Total Synthesis of (−)-FR901483

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Abstract: The first synthesis of the immunosuppressant (−)-FR901483 (**1**) has been accomplished in 2% overall yield from *O*-methyltyrosine methyl ester (**31**) in 22 steps establishing the absolute stereochemistry of the natural product. A 1,3-dipolar cycloaddition of nitrone **5b** with ethyl acrylate gave predominantly isoxazolidine **4b** that was hydrogenated to give azaspirolactam **3b** with the correct absolute and relative stereochemistry for the synthesis of **1**. Elaboration of **3b** to keto aldehyde **38** and an intramolecular aldol reaction gave tricyclic keto alcohol **40** with reasonable selectivity using KO-*t*-Bu in *t*-BuOH. Further elaboration afforded (−)-**1** in 9 steps with spectral data identical to that of the natural product.

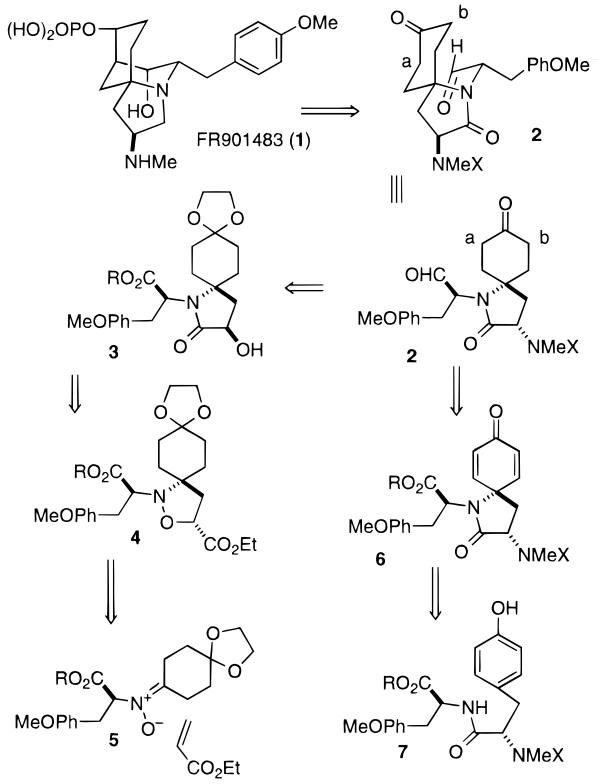
Introduction

The novel immunosuppressant FR901483 (**1**) was isolated from the fermentation broth of *Cladobotrym* sp. No. 11231 by a Fujisawa group.[1] The structure was determined X-ray crystallographically, and the absolute stereochemistry was not assigned. 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 may be derived biosynthetically from the methylated tyrosine-tyrosine dipeptide **7** by oxidative coupling to provide spirocycle **6** (see Scheme 1).[2] The tricyclic skeleton of **1** may be biosynthesized by an aldol reaction of keto aldehyde **2**. This hypothesis is supported by the fact that dipeptide **7** is derived from two molecules of tyrosine with the same stereochemistry.

This analysis suggested that **1** might be accessible by an aldol reaction of keto aldehyde **2**. While this approach should provide efficient access to the ring system, there were stereochemical concerns since the aldol reaction of **2** can give eight products. Enolization of the ketone can occur to either carbon 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 can be constructed by a highly convergent 1,3-dipolar cycloaddition of nitrone **5** with ethyl acrylate. Although this route to spirocyclic lactams is well-precedented with simple nitrones,[3] there are untested stereochemical questions in the cycloaddition with **5**,[4] 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.[5]

Scheme 1



Results and Discussion

Preparation of Spirocycle 3a. Hydroxylamine **9**, the precursor to nitrone **5**, can be prepared easily in optically pure form as described below. Racemic **9** was used for initial studies of the stereochemistry of the cycloaddition and aldol reactions.[6] *p*-Methoxybenzaldehyde and hydantoin were converted to

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

(2) For a recent oxidative coupling in a related system with $PhI(OAc)_2$, see: Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667−4670.

(3) (a) Funk, R. L.; Daggett, J. U. *Heterocycles* **1987**, *26*, 2175−2182. (b) Blum, C.; Hutchison, A. US Pat. US005286860A; *Chem. Abstr.* **1994**, *120*, 245160b.

(4) For a review of asymmetric 1,3-dipolar cycloadditions, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425.

(5) For other approaches to this ring system, see: (a) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391−1402. (b) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280−8281.

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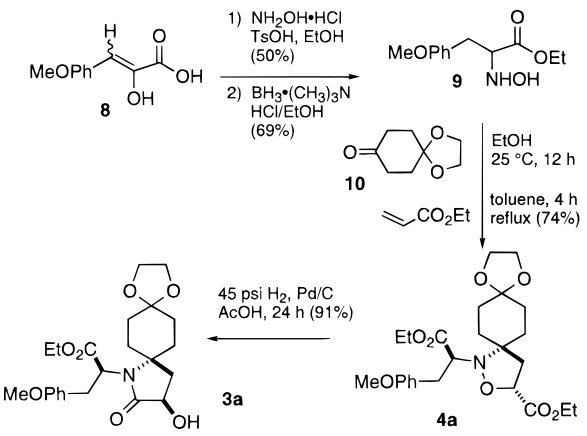
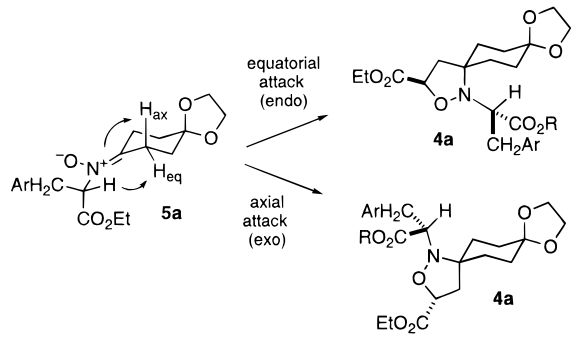
p-methoxyphenylpyruvic acid (**8**).[7] Reaction of **8** with hydroxylamine hydrochloride and TsOH in EtOH[8] afforded 50% of the oxime ethyl ester, which was reduced with borane-trimethylamine in acidic ethanol[9] to give 69% of hydroxylamine **9**.



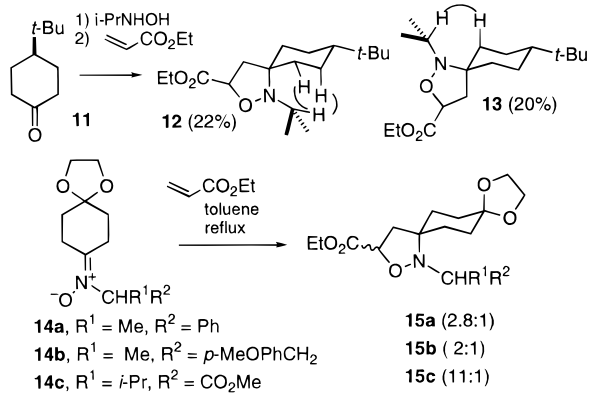
Condensation of hydroxylamine **9** with ketone **10** in EtOH at 25 °C for 12 h gave nitrone **5a**, which was treated with ethyl acrylate in toluene at reflux for 4 h to give 74% of a 8−9:1 mixture of isoxazolidine **4a** and the diastereomer. This mixture was reduced over 10% Pd/C under 45 psi H_2 in AcOH for 24 h to give 91% of 8−9:1 mixture of lactam **3a** and the diastereomer. Recrystallization in a mixture of CH_2Cl_2, hexane and EtOAc gave diffraction-quality crystals that still contained a little of the minor diastereomer. To our delight, X-ray crystallographic structure determination established that the stereochemistry of the major diastereomer **3a** was that needed for elaboration to FR901483.[10]

Analysis of the Stereochemistry of the Nitrone Cycloaddition. Although high levels of stereocontrol in cycloadditions of nitrones prepared from aldehydes is well-precedented, stereocontrol in cycloadditions of nitrones prepared from ketones is much rarer.[4] We therefore briefly studied the factors responsible for the selective formation of lactam **3a** from nitrone **5a**. Examination of the ^1H NMR spectrum of **5a** indicated that



the cyclohexane ring existed predominantly in one of the two chair conformers. For instance H_{ax} absorbs at δ 2.59 (ddd, 1, J = 15.6, 9.6, 6.0 Hz) and H_{eq} absorbs at δ 2.67 (ddd, 1, J = 15.6, 6.4, 6.4 Hz). These nonaveraged coupling constants indicate that steric interactions between the substituents on the chiral center adjacent to the nitrogen stabilize one chair conformer relative to the other. A large NOE between the methine hydrogen and H_{eq}, a smaller NOE between the methine hydrogen and H_{ax}, and the absence of an NOE between the ring hydrogens and the benzylic hydrogens suggests that the predominant conformation is that shown below. If this most stable conformation is also the most reactive conformation, the major product **4a** can be formed by equatorial attack (top face) with the acrylate ester endo in the transition state and/or by axial attack (bottom face) with the acrylate ester exo in the transition state.

To our surprise, the preference for axial versus equatorial attack in nitrones derived from cyclohexanone was not known. We therefore prepared the nitrone from 4-*tert*-butylcyclohexanone (**11**) and isopropylhydroxylamine and treated it with ethyl acrylate in toluene at reflux to give a 42% unoptimized yield of a 1.1:1 mixture of **12** formed by equatorial attack and **13** formed by axial attack. The stereochemistry of the cycloaddi-



tions was determined by the NOEs shown. The very slight preference for equatorial attack indicates that **4a** is either formed by both the pathways shown or that the substituent on the nitrone nitrogen has a profound effect on the direction of acrylate approach. For instance, it is possible that the ester group of **5a** in the most stable conformation blocks the bottom face so that equatorial attack with an endo ester group could be the predominant pathway. In an attempt to combine a chiral nitrone with a rigid cyclohexanone, we investigated cycloadditions with cyclohexanone **11** and chiral hydroxylamine **9**, which gave two diastereomeric nitrones. These nitrones were separated, but equilibrated under the cycloaddition conditions, so that both gave an intractable 12:4.8:2.4:1 mixture of four cycloadducts.

