Table 2. Calculated (Gaussian 94, RHF, LANL2DZ) geometric parameters and charges (Mulliken) of $C_6F_5Xe\text{-}Z$ molecules[a].

$C_6F_5Xe\text{-}Z$	Molecule	Sym.	Selected geometric parameters[b]			Selected Mulliken charges			
			C(1)-Xe	Xe-Z	C(2)-C(1)-C(6)	Xe	C_6F_5	C(1)	Z
$C_6F_5Xe\text{-}F$	**1**	C_s	2.20	2.13	117.7	1.148	– 0.415	– 1.001	– 0.733
$C_6F_5Xe\text{-}C_6F_5$	**2**	C_1	2.34	2.34	117.4	0.980	– 0.490	– 0.687	– 0.490
$C_6F_5Xe\text{-}CN$	**3**	C_s	2.24	2.38	118.1	0.967	– 0.403	– 0.853	– 0.564[c]
for comparison see ref [12]									
$C_6F_5Xe\cdots F\text{-}AsF_5$		$\approx C_s$	2.12	2.56	121.3	1.083	– 0.134	– 1.032	– 0.948
$[C_6F_5Xe]^+$		C_s	2.16	–	122.7	0.886	0.114	– 0.870	–
FXeF		$D_{\infty h}$	–	2.03	–	1.306	–	–	– 0.653

[a] Z = second ligand bound to Xe^{II}; [b] in [Å] or [°], repectively; [c] Mulliken charges of C in the CN ligand: – 0.466.

The results of ab initio calculations for **1**–**3** show the following sequence of C-Xe distances: **2** > **3** > **1**, thus opposite to the sequence of Mulliken charges of the ligand Z in C_6F_5XeZ (Table 2). The comparison of data for **1** and $C_6F_5Xe\cdots FAsF_5$ [12] elucidates clearly the change when going from the asymmetric hypervalent C-Xe-F bond to a significant C-Xe$\cdots$F contact: the negative charge on Z gets closer to – 1 whereas the negative charge of the C_6F_5 group decreases significantly. The high anionic character of the C_6F_5 group in **1**–**3** agrees with the observed reactivities towards electrophiles and explains the lower-frequency chemical shifts of the *p*-F atom compared to $[C_6F_5Xe]^+$.

Experimental Section

1: A cold solution of $[NMe_4]F$ (25 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of $[C_6F_5Xe][AsF_6]$ (131 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL) at – 78 °C in an 8 mm FEP trap. The suspension was stirred over 2 days at – 78 °C until all the fluoride was consumed. The mother liquor was separated from solid $[NMe_4][AsF_6]$ and the quantity of **1** was determined (^{19}F NMR): 0.19 mmol, 70%. The other reactions were usually performed directly with the cold solutions of **1**. By evaporating CH_2Cl_2 at 10^{-2} hPa/ ≤ – 55 °C and later drying at ≤ – 40 °C **1** was obtained as a colorless solid, which after warming to 20 °C decomposed totally within 4 h. In CH_2Cl_2 solution noticeable decomposition proceeded above – 30 °C with the formation of C_6F_5H and traces of C_6F_5Cl.

2: A cold solution of $Cd(C_6F_5)_2$ (17 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of **1** (0.08 mmol) in CH_2Cl_2 (1.5 mL) at – 78 °C. After 5 min of stirring CdF_2 precipitated. The reaction was complete (^{19}F NMR) after further 10 min. The mother liquor was collected. In addition to **2** (0.06 mmol, 75%) the solution contained C_6F_5H (4 μmol) and $(C_6F_5)_2$ (2 μmol). The isolation of solid **2** was achieved as described for **1**. Solid **2** decomposes completely at room temperature within 1 h and in CH_2Cl_2 solution at – 40 °C within 9 h [$C_6F_5H:(C_6F_5)_2 = 1:0.1$].

3: A cold solution of Me_3SiCN (14 μL, 0.10 mmol; or the labeled ^{13}CN and $C^{15}N$ derivatives) in CH_2Cl_2 (0.5 mL) was added to a solution of **1** (0.10 mmol) and CH_2Cl_2 (1.5 mL) at – 78 °C and stirred. After 5 min the reaction was complete (^{19}F NMR: quantitative reaction) giving a 1:1 mixture of **3** and Me_3SiF. CH_2Cl_2 and Me_3SiF were distilled at ≤ – 55 °C/ 10^{-2} hPa and the white solid product was dried at ≤ – 40 °C/10^{-2} hPa. The solid spontaneously decomposed during the rapid warming to room temperature. CH_2Cl_2 solutions of **3** decomposed completely at – 40 °C within 2 h with the formation of C_6F_5CN and C_6F_5H (4:1).

