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N-Methoxy-*N*-acylnitrenium Ions: Application to the Formal Synthesis of (±)-Desmethylamino FR901483

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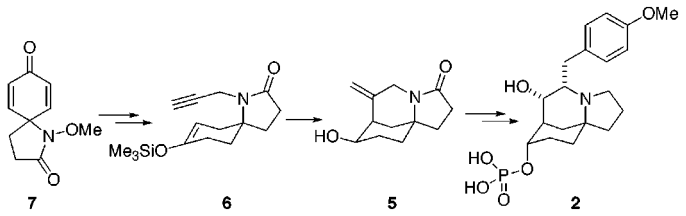
ABSTRACT



The formal synthesis of (±)-desmethylamino FR901483 (2) is described. Construction of the unique azatricyclic skeleton of 2 was accomplished by a sequence which involved (i) preparation of dienone 7 by an *N*-methoxy-*N*-acylnitrenium ion-induced spirocyclization, (ii) formation of 2-azabicyclo[3.3.1]nonane 5 by the 6-(*π-exo*)-*exo-trig* radical cyclization of 1,7-enyne 6, and (iii) installation of the C-5 *p*-methoxybenzyl side chain by Lewis acid-mediated alkylation of silyl enol ether 18.

The immunosuppressive natural products cyclosporin A and FK506 have played a key role in the advancement of transplant surgery and the treatment of autoimmune diseases.[1,2] However, these drugs have serious side effects[3] and as a result, there is a need to develop less toxic immunosuppressants that selectively inhibit organ rejection but leave the native immune system able to respond to viral, fungal, and tumor antigens. FR901483 (**1**) (Figure 1), a secondary metabolite of *Cladobotryium* sp. No. 11231 isolated by a group at Fujisawa, is a potent immunosuppressant which significantly increases the survival time of grafts in the rat allograft model.[4,5] This intriguing alkaloid contains 2-azabicyclo[3.3.1]nonane and pyrrolidine rings spiro-fused to form a azatricyclic skeleton previously unprecedented in Nature. It is not surprising then that synthetic interest in this target has been considerable. To date, syntheses of **1** have been reported by Snider,[6a,b] Sorenson,[6c] Ciufolini,[6d] and, most recently, by Funk.[6e] In addition, a number of approaches to the azatricyclic core of **1** have also been published.[7] We

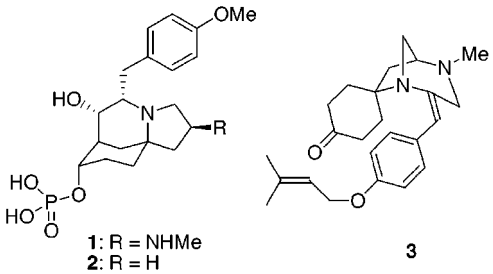


Figure 1. 1-Azaspiro[4.5]decane alkaloids: FR901483 (**1**), desmethylamino FR901483 (**2**), and TAN1251A (**3**).

(1) *Cyclosporin* A; Borel, J. F., Ed.; Elsevier Biochemical Press: Amsterdam, 1982.

(2) Schreiber, S. L. *Cell* **1992**, *70*, 365−368.

(3) (a) Myers, B. D.; Ross, J.; Newton, L.; Leutscher, J.; Perlroth, M. *N. Engl. J. Med.* **1984**, *311*, 699−705. (b) Shapiro, R.; Jordan, M.; Fung, J.; McCauley, J.; Johnston, J.; Iwaki, Y.; Tzakis, A.; Hakala, T.; Todo, S.; Starzl, T. E. *Transplant Proc.* **1991**, *23*, 920−923.

(4) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.

(5) Although the mode of action of **1** remains to be elucidated, it has been suggested that FR901483 may interfere with the biosynthesis of purine: refs 3 and 6e.