We then returned to cycloadditions of nitrones **14** derived from **10** and other chiral hydroxylamines. Nitrone **14a** derived from α-methylbenzyhydroxylamine did not show a preference for a single chair conformer and gave **15a** as 2.8:1 mixture of stereoisomers. Nitrone **14b**, in which the carboethoxy group of **5a** has been replaced by a methyl group, showed the same conformational preferences as **5a**, but gave **15b** as a 2:1 mixture of isomers. Finally, the conformation of nitrone **14c** prepared from valine[11] could not be determined because of overlapping absorptions. However, this nitrone gave **15c** as an 11:1 mixture of stereoisomers suggesting that optimal stereocontrol is obtained with a hydrogen, an ester group, and a large alkyl group on the chiral center.

Investigation of the Aldol Reaction in a Model System. Because of concerns about the possible stereochemical complexity of the aldol reaction of **2**, we decided to investigate this

(6) For a preliminary communication describing the application of this chemistry to the synthesis of desmethylamino FR901483, see: Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442−6443.

(7) Billek, G. *Org. Synth. Coll. Vol. V* **1973**, 627−632.

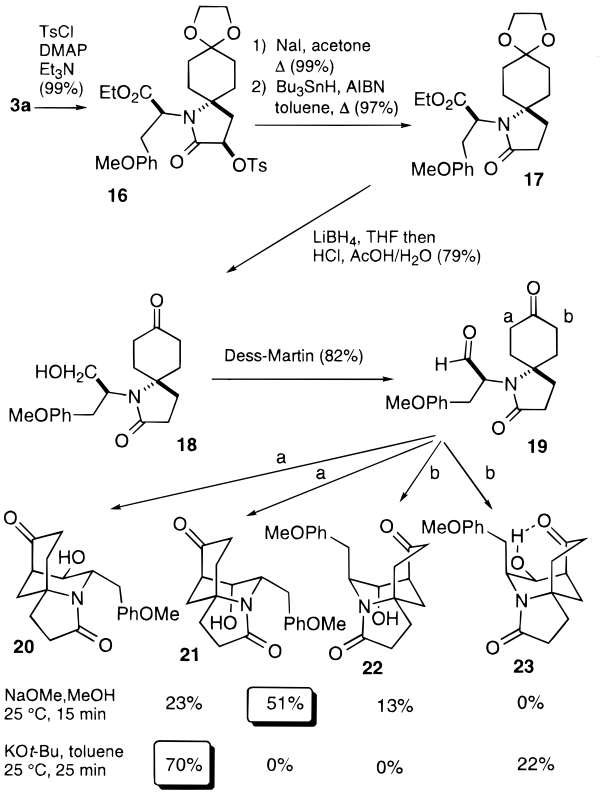
(8) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147−2154.

(9) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309−314.

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

(11) Grundke, G.; Keese, W.; Rimpler, M. *Synthesis* **1987**, 1115−1116.

Scheme 2



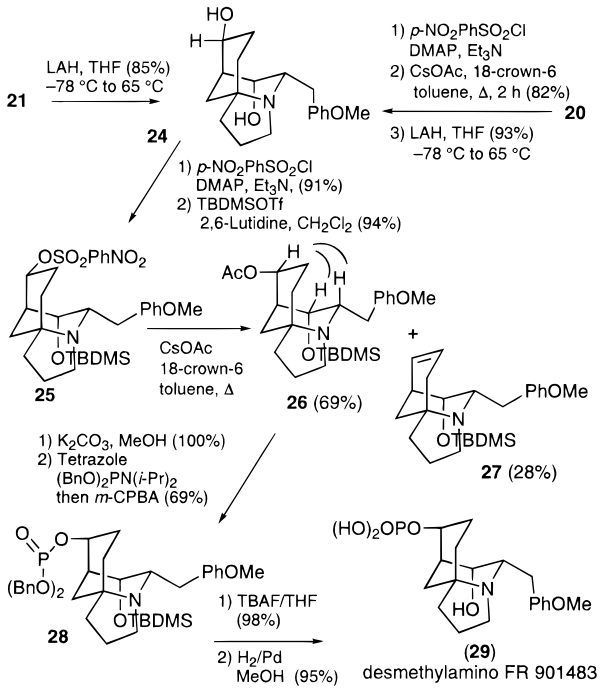
step first on model keto aldehyde **19** lacking the protected *N*-methylamino substituent (Scheme 2). Tosylation of the racemic 8−9:1 mixture of **3a** and the diastereomer (TsCl, DMAP, Et_3N in CH_2Cl_2, 12 h) provided 99% of tosylate **16**, which was treated with NaI in acetone at reflux to afford 99% of the iodide, which was reduced with $SnBu_3H$ and AIBN in toluene at reflux to give 97% of lactam **17**. 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 keto alcohol **18**. Oxidation of the primary alcohol with Dess−Martin reagent provided 82% of the requisite keto aldehyde **19**, which can only give four, rather than the eight, aldol products possible from **2**. Keto aldehyde **19** 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[12] occurred readily with acceptable stereocontrol. Cyclization of **19** with 2.4 equiv of NaOMe in MeOH for 15−30 min at 25 °C provided 51% of the desired stereoisomer **21**, 23% of **20** with the required equatorial *p*-methoxybenzyl group, but the undesired equatorial hydroxyl group, and 13% of **22** 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 **20** and 22% of the fourth diastereomer **23**. 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 **21** is the major product (51%) with

(12) 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*, 4986−5000. (b) Patir, S.; Rosenmund, P.; Götz, P. H. *Heterocycles* **1996**, *43*, 15−22. (c) Taylor, R. J. K.; Turner, S. M.; Horwell, D. C.; Howarth, O. W.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2145−2150.

Scheme 3



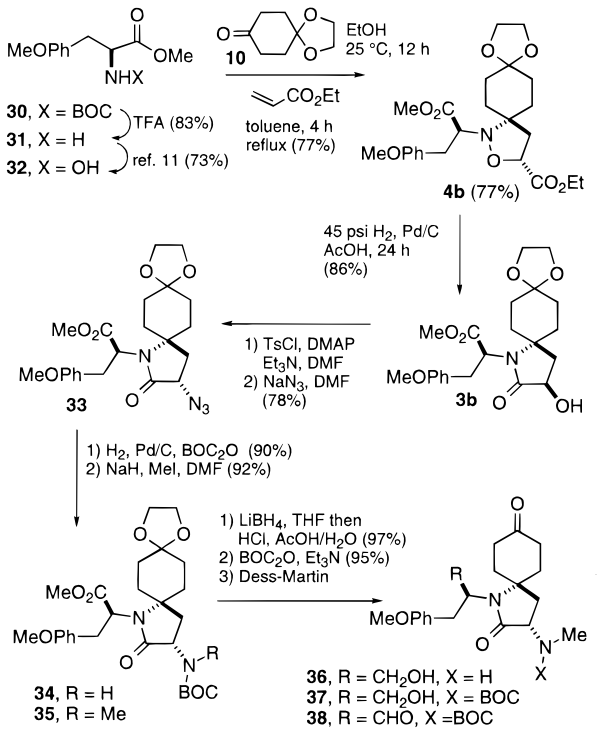
NaOMe in MeOH, while the undesired equatorial alcohol **20** is isolated in 70% yield as one of only two stereoisomers with KO-*t*-Bu in toluene. In toluene, only aldol products **20** and **23** with equatorial alcohols are formed since the potassium alkoxide formed in the aldol reaction can only be stabilized by chelation with the ketone. In MeOH, an axial sodium alkoxide, which cannot chelate with the ketone, can be stabilized by coordination to the solvent. Apparently this solvation is more important than chelation since axial alcohols **21** and **22** are major products in MeOH.

Completion of the Synthesis of Desmethylamino FR901483 (29). Fortunately, both **20** and **21** can be elaborated to desmethylamino FR901483 (**29**) via diol **24** (Scheme 3). Reaction of axial alcohol **21** with LAH in THF at −78 °C to reflux reduced the amide and the ketone stereospecifically to give 85% of **24**. As expected LAH reduced the ketone of **21** from the less hindered exo face to give **24** with the undesired endo alcohol. Reaction of equatorial alcohol **20** 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[13] for 2 h to give the acetate of axial alcohol **21** in 82% yield from **20**. Reaction of this acetate with LAH reduced the acetate, ketone, and amide groups providing 93% of **24**.

Inversion of the stereochemistry of the hydroxyl group was accomplished by reaction of **24** 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 **25** in 94% yield. Reaction of **25** with CsOAc and 18-crown-6 in toluene at reflux[13] afforded 69% of the desired acetate **26** and 28% of the readily separable elimination product **27**. The stereochemistry of **26** 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.

(13) (a) Sato, K.-I.; Yoshitomo, A.; Takai, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 885−890. (b) Liotta, C. L.; Berkner, J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; pp 1403−1407.

Scheme 4



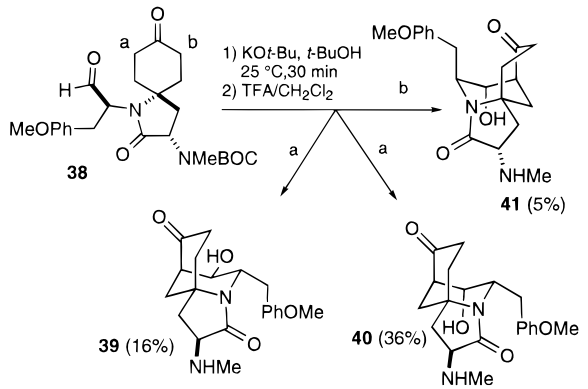
Elaboration of **26** to desmethylamino FR901483 (**23**) was accomplished by hydrolysis of the acetate with K_2CO_3 to give the alcohol quantitatively, which was treated with tetrazole and $(BnO)_2PN(i\text{-}Pr)_2$ to give the dibenzyl phosphite ester,[14] which was oxidized to give 69% of dibenzyl phosphate ester **28** with *m*-CPBA. Hydrolysis of the TBDMS group of **28** with TBAF in THF (98%) followed by hydrogenolysis of the dibenzyl phosphate ester (95%) afforded **29**. To our surprise, the ^{1}H NMR spectrum of **29** 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.[15] Treatment of **29** with K_2CO_3 gave the dipotassium salt of **29** as a single compound.