Checking the purity of the cold solid products after dissolution in CH_2Cl_2 at – 78 °C showed in the case of **1** and **2** degrees of decomposition of up to 10% and for the thermally more sensitive product **3** up to 30%.

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An Enantiospecific Synthesis of the Potent Immunosuppressant FR901483**

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Bond formations induced by phenol oxidations have a rich history in organic chemistry. The influential two-step synthesis of usnic acid by Sir Derek Barton and co-workers[1] followed a set of simple rules that provided guidelines for rationalizing the course of oxidative phenolic radical couplings occurring in the biogeneses of a number of natural products.[2] We were

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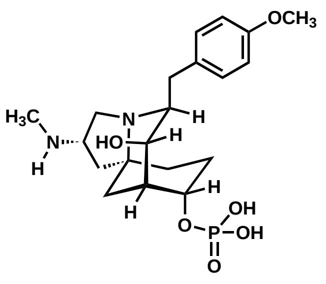


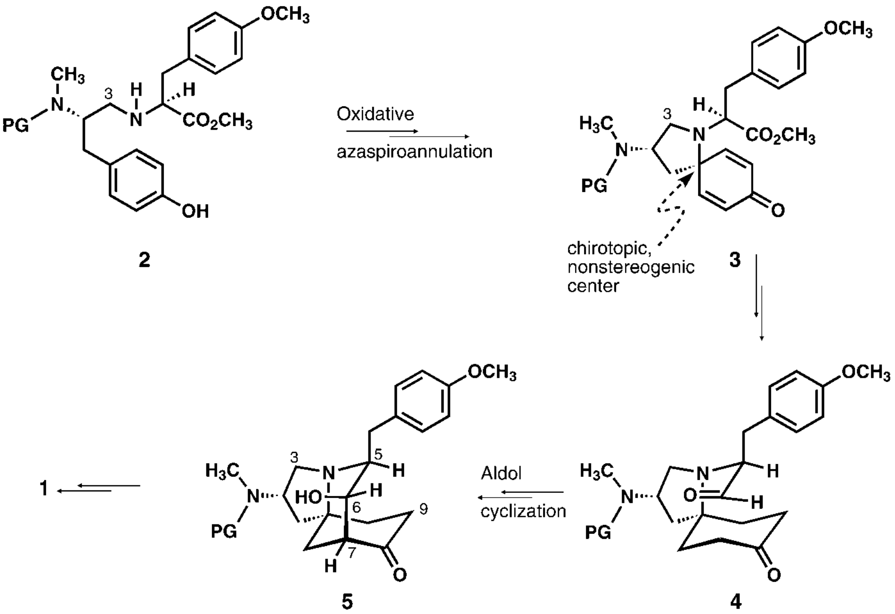
1: FR901483

drawn to the possibility that the azaspiro[4.5]decane nucleus of the powerful immunosuppressant FR901483 (**1**)[3] may form during the course of an oxidation of a tyrosine phenol moiety. This fungal-derived natural product comprises a novel tricyclic core framework and a salient monophosphate ester. At the outset, we noted that the intriguing structure of **1** seemed to conceal most of the atoms of two molecules of tyrosine and surmised that a laboratory synthesis of this substance could be facilitated by oxidative azaspiroannulation and intramolecular aldol addition reactions.[4] This general analysis was guided by the supposition that such reaction processes may have counterparts in the biosynthesis of this natural product. Our goal was to evaluate the feasibility of these reactions in the course of a synthesis of **1**. In this communication, we describe our convergent, enantiospecific synthesis of this promising immunosuppressant from L-tyrosine, which was executed along these lines.[5]

We anticipated that the N–C3 bond of an amino phenol **2** (Scheme 1) could be established in the course of a reductive coupling of two derivatives of L-tyrosine. The cornerstone of our strategy is the idea that exposure of **2** to an appropriate oxidant, such as iodobenzene diacetate,[6] could give rise to **3**. This appealing ring-closure would create the azaspiro[4.5]decane substructure of **1** and would not be complicated by the formation of diastereoisomers.[7–9] Our goal was to effect intramolecular carbon–nitrogen bond formations with substrates possessing the natural oxidation state at C-3, and we maintained our commitment to this plan even in the face of a potentially problematic oxidation of the secondary amine of **2** by hypervalent iodine-based oxidants. To construct the remaining ring and C-6 stereocenter of **1**, we hoped to utilize an intramolecular aldol reaction (see **4**→**5**).[10] Despite concerns about diastereoselectivity issues and potential epimerization problems, this process was deemed well-suited for the task of completing the architecture of **1**.[4] A synthesis of **5** would then allow us to explore an uncommon strategy for introducing the conspicuous phosphate ester of **1** (see below). A laboratory synthesis of **1** based on these concepts was achieved as described below.