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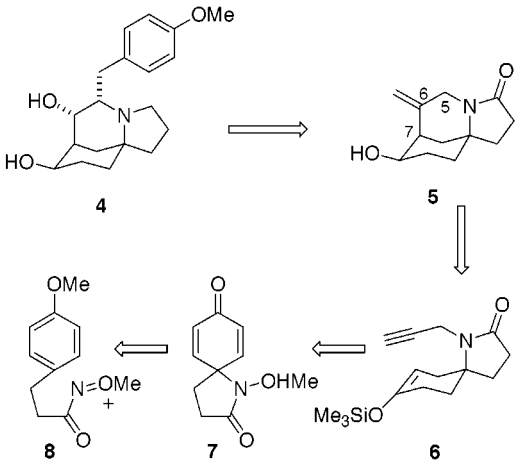
recently reported the synthesis of (+)-TAN1251A (**3**),[8] which shares a common 1-azaspiro[4.5]decane skeleton with FR901483, utlizing the Ar_1-5 spirocyclization of *N*-methoxyl-*N*-acylnitrenium ion **8** (Scheme 1).[9] Having completed the

Scheme 1. Retrosynthetic Analysis for Desmethylamino FR901483 (**2**)

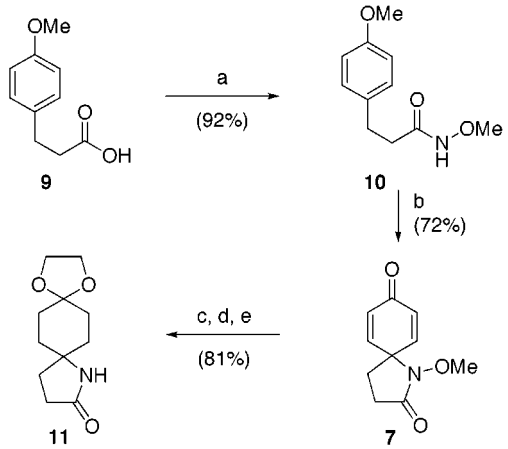


first leg of our divergent study, we now report the application of this chemistry to the formal synthesis of (±)-desmethylamino FR901483 (**2**).

As indicated in Scheme 1, the ultimate goal of the study reported here was tricycle **4**, an advanced intermediate in Snider's pioneering synthesis of desmethylamino FR901483 (**2**).[6a] We viewed **4** as being accessible from tricycle **5** through a sequence involving alkylation of the corresponding C-6 ketone. In common with other groups,[6] we deemed formation of the C-6/C-7 bond as the most convenient strategy to access the 2-azabicyclo[3.3.1]nonane ring system.[10] However, while all reported syntheses of **1** have achieved this bond formation through internal aldol reactions (or variants thereof), we were somewhat concerned about both the issue of C-6 stereocontrol and the likelihood of epimerization at the adjoining benzylic stereocenter. To side step these issues, we opted to prepare **5** from enol ether **6** via a 6-(*π-exo*)-*exo-trig* radical cyclization,[11−13] mediated by the addition of a stannyl radical,[14] and then capitalize on the facial dissymmetry of **5** to install the C-5 *p*-methoxybenzyl side chain and C-6 stereocenter at a late stage in the synthesis.[15] The cyclization precursor **6** could be obtained from dienone **7** which, in turn, would be accessible through the spirocyclization of the *N*-acyl-*N*-methoxynitrenium ion **8**, as reported in our synthesis of TAN1251A.[9]

Our route to **4** commenced from commercially available **9** which was coupled with methoxylamine hydrochloride (DCC, Et_3N) to provide **10** in excellent yield (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (a) $MeONH_2$·HCl, DCC, Et_3N, CH_2Cl_2, 0 °C → rt, 21 h; (b) i. $PhI(OCOCF_3)_2$, CH_2Cl_2, MeOH, 0 °C, 15 s; ii. $NaHCO_3$, H_2O, 0 °C, 5 min; (c) H_2 (1 atm), Pd/C, EtOAc, rt, 20 h; (d) $(CH_2OH)_2$, PPTS, PhH, reflux, 3.5 h; (e) i. Na, NH_3, THF, −78 °C, 30 min; ii. NH_4Cl, 0 °C → rt, 3 h.