Synthesis of Optically Active Spirolactam 3b. Before adapting the chemistry developed in the preparation of **29** to the synthesis of FR901483 (**1**), we prepared (*S*)-hydroxylamine **32** in order to obtain optically pure **1**. Although the absolute stereochemistry of **1** was unknown, it is more likely to be derived from **7** formed from two L-tyrosines than from two D-tyrosines. Methylation of *N*-BOC L-tyrosine with excess KOH and MeI in DMF afforded 97% of **30** (see Scheme 4). Hydrolysis of the BOC group of **30** in 3:1 CH_2Cl_2/TFA afforded 83% of amine **31**, which was converted to hydroxylamine **32** by the procedure of Grundke.[11] Condensation of **31** with anisaldehyde in MeOH at 25 °C for 48 h afforded the imine, which was oxidized to the oxaziridine with *m*-CPBA. Reaction of the oxaziridine with hydroxylamine hydrochloride afforded 73% of **32** in 98% ee as determined by analysis of the NMR spectrum of the *O*-acetyl mandelate ester. Racemization can occur readily in this and subsequent steps because of the presence of the ester group. For instance, condensation of amine **31** with anisaldehyde in benzene at reflux followed by oxidation and cleavage of the oxaziridine afforded racemic **32**.

Condensation of **32** with **10** in EtOH at 25 °C for 48 h provided the optically active nitrone which was heated with ethyl acrylate in toluene at 100 °C to afford 77% of an inseparable 6:1 mixture of **4b** and the diastereomer. Hydrogenolysis of this mixture as for the preparation of **3a** gave a 6:1 mixture of **3b** and the diastereomer. The diastereoselectivity appeared to be slightly lower with the methyl ester of **32** leading to **3b** than with the ethyl ester of **9** leading to **3a**. Analysis of the ^{1}H NMR spectrum of the *O*-acetyl mandelate ester indicated that **3b** was formed in 85% ee indicating that some racemization occurred before the nitrone cycloaddition. Flash chromatography provided 86% of **3b** and the diastereomer. Recrystallization of this mixture from hexane/EtOAc/CH_2Cl_2 provided 2% of a 4:1 racemic mixture of **3b** and the diastereomer. The mother liquor contained 84% of a 6:1 mixture of **3b** (87% ee) and the diastereomer that was used for subsequent steps. Apparently the racemic mixture is more crystalline than the optically pure material so that the mother liquor is more highly resolved.[16]

Preparation of Aldol Product 40. The 6:1 mixture of **3b** and the diastereomer was converted to the tosylate as described for the preparation of racemic tosylate **16**. Reaction of the crude tosylate with sodium azide in DMF at 25 °C for 12 h provided 78% of pure azide **33** and 12% of the diastereomer, which were easily separated. Hydrogenolysis of azide **33** over Pd/C in the presence of $(BOC)_2O$[17] gave 90% of carbamate **34** which was methylated with NaH and MeI in THF/DMF[18] to provide 92% of *N*-methylcarbamate **35**. Reduction of **35** with $LiBH_4$ in THF and cleavage of the ketal with HCl in AcOH/H_2O was accompanied by cleavage of the BOC protecting group giving 97% of **36**. The BOC group was reintroduced with $(BOC)_2O$ to provide 95% of carbamate alcohol **37** which was oxidized with the Dess−Martin reagent to give crude keto aldehyde **38**.

We were delighted to find that the aldol reaction of **38** proceeded analogously to that of model keto aldehyde **19** without enolization of the aldehyde, which would result in formation of the diastereomer. Treatment of crude **38** with KO-*t*-Bu in *t*-BuOH for 30 min at 25 °C and deprotection of the BOC group with TFA/CH_2Cl_2 provided 16% of **39** and 41% (from **37**) of an inseparable 7:1 mixture of the desired aldol adduct **40** and the diastereomer **41**. Slightly lower selectivity



for **40** was observed with NaOMe in MeOH. Reduction of the 7:1 mixture with LAH at −78 °C to reflux afforded a 7:1 mixture of diol **42** and the diol obtained from **41**, which was

(14) Yu, K.-L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979−982.

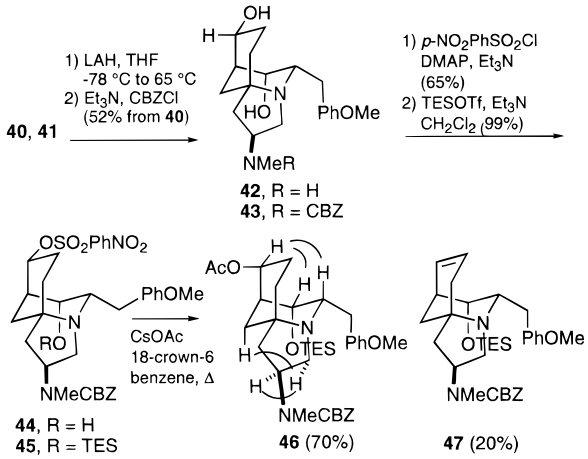
(15) The formation of diastereomeric ammonium salts by protonation of tertiary amines is well-known: (a) Glaser, R.; Peng, Q.-J.; Perlin, A. S. *J. Org. Chem.* **1988**, *53*, 2172−2180. (b) Glaser, R.; Charland, J.-P.; Michel, A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1875−1880.

(16) For other examples of this phenomenon, see: Ushio, T.; Tamura, R.; Takahashi, H.; Azuma, N.; Yamamoto, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2372−2374.

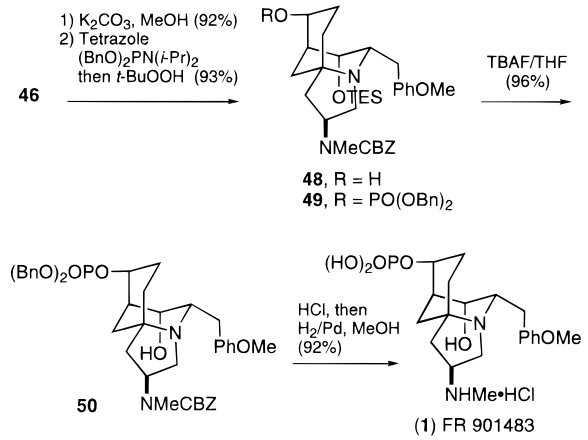
(17) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

(18) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630−1631.

treated with Et_3N and CBZCl to give carbamate **43** in 52% yield from **40** after flash chromatography.



Completion of the Synthesis of FR901483 (1). The equatorial alcohol of **43** was converted to the nosylate to afford 65% of **44**. The axial alcohol of **44** was protected as the triethylsilyl ether to give 99% of **45**. The TBDMS ether which was successfully used in the synthesis of **29** was cleaved very slowly in the real system, probably because the *N*-methylcarbamate forces the pyrrolidine ring into closer proximity with the silyl ether thereby increasing its steric hindrance. Displacement of the nosylate of **45** with CsOAc[13] and 18-crown-6 in benzene at reflux for 2 h afforded 70% of acetate **46** and 20% of elimination product **47**. The NOEs shown convincingly established the stereochemistry of **46** and indicated that the *N*-methylcarbamate was on the appropriate face of the pyrrolidine. Hydrolysis of acetate **46** provided 92% of alcohol **48**.



The phosphate was introduced by reaction of **48** with tetrazole and $(BnO)_2PN(i\text{-}Pr)_2$ to give the dibenzyl phosphite ester,[14] which was oxidized with *tert*-butyl hydroperoxide[19] to give 93% of dibenzyl phosphate ester **49**. Oxidation of the phosphite ester with *m*-CPBA was capricious since oxidation of the tertiary amine to the amine oxide occurred if more than 1 equiv of *m*-CPBA was used. Hydrolysis of the TES group of **49** with TBAF in THF at 25 °C for 2 h provided 96% of **50**.

Hydrogenolysis of the dibenzyl phosphate ester and carbamate of **50** over Pd/C in MeOH (92%) afforded (−)-FR901483 (**1**). As expected for a diamino monophosphate ester, the spectral and chiroptical properties of **1** were very dependent on the pH of the solution in MeOH or CD_3OD. The data reported for **1** are for the monohydrochloride salt.[1] By addition of 1 equiv of hydrochloric acid to the material prepared by hydrogenolysis of **50**, we were able to obtain spectral data that were similar to, but not identical to, that reported for **1**, since a slight excess or deficiency of HCl caused significant shifts in the spectra.

Eventually we concluded that the best way to prepare the monohydrochloride salt of **1** was to prepare and hydrogenolyze the hydrochloride salt of **50** which has only one basic site. Concentration of a solution of **50** in excess hydrochloric acid gave the monohydrochloride salt of **50** which was hydrogenolyzed to give the monohydrochloride salt of **1** with ^1H and ^{13}C NMR spectra identical to those reported.[1] The optical rotation for our synthetic material, $[\alpha]_D = -10$, corresponds well with the reported value of -11[1,20] and establishes that the natural product has the absolute stereochemistry shown and could be derived biosynthetically from two molecules of L-tyrosine. The optical rotation in MeOH is also pH dependent, shifting from −10 for the monohydrochloride salt to +5 upon the addition of 0.2 equiv of additional hydrochloric acid.

In conclusion, we have developed an efficient synthesis of (−)-FR901483 (**1**) in 2% overall yield from *O*-methyltyrosine methyl ester (**31**) in 22 steps. The 1,3-dipolar cycloaddition proceeded with 6−9:1 selectivity, and the intramolecular aldol reaction of keto aldehyde **38** gave tricycle **40** with reasonable selectivity using KO-*t*-Bu in *t*-BuOH.

Experimental Section

General Procedures. Experimental procedures for the preparation of **29** are provided in the supporting material for ref 6. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated, chemical shifts are reported in δ, coupling constants in hertz, and IR spectra in cm^{-1}. The NMR spectra of amines vary greatly depending on the exact amount of HCl present in the $CDCl_3$ solvent. Chemical shifts change significantly upon protonation; some proton and carbon spectra are broad due to slow conformational changes or chemical exchange.