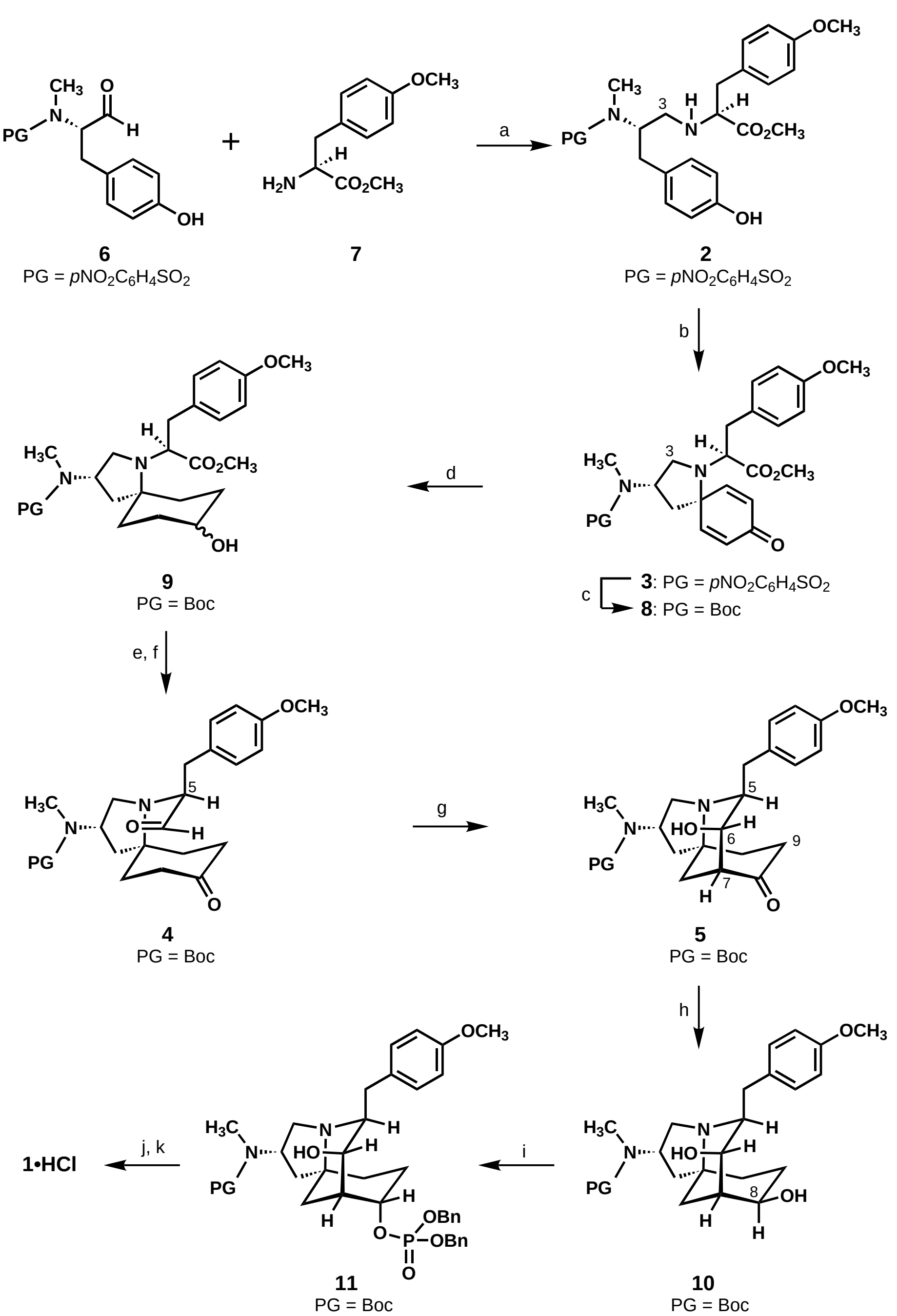
By straightforward reaction sequences, aldehyde **6** and amine **7** (Scheme 2) were created from commercially available *N*-Boc-L-tyrosine[11] and subsequently joined under reducing conditions to give **2** (PG = $p\mathrm{NO_2C_6H_4SO_2}$).[12] After much experimentation, we found that exposure of a solution of **2** in 1,1,1,3,3,3-hexafluoro-2-propanol to iodobenzene diacetate at room temperature resulted in the formation of azaspiro[4.5]decadienone **3** in 51% yield (based on 70% consumed **2**). The outcome of this ring closure, which established a significant portion of the structure of **1**, is noteworthy because analogous amino phenols are converted into fused ring systems under similar reaction conditions.[9c] At this stage, it was necessary to replace the 4-nitrobenzenesulfonamide protecting group[13] in **3** with a more compatible *tert*-butoxycarbonyl group (**3**→**8**, Scheme 2). Treatment of a solution of **8** in EtOAc/EtOH with Raney nickel under an atmosphere of hydrogen caused a complete reduction of the dienone moiety and afforded a mixture of epimeric alcohols shown as **9**. A reduction of the methyl ester with lithium aluminum hydride then produced a mixture of diols that could subsequently be converted by Swern oxidation into a single ketoaldehyde **4** in good overall yield.[14, 15]