Treatment of **10** with bis(trifluoroacetoxy)iodobenzene resulted in rapid spirocylization to furnish **7**. While this material proved prone to decomposition under acidic conditions, by reducing the reaction time to a mere 15 s and immediately quenching the reaction with aqueous $NaHCO_3$ we were able to prepare multigram quantities of **7** in reasonable yield. Dienone hydrogenation (H_2, Pd/C), protection of the resulting ketone as the 1,3-dioxolane acetal, and reductive cleavage of the *N*-methoxyl amide under Birch conditions[16] now provided pyrrolidone **11**. *N*-Alkylation with propargyl bromide[17] and acetal hydrolysis furnished **12** which

(6) (a) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442−6443. (b) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786. (c) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593−4596. (d) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765−767. (e) Funk, R. L.; Maeng, J. H. *Org. Lett.* **2001**, *3*, 1125−1128.

(7) (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280−8281. (b) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157−1162. (c) Sole, D.; Peidro, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225−2228. (d) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013−3015. (e) Brummond, K.; Lu, J. *Org. Lett.* **2001**, *3*, 1347−1349.

(8) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. PCT Int. Appl. WO 91 13,887,1991; *Chem. Abstr.* **1992**, *116*, 39780t.

(9) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053−1056.

(10) For a review of earlier synthetic studies on the 2-diazabicyclo[3.3.1]-nonane ring system, see: Bosch, J.; Bonjoch, J. *Heterocycles* **1980**, *14*, 505−529.

(11) For a leading reference to the application of 6-*exo-trig* radical cyclizations in synthesis, see: Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Rosón, C. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2809−2821 and references therein.

(12) For reports of 6-*exo-trig* cyclizations involving the addition of radicals to the distal terminus of enol and thioether acceptors, see: (a) Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* **1993**, *58*, 4293−4297. (b) Batty, D.; Crich, D.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1366−1368. (c) Reference 7b.

(13) The 6-*endo-trig* cyclization of alkenyl radicals with silyl enol ether acceptors has also been reported: Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 1355−1358.

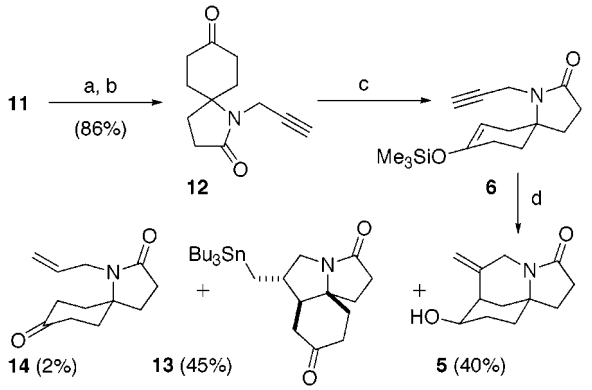
(14) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**, *109*, 2829−2831.

(15) While this work was in progress Bonjoch and co-workers reported a route to 2-azabicyclo[3.3.1]nonanes involving the 6-*exo-trig* cyclization of 1-(carbamoyl)dichloromethyl radicals with silyl enol ethers: ref 7b.

(16) Davies, S. G.; Smyth, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2467−2477.

was converted to the corresponding trimethylsilyl enol ether using trimethylsilyl iodide and $(TMS)_2NH$ (Scheme 3).[18] This

Scheme 3[a]



[a] Reagents and conditions: (a) i. NaH, DMF, 0 °C, 3 h; ii. $BrCH_2C{\equiv}CH$, 0 °C, 4 h; (b) 0.5 M HCl, acetone, 50 °C, 18 h; (c) i. $(Me_3Si)_2NH$, CH_2Cl_2, rt, 30 min; ii. Me_3SiI, −20 °C, 10 min then rt, 3 h; (d) i. Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), PhH (0.08 M), 80 °C, 4.5 h; ii. MeOH, HCl, H_2O, rt, 2 h.

material was found to be of sufficient purity, by ^1H NMR spectroscopy, to allow direct submission to the radical cyclization.

