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A new synthetic entry to the tricyclic skeleton of FR901483 by palladium-catalyzed cyclization of vinyl bromides with ketone enolates

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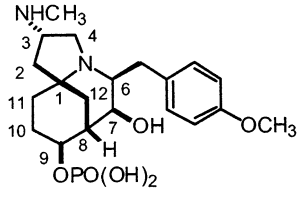
Abstract—A new synthetic entry to the FR901483 core is described. The Pd-mediated cyclization of amino-tethered vinyl halides and ketone enolates from the azaspiro[4.5]decan-8-ones **5** and **10** gives the functionalized 7,10a-methanoperhydropyrrolo[1,2-*a*]-azocines **1** and **11**, respectively.

FR901483, a natural potent immunosuppressant, contains a 2-azabicyclo[3.3.1]nonane framework and a pyrrolidine ring, which form an azaspirotricyclic skeleton (Fig. 1).[1] The four total syntheses reported so far for this natural product use an aldol process,[2–5] in which the C(7)–C(8) bond is formed, for the ring closure of the azatricyclic core. In this work, we report a new synthetic entry to the tricyclic skeleton of FR901483,[6–9] involving the formation of the C(7)–C(8) bond through a Pd-mediated intramolecular coupling of an amino-tethered vinyl halide and ketone enolate.[10–12]

Initial investigations to evaluate the feasibility of this strategy centered around the synthesis of **1**. To access the tricyclic skeleton of FR901483 through the proposed methodology we required a cyclization precursor embodying a 1-azaspiro[4.5]decan-8-one framework. Initially, to assemble this azabicyclic system we decided to use a protocol inspired by the classical procedure for preparing spirolactams from nitrocyclohexanes, based on the α-alkylation of a nitrocycloalkane followed by the reduction and subsequent lactamization of the nitro ester obtained (Scheme 1).[13,14]



FR901483

Figure 1.

The unknown 4-nitrocyclohexanone was achieved by a Diels–Alder reaction between nitroethylene and 2-(trimethylsilyloxy)-1,3-butadiene. Treatment of the resulting Diels–Alder adduct with ethylene glycol in benzene at reflux in the presence of a catalytic amount of TsOH furnished the nitro acetal **2**,[15] which on reaction with tetramethylguanidine (TMG) and methyl acrylate[16] gave the nitro ester **3**. This compound was quite resistant to the reduction process, but Pd/C and ammonium formate[17] provided the corresponding lactam, which after treatment with $NaBH_4$ in acetic acid[18] led to spiro compound **4**. Alkylation with 2,3-dibromopropene followed by hydrolysis of the acetal provided the amino tethered vinyl halide **5**, which was submitted to the Pd-promoted cyclization in the presence of KO*t*-Bu. NMR analysis of spiro compound **5** showed that in its preferred conformation the bond between the spiro carbon and the nitrogen atom is equatorial,[19] hence a conformational change is necessary for the success of this intramolecular vinylation,[20] in which a nucleophilic substitution takes place upon the vinylpalladium intermediate. This ring-forming reaction, involving the treatment of a THF solution of **5** with 0.2 equiv. of $Pd(PPh_3)_4$ and 1.5 equiv. of KO*t*-Bu at reflux tempera-