Our intention was to create the C6–C7 bond and the remaining ring of **1** in the course of an aldol cyclization, although we were aware that this objective could be difficult to achieve owing to the various sites at which compound **4** could undergo deprotonation in the presence of bases. Nevertheless, we were mindful of the work of Snider and co-workers[4] and could convert **4** into the desired compound **5** in 34% yield under the conditions shown.[16] When **4** was dissolved in THF and treated with pyrrolidine (0.3 equiv) and AcOH (1.2 equiv) at 0°C→RT, the equatorial C-6 epimer of **5** was formed in 51% yield.[17] Despite the modest yield for the methoxide-induced aldol cyclization of **4**, we could procure significant quantities of hydroxyketone **5**.



Scheme 1. A strategy for the synthesis of FR901483 (**1**) featuring oxidative azaspiroannulation and aldol cyclization reactions. PG = protecting group.

Owing to its rigid and concave architecture, hydroxyketone **5** was converted into diol **10** in a completely diastereoselective fashion by hydrogenation. To achieve a synthesis of **1** from **10**, inversion of stereochemistry at C-8 and production of a C-8 monophosphate ester are required. Gratify-



Scheme 2. Synthesis of FR901483 (**1**)·HCl: a) **6** (1.0 equiv), **7** (1.5 equiv), NaBH(OAc)$_3$ (1.5 equiv), 4 Å MS, 0 °C, 1 h, then RT, 24 h, 80 %; b) PhI(OAc)$_2$, (1.1 equiv), (CF$_3$)$_2$CHOH, RT, 10 min, 51 % (based on 70 % consumed **2**); c) NaSPh (1.5 equiv), DMSO, RT, 3 h; then (Boc)$_2$O (2 equiv), pyr (2 equiv), RT, 12 h, 71 % from **3**; d) H$_2$, Raney Ni, EtOAc/EtOH (2:1), RT, 15 h, 93 %; e) LiAlH$_4$ (3 equiv), THF, -78 °C, 1 h then 0 °C, 2 h, 90 %; f) (COCl)$_2$ (8 equiv), DMSO (16 equiv), CH$_2$Cl$_2$, -78 °C, 30 min; then *i*Pr$_2$NEt (20 equiv), -78 °C, 30 min; then 0 °C, 1 h, ≈100 %; g) NaOMe (1.1 equiv), MeOH, 0 °C, 2 h, 34 % of **5** (74 % total yield of aldol adducts); h) H$_2$, Raney Ni, EtOAc/EtOH (1:10), RT, 4 h, 92 %; i) dibenzyl hydrogen phosphate (6 equiv), tris(4-chlorophenyl)phosphine (3 equiv), DIAD (3 equiv), Et$_3$N (10 equiv), toluene, RT, 26 h, 37 % of **11** + 17 % of alkene; j) H$_2$, Pd/C, MeOH, RT, 5 h, 95 %; k) 4 N HCl, dioxane, 0 °C, 30 min; then RT, 2 h, 84 % of **1**·HCl (precipitated from MeOH with Et$_2$O). MS = molecular sieves, RT = room temperature, Boc = *tert*-butoxycarbonyl, pyr = pyridine, DIAD = diisopropyl azodicarboxylate, Bn = benzyl.

ingly, it was possible to accomplish both objectives in a single step by a Mitsunobu reaction between **10** and dibenzyl hydrogen phosphate (**10** → **11**).[18, 19] Despite its modest yield, this type of reaction is, to our knowledge, unprecedented in complex natural-product total synthesis, can be achieved in the presence of a free C-6 hydroxyl group,[20] and directly produces the natural stereochemistry and the phosphate ester moiety at C-8. Hydrogenolysis of the dibenzylphosphate of **11** followed by cleavage of the Boc group afforded FR901483 (**1**) as its hydrochloride salt.