After screening a number of radical initiators and solvents, we found that slow addition of a mixture of *n*-Bu_3SnH and AIBN in benzene to a solution of **6** in the same solvent at reflux over 4.5 h followed by protodestannylation (HCl, MeOH) of the crude reaction mixture gave the desired cyclization product **5** together with tricycle **13**[19] and a small amount of reduction product **14**. Both **5** and **13** where isolated as single diastereomers whose relative stereochemistries were determined through a combination of COSY, NOESY, and HMQC experiments.

Interestingly, the outcome of the cyclization reaction displayed a significant temperature dependency, e.g., use of toluene as the reaction medium favored the translocation−cyclization pathway and led to the formation of **13** and **5** in a 2:1 ratio. As illustrated in Figure 2, we have rationalized these observations in terms of conformers **15** and **16**. While **15** can adopt the geometry necessary for 6-*exo-trig* cyclization to take place,[20] **16** is unable to cyclize. However **16** does meet the stereoelectronic requirements for 1,5-transfer of the adjacent allylic hydrogen atom.[21,22] The allylic radical thus generated then undergoes diastereoselective cyclization with the pendant vinyl stannane to form **13**.[23]

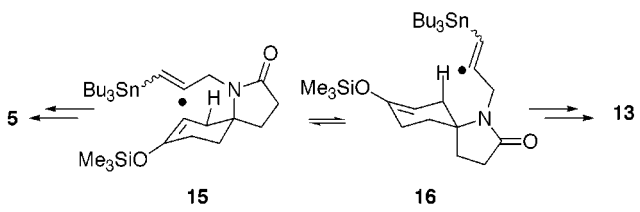
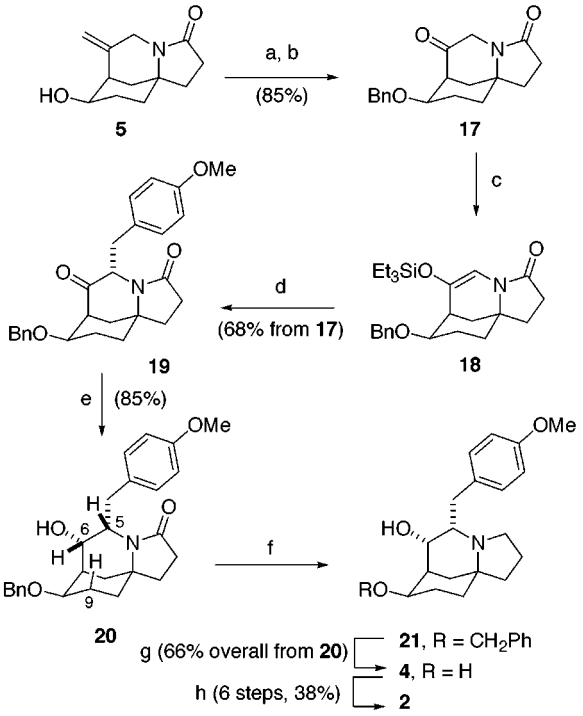


Figure 2. Competing radical pathways: 6-(*π-exo*)-*exo-trig* cyclization vs 1,5-hydrogen atom transfer/5-(*π-exo-*)-*exo-trig* cyclization.