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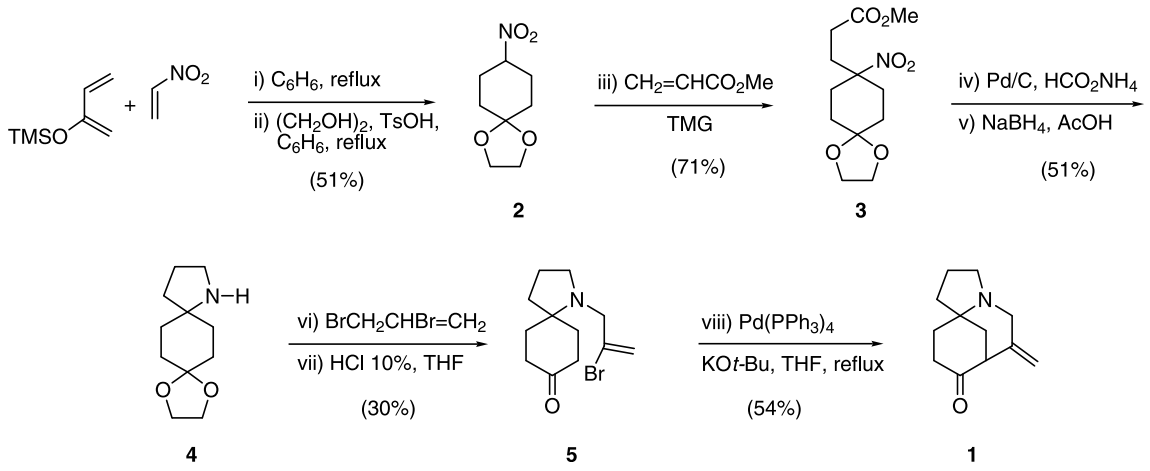
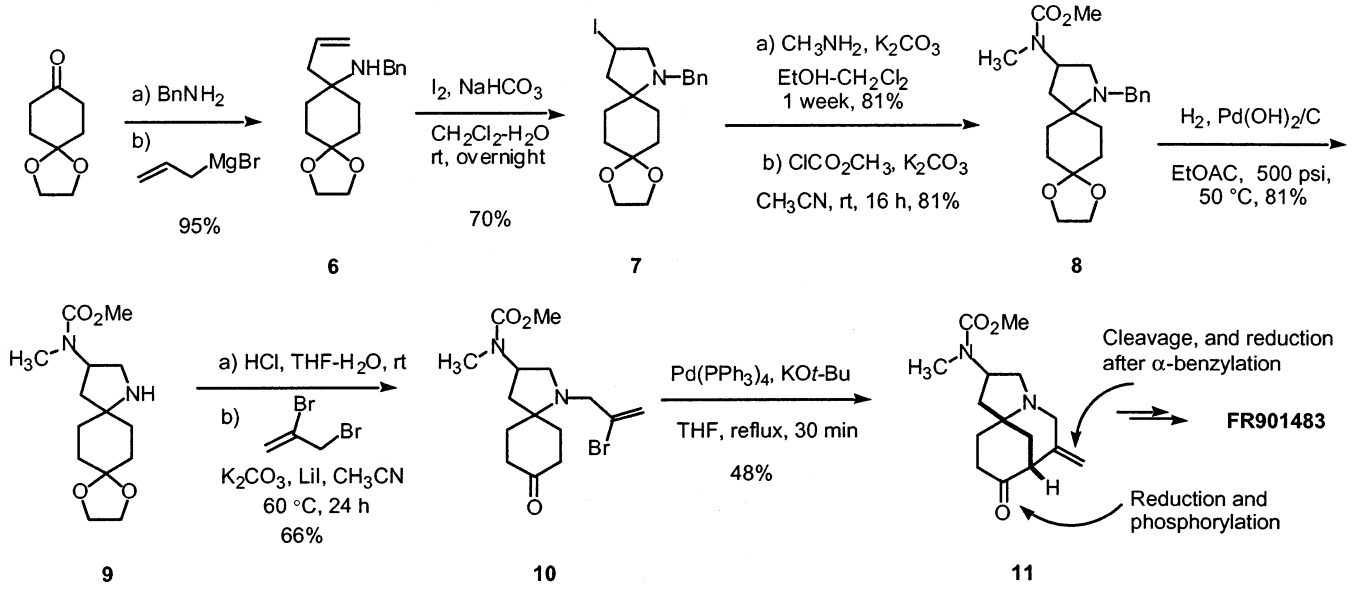


Scheme 1.

ture for 30 min, led to the azatricyclic compound **1** in 54% yield and constitutes a novel approach to the heterocyclic system found in FR901483.