Methyl (*S*)-*N*-BOC-*O*-methyltyrosine (30). A solution of (*S*)-*N*-BOC-tyrosine (2.81 g, 10 mmol) in 20 of mL of DMF was treated with ground KOH (617 mg, 11 mmol) and then MeI (0.70 mL, 11 mmol) in 5 mL of DMF at 0 °C. The reaction mixture was stirred at 25 °C for 0.5 h, and an additional 11 mmol of ground KOH and MeI in DMF solution was added at 0 °C. The reaction mixture was stirred at 25 °C for 3 h and poured onto ice, which was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL) and brine and dried ($MgSO_4$). Removal of the solvent gave 3.01 g (97%) of crude **30**: ^1H NMR 7.04 (d, 2, $J = 8.4$), 6.83 (d, 2, $J = 8.4$), 5.00 (d, 1, $J = 7.6$, NH), 4.54 (ddd, 1, $J = 7.6$, 6.0, 5.6), 3.78 (s, 3), 3.71 (s, 3), 3.05 (dd, 1, $J = 14.0$, 5.6), 2.99 (d, 2, $J = 14.0$, 6.0), 1.42 (s, 9); ^{13}C NMR 172.4, 158.6, 155.0, 130.2 (2 C), 127.9, 113.9 (2 C), 79.8, 55.1, 54.5, 52.1, 37.4, 28.2 (3 C). The data are identical to those previously reported.[21]

Methyl (*S*)-*O*-Methyltyrosine (31). A solution of crude **30** (3.01 g, 9.7 mmol) in 30 mL of CH_2Cl_2 and 10 mL of TFA was stirred at 25 °C for 2 h. The solvent was evaporated, and the residue was diluted with 100 mL of CH_2Cl_2 which was carefully neutralized with saturated aqueous Na_2CO_3 solution. The aqueous layer was discarded, and the organic layer was dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue on silica gel (1:1 hexane/EtOAc, then 1:1 CH_2Cl_2/EtOAc) gave 1.68 g (83%) of **31**: ^1H NMR 7.10 (d, 2, $J = 8.4$), 6.84 (d, 2, $J = 8.4$), 3.78 (s, 3), 3.73 (m, 1), 3.71 (s, 3), 3.04

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(20) We thank Dr. Seiji Hashimoto, Exploratory Research Laboratories, Fujisawa Pharmaceutical Co. for copies of the spectral data of **1**. The optical rotation reported in ref 1 was obtained in MeOH, not $CHCl_3$ as reported. Private communication from Dr. Motohiro Hino, Fujisawa Research Laboratories.

(21) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051−6064.

(dd, 1, J = 14.0, 4.0), 2.85 (dd, 1, J = 14.0, 7.6), 2.50 (br s, 2, NH_2); ^{13}C NMR 174.8, 158.5, 130.2 (2 C), 128.6, 114.0 (2 C), 55.6, 55.1, 52.0; $[\alpha]_D$ +11 (*c* 0.15, $CHCl_3$). The data are identical to those previously reported.[22]

Methyl (*S*)-*N*-Hydroxy-*O*-methyltyrosine (32). A solution of amine **31** (4.26 g, 20.3 mmol) and anisaldehyde (2.47 mL, 20.3 mmol) in 24 mL of dry MeOH was stirred at 25 °C for 48 h. The solution was evaporated to dryness, and the residue was taken up in 15 mL of CH_2Cl_2. The solution was cooled to −15 °C, and a solution of *m*-CPBA (5.0 g, 70%, 20.3 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise. The reaction mixture was stirred at 25 °C overnight, and the precipitate was filtered off. The filtrate was washed with saturated $NaHCO_3$ solution and water and dried ($MgSO_4$). The solvent was evaporated, and the residue was dissolved in MeOH (25 mL). Hydroxylamine (1.41 g, 20.3 mmol) was added, and the mixture was stirred at 25 °C overnight. The solvent was evaporated, water (20 mL) was added, and the oily oxime was filtered off on Celite. The filtrate was extracted with Et_2O (3 × 25 mL), and the extract was washed with 0.1 N HCl. The combined aqueous solution was carefully saturated with $NaHCO_3$, and the free hydroxylamine was extracted with CH_2Cl_2 (5 × 25 mL). The organic layer was dried (Na_2SO_4). Removal of the solvent and flash chromatography of the residue on silica gel (3:2 hexane/EtOAc) gave 3.336 g (73%) of pure hydroxylamine **32**: ^{1}H NMR 7.10 (br, 1, NH or OH), 7.08 (d, 2, J = 8.6), 6.83 (d, 2, J = 8.6), 5.50 (br, 1, NH or OH), 3.84 (dd, 1, J = 8.0, 6.0), 3.77 (s, 3), 3.72 (s, 3), 2.93 (dd, 1, J = 14.0, 6.0), 2.82 (dd, 1, J = 14.0, 8.0); ^{13}C NMR 173.2, 158.3, 129.8 (2 C), 128.1, 113.8 (2 C), 66.2, 54.9, 51.7, 34.4; IR (neat) 3435, 3267, 1739, 1612, 1514; $[\alpha]_D$ 4.4 (*c* 0.57, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N 6.22. Found: C, 58.73; H, 6.83, N, 6.18.

A solution of **32** (24 mg, 0.11 mmol), (*R*)-*O*-acetylmandelic acid (21 mg, 0.11 mmol), and DCC (23 mg, 0.11 mmol) in 1 mL of CH_2Cl_2 was stirred at 25 °C for 30 min. The white precipitate was filtered off, and the filtrate was evaporated: ^{1}H NMR 3.58 (s, 0.01 × 3), 3.47 (s, 0.99 × 3).

Methyl (α*S*,3*R*)-3-(Ethoxycarbonyl)-α-[(4-methoxyphenyl)methyl]-2,9,12-trioxa-1-azadispiro[4.2.4.2]tetradecane-1-acetate (4b). A mixture of cyclohexane-1,4-dione monoethylene ketal (**10**, 2.307 g, 14.77 mmol), hydroxylamine **32** (3.324 g, 14.77 mmol), and ethanol (23 mL) was stirred at 25 °C for 48 h. The ethanol was removed, and the residue was taken up in 35 mL of toluene. Ethyl acrylate (3.2 mL, 29.54 mmol) was added, and the resulting mixture was heated for 4 h at 100 °C. The solvent was removed, and the resulting isoxazolidine contained a 6:1 mixture of diastereomers as determined by analysis of the ^{1}H NMR spectrum. The crude mixture was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give 5.30 g (77%) of **4b** as an inseparable mixture of diastereomers. The data for the major isomer was determined from the mixture: ^{1}H NMR 7.11 (d, 2, J = 8.6), 6.80 (d, 2, J = 8.6), 4.69 (dd, 1, J = 9.6, 5.6), 4.24 (q, 2, J = 7.2), 3.93 (m, 4), 3.77 (s, 3), 3.75 (dd, 1, J = 10.4, 5.2), 3.53 (s, 3), 3.30 (dd, 1, J = 13.2, 5.2), 3.13 (dd, 1, J = 13.2, 10.4), 2.44 (dd, 1, J = 12.8, 9.6), 2.39 (dd, 1, J = 12.8, 5.6), 1.98−1.71 (m, 5), 1.67−1.52 (m, 3), 1.29 (t, 3, J = 7.2); ^{13}C NMR 172.3, 171.7, 158.2, 130.2 (2 C), 129.0, 113.6 (2 C), 107.8, 75.8, 66.9, 66.4, 64.2, 64.2, 61.2, 55.1, 51.6, 41.1, 37.3, 32.3, 32.0, 31.4, 29.6, 14.1; IR (neat) 1737, 1612, 1514.

Partial data for the minor isomer was determined from the mixture: 4.49 (dd, 1, J = 8.0, 7.6).

Methyl (α*S*,3*R*)-11-Hydroxy-α-[(4-methoxyphenyl)methyl]-10-oxo-1,4-dioxa-9-azadispiro[4.2.4.2]tetradecane-9-acetate (3b). A 6:1 mixture of isoxazolidines **4b** and the diastereomer (5.30 g, 11.4 mmol) and 10% Pd/C (800 mg) in 50 mL of AcOH was shaken under 45 psi of H_2 at 25 °C for 48 h. The Pd/C was filtered off, and the filtrate was concentrated. The residue was dissolved in 110 mL of 10/1 CH_2Cl_2/HOAc and stirred at 25 °C overnight. The solution was carefully neutralized with saturated Na_2CO_3 aqueous solution, then washed with water and brine, dried (Na_2SO_4), and concentrated to give a 6:1 mixture of diastereomers as determined by analysis of the ^{1}H NMR spectrum.

A small sample of crude **3b** (12 mg, 0.029 mmol) was treated with (*R*)-*O*-acetylmandelic acid (6.1 mg, 0.032 mmol), DCC (6.5 mg, 0.032 mmol), and DMAP (3.8 mg, 0.031 mmol) in 0.3 mL of CH_2Cl_2. The white precipitate was filtered off, and the filtrate was concentrated giving a 6:1 mixture of **3b** (85% ee) and the diastereomer: ^{1}H NMR 5.19 (0.064 × 1, dd, J = 8.0, 4.0, *ent*-**3b**), 5.17 (0.792 × 1, dd, J = 8.0, 6.0, **3b**), 5.28 (0.143 × 1, dd, J = 8.0, 8.0, diastereomer).

Flash chromatography of crude **3b** on silica gel (1:1 CH_2Cl_2/EtOAc) gave 4.128 g (86%) of a mixture of **3b** and the diastereomer (**3b** elutes faster). Recrystallization from hexane/EtOAc/CH_2Cl_2 gave 100 mg of a 4:1 mixture of racemic **3b** and the diastereomer as determined by conversion to the mandelate esters. The mother liquor contained a 6:1 mixture of **3b** and the diastereomer in 87% ee as determined by conversion to the mandelate esters.

The data for **3b** were obtained from initial fractions that contained >95% **3b** as an oil: ^{1}H NMR 7.09 (d, 2, J = 8.6), 6.80 (d, 2, J = 8.6), 4.29 (dd, 1, J = 8.4, 7.2), 3.88 (m, 4), 3.86 (dd, 1, J = 10.4, 4.8), 3.77 (s, 3), 3.76 (s, 3), 3.62 (dd, 1, J = 13.6, 10.4), 3.34 (dd, 1, J = 13.6, 4.8), 2.28 (dd, 1, J = 13.2, 8.4), 1.89 (dd, 1, J = 13.2, 7.2), 1.74−1.41 (m, 6), 1.04 (ddd, 1, J = 13.2, 12.8, 5.2), 0.26 (br d, 1, J = 13.2); ^{13}C NMR 174.6, 170.3, 158.5, 130.7 (2 C), 130.0, 113.8 (2 C), 107.0, 68.3, 64.3, 64.2, 61.4, 56.6, 55.3, 52.6, 37.4, 33.8, 33.1, 32.0, 31.0, 30.9; IR (neat) 3378, 1747, 1682, 1613, 1514; $[\alpha]_D$ −22.8 (*c* 1.7, $CHCl_3$). Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.95; H, 6.88; N, 3.24.

A similar reaction with racemic hydroxylamine **32** gave racemic **3b**: mp 207−208.5 °C.