Having established a protocol for formation of the 2-azabicyclo[3.3.1]nonane core of the target, we now proceeded to install the C-5 side chain. Protection of the hydroxyl group of **5** as the benzyl ether and oxidative cleavage of the *exo*-olefin gave ketone **17** (Scheme 4). Our

Scheme 4[a]



[a] Reagents and conditions: (a) BnBr, NaH, Bu_4NBr, DMF, rt, 6 h; (b) i. OsO_4, py, *tert*-BuOH, THF, H_2O, 30 min, rt; ii. $NaIO_4$, 6 h, rt; (c) i. KHMDS, THF, −50 °C, 15 min; ii. Et_3SiCl, −50 °C, 40 min; (d) **18**, *p*-MeOBnBr, $ZnCl_2{\cdot}Et_2O$, Et_2O, −78 °C → −25 °C, 16 h; (e) SmI_2, THF, H_2O, rt, 5 min; (f) $LiAlH_4$, THF, −78 °C → rt, 22 h; (g) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 3 h; (h) see ref 6a.

initial attempts to alkylate various metal enolates of **17** with *p*-methoxybenzyl bromide were unsuccessful, with low yields of **19** and significant amounts of the dialkylated product and starting material being obtained. Encouragingly, we found

(17) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802−4809.
(18) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730−732.
(19) This pyrrolizidine-based tricyclic ring system is present in the remarkable decacyclic alkaloid myrmicarin 663: Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, M.; Francke, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 77−80.
(20) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines and Synthetic Applications*; VCH: Weinheim, 1996; pp 77−82.
(21) (a) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81−82. (b) For an informative review of the application of radical translocation−cyclization reactions in synthesis, see: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103.

that this obstacle could be overcome by Lewis acid-mediated α-alkylation of enol ether **18**.[24] Thus, sequential treatment of **17** with KHMDS and Et_3SiCl furnished **18** which, after isolation, was treated with *p*-methoxybenzyl bromide and $ZnCl_2$ to give **19** as a single stereoisomer. Reduction of the C-6 ketone with samarium diiodide now cleanly generated the desired *exo*-alcohol **20** in good yield.[25] The relative stereochemistry of **20** was confirmed by a NOESY experiment which revealed correlations between H-6 and H-7 and the axially positioned proton at C-9.

Reduction of lactam **20** with $LiAlH_4$ in THF now gave the desired pyrrolidine **21** (28%) and, rather unexpectedly, diol **4** (39%), the product of benzyl ether cleavage.[26] Catalytic hydrogenolysis of **21** over $Pd(OH)_2/C$ now proceeded smoothly to give **4** in 99% yield. The combined overall yield for the conversion of **20** to **21** was 66%. As illustrated in Figure 3, the relative stereochemistry of **4** was confirmed by measurement of NOESY correlations. In addition, a comparison of the spectroscopic data collected for **4** with that reported by Snider indicated a close match.[6a]

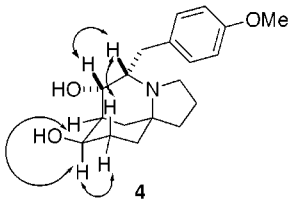


Figure 3. Selected NOESY correlations for 2-azabicyclo[3.3.1]-nonane **4**.

In summary, we have developed a synthetic route to **4** which Snider has previously carried to **2** in six steps with an overall yield of 38%.[6a] Accordingly, the work reported here represents a formal synthesis of desmethylamino FR901483 (**2**). Efforts to complete the asymmetric synthesis of FR901483 (**1**) are now underway and will be reported in due course.

Acknowledgment. We wish to thank the University of Illinois at Chicago, the National Institutes of Health (GM59157-01), and the UIC Campus Research Board for financial support. W.Z. thanks the University of Illinois for a University Graduate Fellowship.

Supporting Information Available: Full experimental procedures and spectral data for compounds **4**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 5421−5424.

(23) For a recent example of a 1,5-hydrogen atom transfer−cyclization process involving a vinyl stannane, see: Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856−1861.

(24) For a review of Lewis acid-mediated α-alkylations, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96−108.

(25) (a) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187−6189. (b) Molander, G. A. *Org. React.* **1994**, *46*, 211−367.

(26) For a report of the cleavage of a benzyl ether under similar conditions, see: Kutney, J. P.; Abdurahman, N.; Glestsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727−1735.