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[11] Aldehyde **6** was prepared from the known amino ester **7** by the following reaction sequence: 1) 4-nitrobenzenesulfonyl chloride, $i\mathrm{Pr_2NEt}$, $\mathrm{CH_2Cl_2}$, RT, 0.5 h, 88%; 2) MeI, $\mathrm{K_2CO_3}$, DMF, RT, 1 h, 91%; 3) $\mathrm{AlCl_3}$, EtSH, $\mathrm{CH_2Cl_2}$, RT, 2.5 h, 92%; 4) $\mathrm{BH_3\cdot THF}$, THF, 0°C, 1 h; then RT, 2 h, 94%; 5) $\mathrm{SO_3\cdot pyr}$, DMSO, $i\mathrm{Pr_2NEt}$, RT, 10 min, approximately 100% (**6** was used in crude form).

[12] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.

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[14] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165–185.

[15] Aldehyde **4** was used in crude form because partial epimerization at C-5 occurred during chromatography on silica. For stimulating discussions of the stability and chemistry of optically active α-amino aldehydes, see: A. G. Myers, D. W. Kung, B. Zhong, *J. Am. Chem. Soc.* **2000**, *122*, 3236–3237.

[16] Compound **5** was the major component of a mixture of three aldol cyclization products. The equatorial C-6 epimer of **5** was formed in approximately 19% yield and a compound tentatively assigned as a C6–C9 aldol adduct was obtained in approximately 21% yield.

[17] This aldol procedure affords **5** in 17% yield and a substance that we tentatively assigned as the C6–C9 aldol adduct in 12% yield (see ref. [16]). We have not yet been able to utilize the C-6 epimer of **5** in our synthesis.

[18] a) O. Mitsunobu, K. Kato, J. Kimura, *J. Am. Chem. Soc.* **1969**, *91*, 6510–6511; b) D. A. Campbell, J. C. Bermak, *J. Org. Chem.* **1994**, *59*, 658–660.

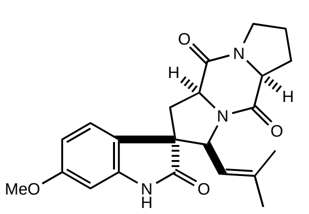
[19] The results of COSY, HMQC, and ROESY NMR spectroscopy experiments were fully consistent with the structure of compound **11**. In addition to **11**, a C8–C9 alkene was formed in 17% yield due to elimination.

[20] Mitsunobu reactions are sensitive to steric environments; therefore, site-selective modification of polyols is feasible. For examples, see: a) D. A. Evans, J. R. Gage, J. L. Leighton, *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453; b) R. S. Coleman, J. R. Fraser, *J. Org. Chem.* **1993**, *58*, 385–392.

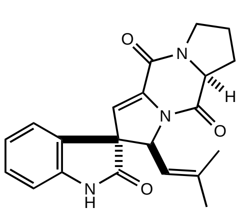
Total Synthesis of (−)-Spirotryprostatin B and Three Stereoisomers**

Larry E. Overman* and Mark D. Rosen

Small-molecule natural products play an important role in contemporary studies to understand and control cellular proliferation.[1] From the fermentation broth of the fungus *Aspergillus fumigatus*, Osada and co-workers recently identified a group of novel diketopiperazine alkaloids that inhibit G2/M phase progression of the mammalian cell cycle at micromolar concentrations.[2, 3] Spirotryprostatins A (**1**) and B (**2**) are the most complex of these alkaloids,[2] all of which appear to arise biosynthetically by prenylation of a diketopiperazine derived from tryptophan and proline.



Spirotryprostatin A (**1**)



Spirotryprostatin B (**2**)

The novelty of their structures and the potential utility of cell-cycle inhibitors make the spirotryprostatins attractive targets for total synthesis. If such an undertaking were to be stereocontrolled, a central challenge would be to relate the stereochemistry of the quaternary spiro carbon to the adjacent stereocenter bearing the 2-methylpropenyl side chain. In 1998, Danishefsky and co-workers reported the total synthesis of spirotryprostatin A (**1**), which constituted the first total synthesis in this area.[4] Earlier this year, the groups of Williams,[5] Danishefsky,[6] and Ganesan[7] disclosed inaugural total syntheses of (−)-spirotryprostatin B (**2**).

Our approach to spirotryprostatin B (**2**) and congeners is distinctly different from the previous syntheses (Scheme 1). The logic of our strategy is to correlate the relative configurations of C3 and C18 in **2**[8] to the geometry of the internal double bond of a triene cyclization substrate **4** by capitalizing on the stereochemical selectivity of two palladium-catalyzed

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.