Methyl (α*S*,3*S*)-11-Azido-α-[(4-methoxyphenyl)methyl]-10-oxo-1,4-dioxa-9-azadispiro[4.2.4.2]tetradecane-9-acetate (33). The 6:1 mixture of spirolactams **3b** and the diastereomer (1.193 g, 2.85 mmol), Et_3N (1.19 mL, 8.06 mmol), DMAP (348 mg, 2.85 mmol), and TsCl (1.086 mg, 5.37 mmol) in 25 mL of CH_2Cl_2 was stirred at 25 °C for 12 h. The reaction was diluted with 150 mL of EtOAc, washed with 50 mL of 0.1 N HCl, 50 mL of water, and 50 mL of brine, dried ($MgSO_4$), and concentrated to give 1.645 g of the crude tosylate.

A solution of the crude tosylate and NaN_3 (371 mg, 5.71 mmol) in 10 mL of dry DMF was stirred at 25 °C for 12 h. The reaction mixture was diluted with 150 mL of EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). Evaporation of the solvent, followed by flash chromatography of the residue on silica gel (1:1 CH_2Cl_2/EtOAc), gave 0.151 g (12%) of the diastereomer of **33** followed by 0.982 g (78%) of pure **33**.

Data for the diastereomer of **33**: ^{1}H NMR 7.10 (d, 2, J = 8.8), 6.81 (d, 2, J = 8.8), 4.07 (dd, 1, J = 8.8, 5.2), 3.88 (m, 4), 3.83 (dd, 1, J = 10.8, 4.8), 3.78 (s, 3), 3.78 (s, 3), 3.62 (dd, 1, J = 13.6, 10.8), 3.36 (dd, 1, J = 13.6, 4.8), 2.01 (dd, 1, J = 13.6, 8.8), 1.87 (dd, 1, J = 13.6, 5.2), 1.77−1.65 (m, 3), 1.57 (ddd, 1, J = 14.0, 14.0, 4.8), 1.46−1.37 (m, 2), 1.11 (ddd, 1, J = 12.8, 12.4, 6.4), 0.17 (dddd, 1, J = 12.8, 3.2, 3.2, 2.8); ^{13}C NMR 170.6, 170.0, 158.5, 130.7 (2 C), 129.9, 113.8 (2 C), 106.8, 64.3, 64.2, 62.1, 57.8, 56.7, 55.3, 52.7, 35.0, 33.3, 32.7, 31.9, 31.6, 31.3; IR (neat) 2112, 1743, 1695, 1612, 1514.

Data for **33**: mp 138.5−140.5 °C; ^{1}H NMR 7.10 (d, 2, J = 8.6), 6.82 (d, 2, J = 8.6), 4.16 (dd, 1, J = 9.2, 9.2), 3.87 (m, 4), 3.82 (dd, 1, J = 10.8, 4.8), 3.78 (s, 3), 3.77 (s, 3), 3.60 (dd, 1, J = 14.0, 10.8), 3.35 (dd, 1, J = 14.0, 4.8), 2.52 (dd, 1, J = 13.2, 9.2), 1.71−1.55 (m, 4), 1.45−1.35 (m, 2), 1.31 (dd, 1, J = 13.2, 9.2), 1.22 (ddd, 1, J = 12.8, 12.8, 5.2), 0.04 (dddd, 1, J = 12.8, 3, 3, 2.4); ^{13}C NMR 171.5, 170.0, 158.5, 130.8 (2 C), 129.8, 113.7 (2 C), 106.8, 64.3, 64.2, 60.8, 57.7, 56.6, 55.2, 52.6, 34.9, 33.7, 32.7, 31.9, 31.1, 31.1; IR (neat) 2110, 1744, 1698, 1613, 1514; $[\alpha]_D$ −187 (*c* 0.70, $CHCl_3$). Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.19; H, 6.33; N, 12.20.

Methyl (α*S*,3*S*)-11-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-[(4-methoxyphenyl)methyl]-10-oxo-1,4-dioxa-9-azadispiro[4.2.4.2]tetradecane-9-acetate (34). Pd/C (5%, 100 mg) was added to a solution of azide **33** (0.982 g, 2.21 mmol) and BOC_2O (530 mg, 2.43 mmol) in 20 mL of EtOH. The reaction mixture was stirred overnight under 1 atm of H_2 and filtered through Celite, which was washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give 1.034 g (90%) of **34**: ^{1}H NMR 7.07 (d, 2, J =

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8.6), 6.81 (d, 2, J = 8.6), 5.15 (br s, 1, NH), 4.24 (m, 1), 3.86 (m, 4), 3.82 (dd, 1, J = 10.6, 5.0), 3.78 (s, 3), 3.74 (s, 3), 3.53 (dd, 1, J = 13.8, 10.6), 3.37 (dd, 1, J = 13.8, 5.0), 2.90 (dd, 1, J = 11.6, 8.0), 1.67−1.55 (m, 4), 1.47 (s, 9), 1.44−1.41 (m, 2), 1.30 (m, 1), 1.23 (dd, 1, J = 11.6, 11.6), 0.03 (m, 1); ^{13}C NMR 173.0, 170.2, 158.4, 156.1, 130.8 (2 C), 130.0, 113.7 (2 C), 107.0, 80.0, 64.3, 64.2, 60.9, 56.6, 55.2, 52.6, 50.8, 37.5, 34.2, 33.3, 32.1, 31.0, 29.9, 28.3 (3 C); IR (KBr) 3364, 1742, 1702, 1612, 1515; $[\alpha]_D$ −76.3 (*c* 2.64, $CHCl_3$). Anal. Calcd for $C_{27}H_{38}N_2O_8$: C, 62.53; H, 7.39; N, 5.40. Found: C, 62.67; H, 7.32; N, 5.38. A similar sequence that started with racemic hydroxylamine **32** gave racemic **34**: mp 156.5−158.5 °C.

Methyl (α*S*,3*S*)-11-[[(1,1-Dimethylethoxy)carbonyl]methylamino]-α-[(4-methoxyphenyl)methyl]-10-oxo-1,4-dioxa-9-azadispiro[4.2.4.2]tetradecane-9-acetate (35). A solution of *N*-BOC spirolactam **34** (1.108 g, 2.14 mmol) in THF (20 mL) and DMF (2.0 mL) was treated with NaH (94 mg, 60%, 2.35 mmol) at 0 °C. The solution was then warmed to 25 °C and stirred for 15 min. The reaction mixture was treated with MeI (0.40 mL, 4.58 mmol) at 25 °C, stirred for 2 h, then cooled in an ice-bath, and neutralized with saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were washed by $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue on silica gel (1:1 hexane/EtOAc) gave 1.043 g (92%) of **35**: ^{1}H NMR 7.11 (d, 2, J = 8.4), 6.80 (d, 2, J = 8.4), 5.01 (dd, 1, J = 10.0, 10.0), 3.88 (m, 4), 3.81 (dd, 1, J = 10.8, 4.8), 3.78 (s, 3), 3.73 (br s, 3), 3.53 (dd, 1, J = 14.0, 10.8), 3.39 (dd, 1, J = 14.0, 4.8), 2.79 (s, 3), 2.46 (dd, 1, J = 11.6, 10.0), 1.72−1.58 (m, 4), 1.47 (s, 9), 1.47−1.31 (m, 4), 0.12 (br d, 1, J = 11.2); ^{13}C NMR 172.0, 170.3, 158.4, 156.0, 130.9 (2 C), 130.2, 113.5 (2 C), 107.0, 80.1, 64.3, 64.2, 59.8, 56.5, 55.3, 55.2, 52.5, 34.4, 33.6, 32.0, 31.7, 31.1, 30.2, 30.0, 28.3 (3 C); IR (neat) 1744, 1694, 1613, 1514; $[\alpha]_D$ −74.0 (*c* 1.34, $CHCl_3$). Anal. Calcd for $C_{28}H_{40}N_2O_8$: C, 63.14; H, 7.57; N, 5.26. Found: C, 63.01; H, 7.47; N, 5.24. A similar sequence that started with racemic hydroxylamine **32** gave racemic **35**: mp 171−173 °C.

(α*S*,3*S*)-1-[2-Hydroxy-1-[(4-methoxyphenyl)methyl]ethyl]-3-methylamino-1-azaspiro[4.5]decane-2,8-dione (36). A solution of **35** (1.043 g, 1.96 mmol) in 20 mL of ether was treated with 1.5 mL of 2.0 M $LiBH_4$ in THF. The reaction mixture was stirred for 2 h, diluted with 100 mL of CH_2Cl_2, washed with 50 mL of saturated NH_4Cl solution and brine, and dried ($MgSO_4$). The solvent was removed, and the resulting material was stirred in a mixture of 10 mL of water, 3 mL of 3 N HCl, and 4 mL of acetic acid for 12 h. The mixture was neutralized with saturated Na_2CO_3 solution and extracted with 5 × 50 mL of CH_2Cl_2. The combined organic layers were washed with water and brine and dried ($MgSO_4$). Removal of the solvent followed by flash chromatography of the residue on silica gel (9:1 CH_2Cl_2/MeOH) gave 687 mg (97%) of keto alcohol **36**: ^{1}H NMR 7.12 (d, 2, J = 8.5), 6.82 (d, 2, J = 8.5), 3.93 (dd, 1, J = 11.9, 5.6), 3.80−3.77 (m, 1), 3.78 (s, 3), 3.46 (dd, 1, J = 9.2, 8.4), 3.28−3.08 (m, 3), 2.69 (dd, 1, J = 12.4, 8.4), 2.51 (s, 3), 2.5−2.3 (m, 3), 2.28−2.21 (m, 1), 1.95 (ddd, 1, J = 13.4, 12.8, 5.5), 1.83−1.71 (m, 2), 1.67 (dd, 1, J = 12.4, 9.2), 1.03−0.97 (m, 1); ^{13}C NMR 208.2, 175.7, 158.4, 130.5 (2 C), 130.5, 113.9 (2 C), 64.1, 61.1, 58.4, 58.0, 55.2, 38.0, 37.3, 35.9, 35.3, 34.3, 33.9, 33.3; IR (neat) 3414, 3330, 1715, 1682; HRMS (CI) calcd for $C_{20}H_{29}N_2O_4$ (MH^+) 361.2127, found 361.2124.