This promising result prompted us to begin the synthesis of compound **11**, which embodies the amino group at C(3) present in FR901483 and thus could be considered as an advanced intermediate for the synthesis of this fungal metabolite.

The synthesis of compound **11** was carried out as depicted in Scheme 2.[21] The required azaspirocyclic system present in compound **10** was prepared following our procedure developed in the synthesis of a seco derivative of FR901483,[1a] in which the N–C(2) bond is formed by iodoaminocyclization of a homoallylamine. Thus, reaction of the monoethylene acetal of 1,4-cyclohexanedione and benzylamine followed by the addition of allylmagnesium bromide upon the initially formed imine gave **6**. Treatment of **6** with iodine provided the iodide **7**, which was converted into the corresponding methylamino derivative **8** either by treatment with a solution of methylamine in EtOH for one week followed by methoxycarbonylation, or by reaction with sodium azide followed by reduction of the azide intermediate with triphenylphosphine to give the corresponding primary amine (not shown), which sequentially reacted with methyl chloroformate and methyl iodide in the presence of sodium hydride. Both sequences to the 3-methylamino protected azabicyclic compound **8** gave similar overall yields. Debenzylation of the latter compound under a slight pressure of hydrogen rendered the amine **9** which, after deprotection of the acetal, was alkylated with 2,3-dibromopropene to give the vinyl halide **10** required for the key cyclization step. Treatment of **10** with 0.2 equiv. of $Pd(PPh_3)_4$ and 1.5 equiv. of KO-*t*Bu in refluxing THF gave **11** in 48% yield as a nearly equimolecular mixture of stereoisomers. It became clear from this result that the substituent at C(3) does not influence the regiocon-



Scheme 2. Synthesis of the azatricyclic core of FR901483.

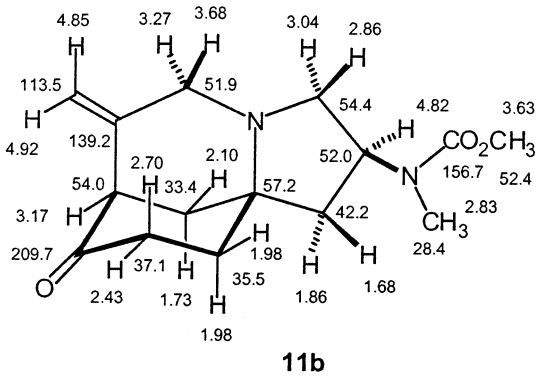


Figure 2. NMR (^{1}H and ^{13}C) data of compound **11b**.

trol in the formation of the enolate that reacts with the intermediate vinylpalladium species. The two stereoisomers formed were separated and the relative stereochemistry of compound **11b**, elucidated by 2D NMR spectra (COSY, HSQC, HMBC, NOESY), corresponded to that of FR901483 (Fig. 2).[22]

In summary, we report a new method for the synthesis of functionalized 7,10a-methanoperhydropyrrolo[1,2-*a*]-azocines embodying the tricyclic core of FR901483, consisting of Pd-promoted cyclization of vinyl bromides with ketone enolates. Work is underway to achieve a regiocontrolled process, install the side-chains and obtain the oxidation level of the natural product.

