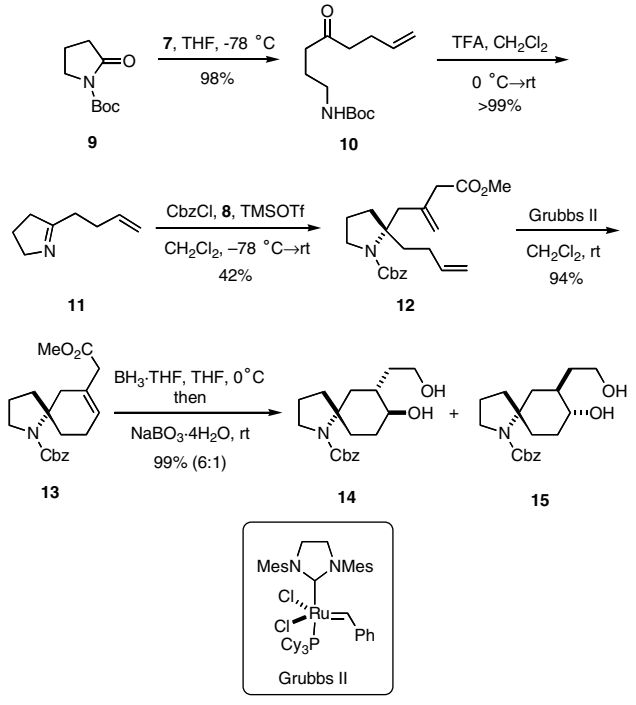
that the azatricycle **2** would be obtained via a base promoted lactone–lactam rearrangement of **3**, which would in turn be accessible from the β,γ-unsaturated ester **4** via a selective hydroboration–oxidation from the less hindered face[4] and a subsequent lactonization. The key step in preparing the spirocycle **4** is a ring closing metathesis (RCM) of the diene **5**,[5] which would be derived from the geminal dialkylation of the carbonyl group in **6** with **7** and **8**. The hydroxyl group in **6** would be expected to direct the addition of the silane **8** to the intermediate acyl iminium ion from the same face as the protected hydroxyl group in analogy with the findings of Woerpel and co-workers.[6]

In order to establish the feasibility of our strategy for fabricating the tricyclic skeleton of **1**, we embarked on a model study on a pyrrolidone substrate lacking the hydroxyl function at C(3). In the event, addition of the Grignard reagent **7** to the Boc-protected lactam **9** provided the linear ketone **10** in 98% yield (Scheme 2).[7] Removal of the Boc protecting group using trifluoroacetic acid and cyclization of the intermediate amino ketone gave the imine **11**[8] in quantitative yield. The imine **11** was then treated with CbzCl and the known allylsilane **8**[9] in the presence of trimethylsilyl triflate (TMSOTf) to deliver the diene **12** in 42% yield.[10] Silver and scandium triflates could also be used instead of TMSOTf to generate the intermediate *N*-acyl iminium ion and to provide **12** in similar yields. However, the addition did not proceed in the absence of a Lewis acid promoter.[11] The cyclization of **12** via RCM, a process we have exploited as a key step in the syntheses of a number of alkaloids and other natural products,[12] was performed using the Grubbs II catalyst,[13] to give the azaspirane **13** in 94% yield.



Scheme 2.

At this stage, we were faced with the challenge of inducing the stereoselective hydroboration of the azaspirane **13**, a reaction for which there was no precedent in azaspirocyclic systems. There are scattered reports, however that hydroboration of conformationally constrained cyclohexenes do lead to equatorial alcohols as the major products.[14] We thus anticipated that the borane reagent would approach the more stable conformer of **13** via a transition state in which the boron atom would be delivered preferentially from an equatorial-like orientation as shown in Figure 1 to establish the requisite stereochemistry at C(8) and C(9).

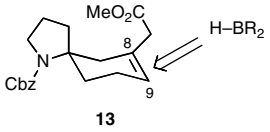
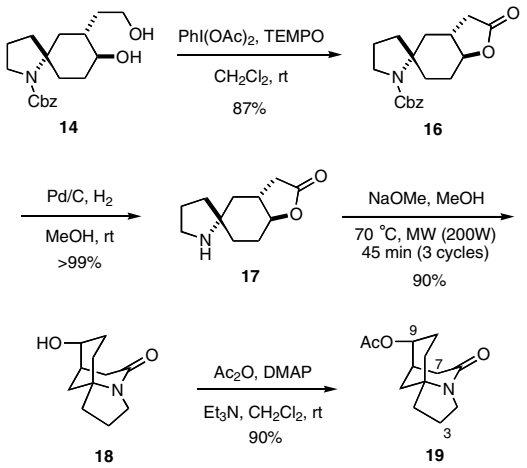


Figure 1.