(α*S*,3*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]methylamino]-1-[2-hydroxy-1-[(4-methoxyphenyl)methyl]ethyl]-1-azaspiro[4.5]decane-2,8-dione (37). A solution of keto alcohol **36** (687 mg, 1.91 mmol), BOC_2O (417 mg, 1.91 mmol) and Et_3N (319 μL, 2.29 mmol) in 19 mL of CH_2Cl_2 was stirred at 25 °C for 3 h. The reaction mixture was diluted with EtOAc, washed with 0.1 N HCl, water, saturated aqueous $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (1:1 CH_2Cl_2/EtOAc) gave 832 mg (95%) of **37**: ^{1}H NMR 7.13 (d, 2, J = 8.8), 6.81 (d, 2, J = 8.8), 5.07 (dd, 1, J = 10.0, 9.2), 4.0−3.9 (m, 2), 3.80 (m, 1), 3.78 (s, 3), 3.3−3.1 (m, 2), 2.85 (s, 3), 2.67 (dd, 1, J = 12.0, 9.2), 2.5−2.2 (m, 4), 2.0−1.7 (m, 4), 1.50 (s, 9), 0.86 (br d, 1, J = 11.2); ^{13}C NMR 208.1, 173.1, 158.4, 156.1, 130.6 (2 C), 130.6, 113.8, 80.6, 64.2, 60.1, 58.2, 55.5, 55.3, 38.0, 37.2, 35.5, 33.9, 32.8, 32.0, 30.6, 28.3 (3 C); IR (neat) 3437, 1688, 1612, 1512; $[\alpha]_D$ −88.3 (*c* 2.20, $CHCl_3$); HRMS (FAB) calcd for $C_{25}H_{37}N_2O_6$ (MH^+) 461.2652, found 461.2635. A similar sequence that started with racemic hydroxylamine **32** gave racemic **37**: mp 155.5−157 °C.

(α*S*,3*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]methylamino]-α-[(4-methoxyphenyl)methyl]-2,8-dioxo-1-azaspiro[4.5]decane-1-acetaldehyde (38). A solution of keto alcohol **37** (832 mg, 1.81 mmol) and Dess−Martin periodinane (844 mg, 1.99 mmol) in CH_2Cl_2 (18 mL) was stirred at 25 °C for 30 min. The reaction mixture was then diluted with 50 mL of ether, washed with 10% $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Evaporation of the solvent gave 800 mg of crude keto aldehyde **38**: ^{1}NMR 9.62 (s, 1), 7.15 (d, 2, J = 8.8), 6.81 (d, 2, J = 8.8), 5.10 (dd, 1, J = 10.4, 9.2), 3.76 (s, 3), 3.46−3.34 (m, 3), 2.83 (s, 3), 2.69 (dd, 1, J = 12.8, 9.2), 2.46 (ddd, 1, J = 15.6, 13.6, 6.4), 2.36 (br d, 1, J = 13.6), 2.22 (ddd, 1, J = 14.8, 14.0, 5.2), 1.94 (m, 1), 1.76−1.62 (m, 3), 1.47 (s, 9), 1.39 (m, 1), 0.59 (br d, 1, J = 11.2); ^{13}C NMR 207.8, 198.1, 172.0, 158.6, 155.9, 130.7 (2 C), 129.3, 113.9 (2 C), 80.5, 63.0, 58.9, 55.4, 55.2, 37.8, 37.1, 35.4, 32.74, 32.67, 32.0, 30.8, 28.3 (3 C).

Aldol Reaction of Keto Aldehyde 38. A solution of crude **38** (800 mg, from 832 mg of pure **37**, 1.81 mmol) and KO-*t*-Bu (243 mg, 2.17 mmol, 1.2 equiv) in *t*-BuOH (35 mL, 0.05M) was stirred at 25 °C for 30 min. HOAc (0.2 mL) was added, and the solvent was removed under reduced pressure. The residue was taken up into 50 mL of CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). Removal of the solvent afforded the crude aldol products.

A solution of the crude aldol products in 12 mL of CH_2Cl_2 and 3 mL of TFA was stirred at 25 °C for 2 h. The solvent was evaporated, and the residue was taken up in 100 mL of CH_2Cl_2, which was washed with Na_2CO_3, water, and brine and dried (Na_2SO_4). Removal of the solvent afforded 521 mg of crude **39**, **40**, and **41**, which were purified by flash chromatography on silica gel (14:5:1 CH_2Cl_2/EtOAc/MeOH) to give 105 mg (16%) of **39**, followed by 268 mg (41%) of an inseparable 7:1 mixture of **40** and **41**.

Data for (2*S*,5*S*,6*R*,7*R*,10a*S*)-tetrahydro-6-hydroxy-5-[(4-methoxyphenyl)methyl]-2-methylamino-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-3,8(2*H*,5*H*)-dione (**39**): ^{1}H NMR 7.20 (d, 2, J = 8.8), 6.81 (d, 2, J = 8.6), 3.93 (dd, 1, J = 14.4, 8.0, $ArCH_2$), 3.83 (dd, 1, J = 10.0, 5.6, H_6), 3.77 (s, 3), 3.53 (ddd, 1, J = 10.0, 8.0, 4.8, H_5), 3.42 (dd, 1, J = 14.4, 4.8, $ArCH_2$), 3.37 (dd, 1, J = 8.4, 6.4, H_2), 2.82 (ddd, 1, J = 5.6, 3.6, 2.4, H_7), 2.58−2.54 (m, 2), 2.39 (s, 3), 2.24 (ddd, 1, J = 14.0, 6.8, 2.4), 2.11 (dd, 1, J = 13.6, 3.6, H_{11}), 2.07 (dd, 1, J = 12.6, 8.4, H_1), 2.03 (m, 1), 1.77 (ddd, 1, J = 13.6, 2.4, 2.4, H_{11}), 1.72 (dd, 1, J = 12.6, 6.4, H_1); ^{13}C NMR 212.9, 174.4, 158.1, 130.6, 130.3 (2 C), 113.8 (2 C), 71.5, 60.8, 60.5, 58.0, 55.2, 50.1, 38.3, 37.9, 35.5, 34.6, 34.5, 32.2; IR (neat) 3326, 1714, 1682, 1613, 1514; $[\alpha]_D$ −3.2 (*c* 1.43, $CHCl_3$); HRMS (EI) calcd for $C_{20}H_{26}N_2O_4$ (M^+) 358.1892, found 358.1880.

The data for (2*S*,5*S*,6*S*,7*R*,10a*S*)-tetrahydro-6-hydroxy-5-[(4-methoxyphenyl)methyl]-2-methylamino-1*H*-7,10a-methanopyrrolo[1,2-*a*]-azocine-3,8(2*H*,5*H*)-dione (**40**) were determined from a 9:1 mixture of **40** and **41** that was obtained in the initial column fraction: ^{1}H NMR 7.12 (d, 2, J = 8.4), 6.80 (d, 2, J = 8.4), 3.84 (m, 1, H_5), 3.77 (s, 3), 3.74 (d, 1, J = 4.0, H_6), 3.46 (dd, 1, J = 10.2, 8.2, H_2), 3.41−3.32 (m, 2), 2.75 (ddd, 1, J = 4.0, 3.6, 3.2, H_7), 2.63−2.46 (m, 2), 2.41 (s, 3), 2.32 (dd, 1, J = 13.6, 4.0), 2.31 (dd, 1, J = 12.4, 8.2, H_1), 2.17 (ddd, 1, J = 15.2, 10.4, 4.0), 2.07 (ddd, 1, J = 15.2, 8.8, 8.4), 1.78 (dd, 1, J = 13.6, 3.2, H_{11}), 1.69 (dd, 1, J = 12.4, 10.2, H_1); ^{13}C NMR 211.4, 175.6, 158.2, 130.5, 129.8 (2 C), 114.0 (2 C), 68.4, 59.6, 59.1, 57.6, 55.2, 50.9, 39.8, 36.9, 34.0, 33.2, 32.3, 28.5; IR (neat) 3316, 1693, 1682, 1613, 1514; $[\alpha]_D$ −32 (*c* 0.17, $CHCl_3$); HRMS (EI) calcd for $C_{20}H_{26}N_2O_4$ (M^+) 358.1892, found 358.1896.

Partial data for (2*S*,5*S*,6*R*,7*S*,10a*R*)-tetrahydro-6-hydroxy-5-[(4-methoxyphenyl)methyl]-2-methylamino-1*H*-7,10a-methanopyrrolo[1,2-*a*]-azocine-3,8(2*H*,5*H*)-dione (**41**) were determined from the 7:1 mixture: ^{1}H NMR 7.12 (d, 2, J = 8.8), 6.83 (d, 2, J = 8.8), 4.19 (dd, 1, J = 8.8, 4.4, H_5), 4.09 (d, 1, J = 4.0, H_6), 3.78 (s, 3), 3.52 (dd, 1, J = 10.4, 7.6, H_2), 2.82 (m, 1, H_7), 2.80 (dd, 1, J = 13.2, 4.4, $ArCH_2$), 2.47 (s, 3), 2.27 (dd, 1, J = 13.2, 8.8, $ArCH_2$); ^{13}C NMR 66.0, 58.8, 58.7, 55.6, 49.0, 48.8, 44.6, 37.2, 36.8, 34.5, 33.9, 30.1.

(2*S*,5*S*,6*S*,7*S*,8*R*,10a*S*)-Octahydro-5-[(4-methoxyphenyl)methyl]-2-methylamino-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-6,8-diol (42).

LAH (2.25 mL, 1.0 M in THF) was added to a solution of the 7:1 mixture of **40** and **41** (268 mg, 0.75 mmol) in dry THF (7.5 mL) dropwise at −78 °C. The resulting mixture was warmed to 0 °C, stirred at 0 °C for 15 min and at reflux for 2 h, and cooled to 0 °C. Excess EtOAc was added to quench the LAH. Water (26 μL), 15% NaOH (26 μL), and water (78 μL) were added. The granular precipitate was removed by filtration, and the filtrate was concentrated to give 223 mg of a crude 7:1 mixture of diols. The data for **42** were determined from the mixture: ^{1}H NMR 7.20 (d, 2, J = 8.8), 6.81 (d, 2, J = 8.8), 3.94 (ddd, 1, J = 11.6, 6.8, 4.8), 3.77 (s, 3), 3.65 (m, 1), 3.53 (dd, 1, J = 9.2, 7.6, $H_{3\beta}$), 3.46 (m, 1), 3.15 (m, 1, H_2), 2.86 (dd, 1, J = 13.2, 4.8), 2.76 (dd, 1, J = 13.2, 10.0), 2.48 (dd, 1, J = 9.2, 5.6, $H_{3\alpha}$), 2.34 (s, 3), 2.23 (m, 1, $H_{9\beta}$), 2.17 (m, 1), 2.0−1.9 (m, 2), 1.84 (dd, 1, J = 12.8, 9.6), 1.70 (m, 1), 1.35 (m, 1), 1.34 (dd, 1, J = 12.4, 2.8), 1.28 (dd, 1, J = 12.8, 2.8).