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15. All yields reported herein refer to isolated, pure materials, which had ^{1}H and ^{13}C NMR, and elemental combustion analysis or high-resolution MS characteristics in accordance with the proposed structures. ^{13}C NMR data (75 MHz, DEPT) for selected compounds of Scheme 1: (**1**). 22.5 (t), 35.2 (t), 35.5 (t), 37.2 (t), 38.6 (t), 52.5 (d), 54.7 (t), 55.4 (t), 57.8 (s), 112.6 (t), 142.0 (s), 210.8 (s). (**2**) 27.8 (t), 32.0 (t), 64.3 (t), 64.4 (t), 82.2 (d), 106.7 (s). (**3**) 28.2 (t), 30.8 (t), 31.2 (t), 34.7 (t), 51.6 (q), 64.1 (t), 64.2 (t), 89.3 (s), 106.9 (s), 172.0 (s). (**4**) 25.4 (t), 32.3 (t), 35.3 (t), 35.4 (t), 45.6 (t), 60.6 (s), 64.2 (t), 64.3 (t), 108.7 (s). (**5**) 21.1 (t), 31.8 (t), 34.2 (t), 38.9 (t), 50.7 (t), 56.7 (t), 61.8 (s), 116.6 (t), 133.1 (s), 211.1 (s).
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19. The NMR data of **5** showed the same pattern of chemical shifts as other related 1-azaspiro[4.5]decan-8-one derivatives in which the preferred conformation had been established by 2D NMR experiments (noted in Ref. 1a). See also: Fujimoto, R. A.; Boxer, J.; Jackson, R. H.; Simke, J. P.; Neale, R. F.; Snowhill, E. W.; Barbaz, B. J.; Williams, M.; Sills, M. A. *J. Med. Chem.* **1989**, *32*, 1259–1265.
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21. ^{13}C NMR data (75 MHz, assignment aided by HSQC) for selected compounds of Scheme 2: (**6**) 30.2 (t), 32.7 (t), 42.0 (t), 45.7 (t), 53.1 (s), 64.1 (t), 64.2 (t), 109.1 (s), 117.9 (t), 126.7 (d), 128.2 (2 d), 134.1 (d), 141.3 (s). (**7**, HSQC) 16.8 (C-3), 29.7 (C-10), 30.8 (C-6), 32.2 (C-9), 32.6 (C-7), 47.7 (C-4), 51.1 (CH_2Ar), 61.5 (C-2), 63.1 (C-5), 64.2 and 64.3 (OCH_2), 108.2 (C-8), 126.7 (*p*-Ar), 128.1 (*o*-, *m*-Ar), 140.0 (*ipso*-Ar). (**8**, HSQC) 25.0 (C-10), 28.4 (NMe), 30.9

(C-6), 32.3 (C-7), 32.9 (C-9), 38.2 (C-4), 51.9 (C-3), 52.0 (CH_2Ar), 52.4 (OMe), 53.6 (C-2), 62.5 (C-5), 64.1 and 64.2 (OCH_2), 108.4 (C-8), 126.5 (*p*-Ar), 128-0 (*o*-, *m*-Ar), 140.4 (*ipso*-Ar), 156.8 (CO_2Me). (**9**) 28.9 (t), 29.7 (t), 30.0 (q), 37.4 (t), 38.0 (t), 39.1 (t), 47.4 (t), 52.3 (q), 52.3 (d), 59.8 (s), 156.4 (s), 210.6 (s). (**10**, HSQC) 27.4 (C-10), 28.6 (NMe), 35.1 (C-6), 38.2 and 38.4 (C-7 and C-9), 39.2 (C-4), 51.7 (C-3), 52.6 (OMe), 53.5 (C-2), 56.2 (NCH_2), 62.1 (C-5), 117.5 ($=CH_2$), 132.5 (C=), 156.9 (CO_2Me), 210.2 (C-8). (**11a**) 28.6 (q), 33.4 (t), 35.3 (t), 36.7 (t), 40.8 (t), 51.9 (t), 52.0 (d), 52.5 (q), 54.0 (t), 57.0 (s), 112.8 (t), 140.8 (s), 156.7 (s), 209.7 (s). (**11b**), see Fig. 2; the ^1H NMR data were recorded at 600 MHz.

22. The most noteworthy NOESY correlations to deduce the relative configurations at C-1 and C-3 in compound **11b** were those observed between H-2 (δ 1.68) and N-Me and H-11ax.