We had originally envisioned that it would be possible to hydroborate the olefin without reducing the ester, but all attempts to do so were unsuccessful. Various reagents including BH_3·THF, BH_3·DMS, 9-BBN, thexylborane, and dicyclohexylborane were examined. Even the salt of the corresponding carboxylic acid, which should be unreactive, underwent reduction under conditions for hydroboration using BH_3·THF. Ultimately, we discovered that optimal conditions for the hydroboration and reduction of **13** involved initial reaction with BH_3·THF (3 equiv) and subsequent oxidation with $NaBO_3{\cdot}4H_2O$[15] to furnish a diastereomeric mixture (6:1) of **14** and **15** in 99% combined yield. Oxidation of the intermediate borane using the more conventional method of H_2O_2/NaOH was lower yielding. Although **14** and **15** were easily separable by column chromatography, it was not possible to unequivocally determine the relative stereochemistry of the major diastereomer at this stage.

That the hydroboration of **13** was accompanied by unavoidable reduction of the ester functionality was only an inconvenience as we were able to selectively oxidize **14** to the γ-lactone **16** in 87% yield using $PhI(OAc)_2$ and catalytic TEMPO (Scheme 3).[16,17] The Cbz-group was removed by catalytic hydrogenation giving amine **17** in virtually quantitative yield. The subsequent NaOMe-promoted lactone–lactam rearrangement in MeOH required heating in a microwave reactor to deliver the azatricycle **18** in 90% yield;[18] rearrangement using conventional heating was incomplete, even after two days of heating under reflux. Formation of a lactam from **17** verified our tentative assignment of the relative stereochemistry of the major diol diastereomer **14** in which the nitrogen atom and the two-carbon side chain are cis. The alcohol moiety of **18** was then acetylated to provide **19**,[19] which was more amenable to full structural characterization by NMR. An NOE interaction was observed between protons C(3)–H and C(7)–H_{ax} in **19** that was not observed in the lactone **16**.



Scheme 3.

In summary, we have developed a novel strategy to construct the azatricyclic skeleton of the potent immunosuppressant FR901483 (**1**). The approach features an addition of a functionalized allylsilane to an acyl iminium ion to provide an intermediate that undergoes a RCM to generate a spirocycle. Stereoselective hydroboration of the resultant olefin and a lactone–lactam rearrangement then delivers the tricyclic core of **1**. Application of this strategy to an enantioselective synthesis of **1** is in progress, and the results will be reported in due course.

Acknowledgments

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17. Spectral data for **16**: ^1H NMR ($CDCl_3$) δ 7.36–7.27 (comp, 5H), 5.11 (d, $J = 12.5$ Hz, 1H), 5.06 (d, $J = 12.5$ Hz, 1H), 3.91 (dt, $J = 6.5$, 11.0 Hz, 1H), 3.55–3.47 (m, 2H), 2.77–2.72 (m, 1H), 2.51–2.44 (comp, 3H), 2.31–2.26 (m, 1H), 2.11–2.01 (m, 2H), 1.92–1.87 (m, 1H), 1.82–1.72 (comp, 3H), 1.62–1.58 (m, 1H), 1.39–1.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.7, 154.4, 136.7, 128.5, 128.0, 127.9, 82.9, 66.6, 62.5, 47.8, 43.9, 40.1, 38.2, 36.1, 31.2, 25.4, 21.6; IR (neat) ν 2922, 1781, 1701, 1454, 1402, 1354, 1203, 1104, 1027 cm^{-1}.

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19. Spectral data for **19**: ^{1}H NMR ($CDCl_3$) δ 4.70 (dt, $J = 4.0$, 8.0 Hz, 1H), 3.48–3.44 (m, 1H), 3.40–3.35 (m, 1H), 3.10 (dd, $J = 14.0$, 6.2 Hz, 1H), 2.77 (dt, $J = 12.8$, 3.8 Hz, 1H), 2.67 (m, 1H), 2.07 (s, 3H), 1.99–1.95 (m, 1H), 1.89–1.78 (comp, 3H), 1.75–1.61 (comp, 4H), 1.23–1.16 (comp, 2H); ^{13}C ($CDCl_3$) NMR δ 172.6, 170.8, 71.8, 64.1, 49.1, 39.6, 34.8, 33.8, 26.9, 25.2, 24.9, 22.7, 21.4; IR (neat) ν 2926, 1732, 1644, 1407, 1246, 1088, 1027 cm^{-1}.