(2*S*,5*S*,6*S*,7*S*,8*R*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-octahydro-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo-[1,2-*a*]azocine-6,8-diol (43). Et_3N (223 μL, 1.60 mmol) was added to a solution of the diol **42** and the diastereomer (223 mg, 0.64 mmol) and CBZCl (137 μL, 0.96 mmol) in 6 mL of CH_2Cl_2 at 25 °C. The reaction mixture was stirred overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (14:5:1 CH_2Cl_2/EtOAc/CH_3OH) to give 163 mg (52% of **43** based on the amount of **40** in the mixture) of pure diol **43**. The ^{1}H NMR spectrum is very broad due to slow rotation about the CBZ group and proton exchange. The only characteristic proton is a broad doublet at δ 1.15. Some peaks become a little sharper when CD_3OD is used as solvent and when the temperature was raised to 40 °C.

(2*S*,5*S*,6*S*,7*R*,8*R*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-octahydro-6-hydroxy-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-yl (4-Nitrobenzene)sulfonate (44). Et_3N (121 μL, 0.87 mmol) was added to a solution of *N*-CBZ diol **43** (139 mg, 0.29 mmol), *p*-nitrobenzenesulfonyl chloride (96 mg, 0.44 mmol), and DMAP (35 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) at −20 °C. The solution was stirred at 0 °C for 5 h and then diluted with 20 mL of EtOAc. The solution was washed with 0.1 N HCl and water and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give 105 mg (65%) of nosylate **44**: ^{1}H NMR (CD_3OD) 8.45 (d, 2, J = 8.8), 8.10 (d, 2, J = 8.8), 7.37 (m, 5), 7.24 (d, 2, J = 8.8), 6.87 (d, 2, J = 8.8), 5.11 (s, 2), 5.04 (ddd, 1, J = 11.2, 8.0, 5.6), 4.76 (m, 1), 3.81 (s, 1), 3.64−3.58 (m, 2), 3.58 (br s, 1), 2.97−2.84 (m, 3), 2.72 (s, 3), 2.36 (m, 1, H_7), 2.29 (br d, 1, J = 13.2), 2.14−1.94 (m, 3), 1.86 (dd, 1, J = 13.4, 9.8), 1.74 (m, 1), 1.50 (dd, 1, J = 13.4, 7.0), 1.15 (dd, 1, J = 13.2, 2.0); ^{1}H NMR ($CDCl_3$) 8.32 (d, 2, J = 9.2), 7.94 (d, 2, J = 9.2), 7.34 (m, 5), 7.14 (d, 2, J = 8.8), 6.84 (d, 2, J = 8.8), 5.09 (s, 2), 4.97 (ddd, 1, J = 9.6, 8.8, 5.2), 4.74 (m, 1), 3.82 (s, 3), 3.51 (m, 1), 3.45 (m, 2), 3.86 (dd, 1, J = 13.4, 6.2), 2.80−2.74 (m, 2), 2.75 (s, 3), 2.36 (m, 1), 2.16 (br d, 1, J = 12.8), 2.06 (m, 3), 1.88 (dd, 1, J = 13.6, 10.4), 1.68 (d, 1, J = 6.4, OH), 1.57 (m, 1), 1.44 (dd, 1, J = 13.6, 6.4), 1.16 (br d, 1, J = 12.8); ^{13}C NMR (CD_3OD) 160.0, 157.8, 152.4, 144.3, 138.3, 132.8, 131.3 (2 C), 130.3 (2 C), 129.7 (2 C), 129.2, 129.0 (2 C), 125.8 (2 C), 114.8 (2 C), 84.5, 68.4, 66.0, 60.8, 59.2, 55.8, 54.9, 53.3, 52.5, 51.6, 43.3, 36.7, 34.9, 29.7, 28.0; ^{13}C NMR ($CDCl_3$) 158.0, 156.2, 150.5, 142.9, 136.7, 130.5, 129.8 (2 C), 128.6 (2 C), 128.4 (2 C), 127.9 (2 C), 127.8, 124.4 (2 C), 113.8 (2 C), 82.9, 67.1, 65.1, 63.6, 59.3, 57.6, 55.2, 51.8, 50.1, 41.9, 41.6, 35.7, 33.1, 29.0, 28.7; IR (neat) 3455, 1694, 1682, 1610, 1538, 1514; $[\alpha]_D$ 22 (*c* 0.28, $CHCl_3$); HRMS (FAB) calcd for $C_{34}H_{40}N_3O_9S$ (MH^+) 666.2485, found 666.2466.

(2*S*,5*S*,6*S*,7*R*,8*R*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-6-(triethylsilyloxy)octahydro-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-yl (4-Nitrobenzene)sulfonate (45). TESOTf (60 μL, 0.25 mmol) was added to a solution of nosylate **44** (83 mg, 0.125 mmol) and Et_3N (73 μL, 0.50 mmol) in 2 mL of CH_2Cl_2 at −20 °C. The solution was stirred at 0 °C for 2 h, diluted with 10 mL of EtOAc, which was washed with 0.1 N HCl, water, and brine and dried (Na_2SO_4). The solvent was removed, and the residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc) to give 93 mg (99%) of **45**: ^{1}H NMR 8.39 (d, 2, J = 8.8), 8.09 (d, 2, J = 8.8), 7.35−7.29 (m, 5), 7.18 (d, 2, J = 8.8), 6.80 (d, 2, J = 8.8), 5.05 (s, 2), 4.97 (ddd, 1, J = 12.4, 7.2, 4.8), 4.74 (m, 1), 3.84 (br s, 1), 3.77 (s, 3), 3.68 (m, 1), 3.62 (m, 1), 2.92 (dd, 1, J = 15.2, 9.6), 2.82 (br d, 1, J = 11.2), 2.73 (dd, 1, J = 15.2, 4.8), 2.41 (s, 3), 2.37 (br s, 1), 2.35 (br d, 1, J = 11.6), 2.23 (dddd, 1, J = 13.6, 13.2, 11.6, 8.0), 2.02 (ddd, 1, J = 14.4, 8.0, 8.0), 1.86−1.69 (m, 3), 1.34 (dd, 1, J = 12.8, 6.8), 0.93 (t, 9, J = 8.0), 0.88 (br d, 1, J = 11.6), 0.55 (q, 6, J = 8.0); ^{13}C NMR 157.8, 156.2, 150.6, 142.8, 136.9, 131.3, 129.5 (2 C), 128.9 (2 C), 128.4 (2 C), 127.8 (2 C), 127.7, 124.4 (2 C), 113.6 (2 C), 83.3, 68.7, 66.8, 57.5, 57.2, 55.2, 51.3, 50.7, 42.9, 42.6, 35.7, 35.0, 28.6, 27.8, 25.4, 7.0 (3 C), 4.9 (3 C); IR (neat) 1694; $[\alpha]_D$ 35 (*c* 0.06, $CHCl_3$); HRMS (FAB) calcd for $C_{40}H_{54}N_3O_9SSi$ (MH^+) 780.3350, found 780.3362.

(2*S*,5*S*,6*S*,7*S*,8*S*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-6-(triethylsilyloxy)octahydro-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-yl Acetate (46). A solution of **45** (93 mg, 0.12 mmol), 18-crown-6 (34 mg, 0.13 mmol), and CsOAc (69 mg, 0.36 mmol) in benzene (2 mL) was stirred at 80 °C for 2 h. The resulting mixture was diluted with 20 mL of CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (3:1 hexane/EtOAc) gave 14.5 mg (20%) of elimination product **47**, followed by 56 mg (70%) of acetate **46**: ^{1}H NMR 7.37−7.27 (m, 5), 7.17 (d, 2, J = 8.4), 6.81 (d, 2, J = 8.4), 5.08 (s, 2), 4.88 (m, 1), 4.80 (m, 1), 3.78 (s, 3), 3.70 (m, 1), 3.59 (br s, 1), 3.52 (m, 1), 2.90 (dd, 1, J = 14.4, 9.2), 2.82 (br d, 1, J = 11.2), 2.73 (dd, 1, J = 14.4, 6.0), 2.51 (s, 3), 2.23 (dddd, 1, J = 13.6, 10.4, 7.2, 7.2), 2.12 (br s, 1), 2.06 (s, 3), 1.96 (m, 1), 1.86 (m, 1), 1.77−1.60 (m, 3), 1.39 (dd, 1, J = 12.8, 6.0), 1.26 (dd, 1, J = 12.4, 2.4), 0.96 (t, 9, J = 7.6), 0.60 (q, 6, J = 7.6); ^{13}C NMR 170.5, 157.8, 156.2, 137.0, 131.6, 129.6 (2 C), 128.4 (2 C), 127.8, 127.7 (2 C), 113.6 (2 C), 71.5, 70.3, 66.8, 58.0, 56.1, 55.3, 51.6, 50.6, 44.1, 42.8, 35.7, 31.7, 28.0, 26.8, 21.4, 21.1, 7.0 (3 C), 5.0 (3 C); IR (neat) 1732, 1694, 1613, 1514; $[\alpha]_D$ −6 (*c* 0.11, $CHCl_3$); HRMS (FAB) calcd for $C_{36}H_{53}N_2O_6Si$ (MH^+) 637.3673, found 637.3683.

Data for (2*S*,5*S*,6*S*,7*S*,10a*S*)-2-[[(benzyloxy)carbonyl]methylamino]-6-(triethylsilyloxy)-2,3,5,6,7,10-hexahydro-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine (**47**): ^{1}H NMR 7.37−7.27 (m, 5), 7.16 (d, 2, J = 8.4), 6.79 (d, 2, J = 8.4), 5.87 (ddd, 1, J = 9.6, 3.2, 3.2), 5.37 (ddd, 1, J = 9.6, 6.4, 6.4), 5.08 (s, 2), 4.81 (m, 1), 3.83 (m, 1), 3.77 (s, 3), 3.54 (ddd, 1, J = 9,6, 6.0, 2.0), 3.40 (dd, 1, J = 2.8, 2.0), 2.86 (dd, 1, J = 14.4, 9.6), 2.78 (br d, 1, J = 10.4), 2.65 (dd, 1, J = 14.4, 6.0), 2.50 (ddd, 1, J = 6.0, 6.0, 2.8), 2.47 (s, 3), 2.37 (br d, 1, J = 18.8), 2.22 (m, 1), 2.06 (br d, 1, J = 18.8), 1.95 (m, 1), 1.40 (dd, 1, J = 12.0, 5.0), 1.08 (dd, 1, J = 12.0, 2.8), 0.98 (t, 9, J = 8.0), 0.61 (q, 6, J = 8.0); ^{13}C NMR 157.7, 156.3, 137.1, 132.1, 130.8, 129.7 (2 C), 128.6, 128.4 (2 C), 127.8, 127.8 (2 C), 113.4 (2 C), 70.6, 66.8, 58.3, 55.3, 52.7, 51.7, 49.8, 43.3, 39.0, 38.3, 35.6, 28.0, 24.8, 7.1 (3 C), 5.1 (3 C); IR (neat) 1699, 1612, 1585, 1514; $[\alpha]_D$ −77.1 (*c* 0.68, $CHCl_3$); HRMS (FAB) calcd for $C_{34}H_{49}N_2O_4Si$ (MH^+) 577.3462, found 577.3453.

(2*S*,5*S*,6*S*,7*S*,8*S*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-6-(triethylsilyloxy)octahydro-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-ol (48). A solution of acetate **46** (56 mg, 88 μmol) and 10 mg of K_2CO_3 in MeOH (1 mL) was stirred at 25 °C for 3 h. The solution was filtered, and the filtrate was concentrated under the reduced pressure. The residue was dissolved in 10 mL of EtOAc, which was washed with water and brine and dried (Na_2SO_4). Removal of the solvent afforded 48 mg (92%) of alcohol **48**: ^{1}H NMR 7.37−7.27 (m, 5), 7.18 (d, 2, J = 8.4), 6.81 (d, 2, J = 8.4), 5.08 (s, 2), 4.82 (m, 1), 3.90 (m, 1), 3.77 (s, 3), 3.63 (m, 1), 3.57 (ddd, 1, J = 9.2, 6.0, 2.4), 3.51 (dd, 1, J = 2.4, 2.4), 2.90 (dd, 1, J = 14.4, 9.2), 2.81 (dd, 1, J = 11.2, 2.8), 2.73 (dd, 1, J = 14.4, 6.0), 2.53 (s, 3), 2.26 (dddd, 1, J = 14.4, 10.4, 6.8, 6.8), 2.11 (br s, 1), 2.03 (m, 1), 1.91 (m, 2), 1.70 (m, 1), 1.60 (m, 1), 1.39 (dd, 1, J = 12.8, 6.8), 1.36 (dd, 1, J = 12.4, 2.8), 0.97 (t, 9, J = 7.6), 0.61 (q, 6, J = 7.6); ^{13}C NMR 157.7, 137.0, 131.7, 129.6 (2 C), 128.4 (2 C), 127.8, 127.7 (2 C), 113.5 (2 C), 71.8, 67.5, 66.8, 58.4, 56.2, 55.2, 51.6, 50.7, 45.9, 44.0, 35.7, 31.6, 30.2, 28.1, 20.6, 7.1 (3 C), 5.1 (3 C), (CBZ carbonyl was not observed); $[\alpha]_D$ −19 (*c* 0.17, $CHCl_3$).

(2*S*,5*S*,6*S*,7*R*,8*S*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-6-(triethylsilyloxy)octahydro-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-yl Dibenzyl Phosphate (49). A solution of alcohol **48** (48 mg, 81 μmol), 1-*H*-tetrazole (13 mg, 0.19

mmol) and *N*,*N*-diisopropyl dibenzyl phosphoramidite (50 μL, 148 μmol) in 1 mL of CH_2Cl_2 was stirred at 25 °C for 2 h and then cooled to 0 °C. *t*-BuOOH (23 μL, 5−6 M in decane, 127 μL) was added. The resulting solution was stirred at 0 °C for 45 min. The reaction mixture was diluted with 5 mL of CH_2Cl_2, washed with Na_2SO_3 solution, water, and brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (1:1 hexane/EtOAc) gave 64 mg (93%) of phosphate **49**: ^{1}H NMR 7.37−7.30 (m, 15), 7.14 (d, 2, J = 8.4), 6.80 (d, 2, J = 8.4), 5.08 (s, 2), 5.04−5.00 (m, 4), 4.79 (m, 1), 4.54 (m, 1), 3.77 (s, 3), 3.65 (m, 1), 3.48 (m, 1), 3.47 (br s, 1), 2.86 (dd, 1, J = 14.8, 8.8), 2.80 (dd, 1, J = 10.4, 2.0), 2.69 (dd, 1, J = 14.8, 9.6), 2.50 (s, 3), 2.30 (br s, 1), 2.20 (m, 1), 2.04−1.75 (m, 4), 1.55 (dd, 1, J = 13.6, 6.8), 1.35 (dd, 1, J = 12.8, 6.0), 1.25 (dd, 1, J = 12.8, 3.2), 0.92 (t, 9, J = 7.6), 0.54 (q, 6, J = 7.6); ^{13}C NMR 157.8, 156.2, 137.9, 135.86 (J_{cp} = 6), 135.81 (J_{cp} = 6), 131.4, 129.5 (2 C), 128.52 (4 C), 128.45 (3 C), 128.38 (2 C), 127.80 (3 C), 127.77 (2 C), 127.75, 113.6 (2 C), 75.5 (J_{cp} = 6.1), 70.9, 69.14 (J_{cp} = 6.0), 69.07 (J_{cp} = 6.0), 66.8, 57.9, 56.4, 55.2, 51.5, 50.7, 44.1 (J_{cp} = 3.8), 43.9, 35.6, 31.4, 28.4 (J_{cp} = 4), 28.0, 20.4, 7.0 (3 C), 5.0 (3 C); ^{31}P NMR (85% H_3PO_4 as external reference) −1.03; IR (neat) 1694, 1612, 1513; $[\alpha]_D$ −4.3 (*c* 0.24, $CHCl_3$); HRMS (FAB) calcd for $C_{48}H_{64}N_2O_8PSi$ (MH^+) 855.4170, found 855.4174.

(2*S*,5*S*,6*S*,7*R*,8*S*,10a*S*)-2-[[(Benzyloxy)carbonyl]methylamino]-octahydro-6-hydroxy-5-[(4-methoxyphenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-yl Dibenzyl Phosphate (50). A solution of phosphate **49** (48 mg, 58 μmol) and 65 μL of 1 M TBAF in THF in 0.5 mL of THF was stirred at 25 °C for 2 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). Removal of solvent followed by flash chromatography of the residue on silica gel (1:1 CH_2Cl_2/EtOAc) gave 40 mg (96%) of alcohol **50**: ^{1}H NMR 7.4−7.3 (m, 15), 7.16 (d, 2, J = 8.0), 6.83 (d, 2, J = 8.0), 5.11 (s, 2), 5.05−4.94 (m, 4), 4.80 (m, 1), 4.33 (m, 1), 3.79 (s, 3), 3.44 (m, 1), 3.29 (m, 1), 3.15 (m, 1), 2.79 (s, 3), 2.79 (m, 1), 2.74 (dd, 1, J = 9.6, 5.6), 2.12 (m, 1), 2.03 (m, 1), 1.93−1.74 (m, 5), 1.68 (d, 1, J = 5.6, OH), 1.61 (m, 1), 1.49 (br d, 1, J = 13.6), 1.42 (dd, 1, J = 13.6, 6.0); ^{13}C NMR 158.0, 156.3, 136.8, 135.9 (J_{cp} = 6.0, 2 C), 130.7, 130.0 (2 C), 128.53 (4 C), 128.50 (3 C), 128.44 (2 C), 127.92 (3 C), 127.90 (2 C), 127.85, 113.8 (2 C), 74.9 (J_{cp} = 6), 69.21 (J_{cp} = 5), 69.20 (J_{cp} = 5), 67.1, 67.0, 58.4, 58.3, 55.2, 51.8, 50.1, 43.5 (J_{cp} = 4), 42.9, 35.6, 29.7, 28.9, 28.7 (J_{cp} = 4), 24.2 (br); IR (neat) 3419, 1694, 1613, 1514; $[\alpha]_D$ 7.3 (*c* 0.27, $CHCl_3$).

Synthetic (−)-FR901483 (1). Aqueous 3 N HCl (6 μL) was added to a solution of alcohol **50** (12 mg, 0.016 mmol) in MeOH (1 mL). The solvent was removed under reduced pressure giving **50**·HCl, which was dissolved in 0.2 mL of MeOH. Pd/C (5 mg, 10%) was added, and the mixture was stirred at 25 °C under 1 atm of H_2 for 3 h and filtered through Celite, which was washed with MeOH. The combined filtrate was concentrated to give 7.4 mg (92%) of (−)-FR901483 (**1**): mp 220−225, decomp (lit.[1] mp 210−213 °C); ^{1}H (CD_3OD) 7.32 (d, 2, J = 8.4), 6.89 (d, 2, J = 8.4), 4.46 (dd, 1, J = 12.8, 10.0), 4.24 (br d, 1, J = 8.0), 4.19 (m, 1), 3.82 (m, 2), 3.78 (s, 3), 3.59 (br s, 1), 3.29 (dd, 1, J = 11.6, 10.4), 3.04 (br d, 1 J = 10.4), 2.71 (s, 3), 2.60 (dd, 1, J = 12.8, 9.2), 2.44 (br s, 1), 2.29−2.06 (m, 6), 1.89 (br d, 1, J = 10.4); ^{13}C NMR 160.4, 131.7 (2 C), 128.7, 115.3 (2 C), 71.0 (J_{cp} = 5), 68.2, 64.1, 61.6, 55.7, 54.9, 51.8, 42.9 (J_{cp} = 3), 41.9, 34.0, 32.3, 28.3, 28.0, 22.4; IR (KBr) 3394, 2958, 2713; $[\alpha]_D$ −10 (*c* 0.37, MeOH) ($[\alpha]_D$ changed to +5 upon the addition of 3 μL (20% mol) of 1 N aqueous HCl) [lit.[1,20] $[\alpha]_D$ −11 (*c* 0.74, MeOH)]; HRMS calcd for $C_{20}H_{31}N_2O_6P$·$HCl+NH_4$ 444.2263, found 444.2223. The ^{1}H NMR and ^{13}C NMR spectra are identical to those of the natural product.[1,20]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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