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Enantioselective Total Syntheses of (−)-FR901483 and (+)-8-*epi*-FR901483

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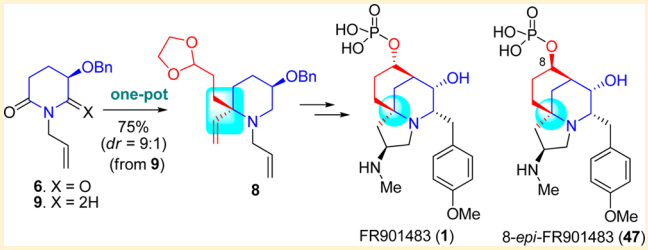
Supporting Information

ABSTRACT: The enantioselective total syntheses of the potent immunosuppressant FR901483 (**1**) and its 8-epimer (**47**) have been accomplished. Our approach features the use of building block **6** as the chiron, the application of the one-pot amide reductive bis-alkylation method to construct the chiral aza-quaternary center (dr = 9:1), regio- and diastereoselective intramolecular aldol reaction to build the bridged ring, and RCM to form the 3-pyrrolin-2-one ring.



INTRODUCTION

Immunosuppressants are molecules capable of exerting selective effects on the immune response, which have become indispensable tools in the prevention of rejection in organ transplantation and in the treatment of immune-related diseases.[1] Search of immunosuppressants from natural products have been proven fruitful, which resulted in the discovery of cyclosporine A, FK506, and rapamycin as effective immunosuppressive agents currently in clinical use. In addition, FK506 and rapamycin have served as tools in the investigation of the molecular mechanisms of signal transduction. However, there is a continuing demand for the development of more potent and less-toxic immunosuppressive agents. FR901483 (**1**, Figure 1)

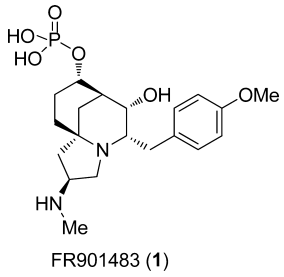


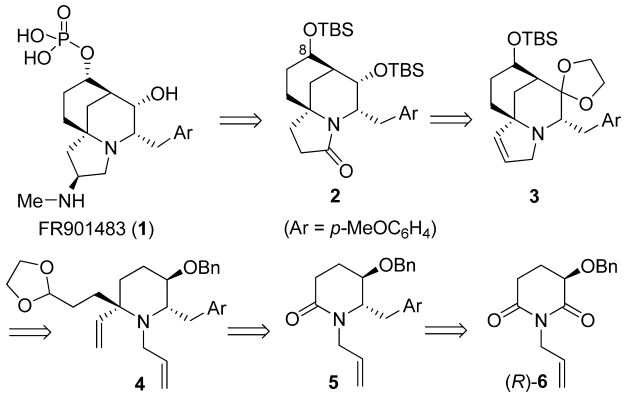
Figure 1. Potent immunosuppressant FR901483 (**1**).

is a potent immunosuppressant isolated from the fermentation broth of the *Cladobotryum* sp. No. 11231 in 1996.[2] The potent activity and unique yet challenging structural features of this molecule have rendered it an attractive target for synthetic organic chemists. Among numerous synthetic studies[3−6] toward FR901483 (**1**), only six enantioselective total syntheses[3a−g] and a formal total syntheses[3h] have been reported. As a continuation of our endeavor to develop step-economical[7] and 3-benzyloxyglutarimide[8]-based synthetic methodologies for the asymmetric synthesis of piperidine ring-containing alkaloids,[9] we have embarked on the enantioselective total synthesis of FR901483. The preliminary results involving a formal enantioselective total synthesis of FR901483 have been reported recently.[10] We describe herein the full details of this work, including the final completion of the total synthesis of (−)-FR901483 (**1**) as well as the synthesis of (+)-8-*epi*-FR901483 (**47**).

RESULTS AND DISCUSSION

As depicted in Scheme 1, our retrosynthetic analysis of FR901483 (**1**) is based on the use of two key synthetic

Scheme 1. Retrosynthetic Analysis of FR901483 (1)



methodologies developed in our laboratory as the cornerstones, namely, the use of the chiral building block **6**[9] as the chiron and the one-pot amides reductive bis-alkylation method[7a] for the synthesis of polysubstituted piperidine **4** from piperidin-2-one

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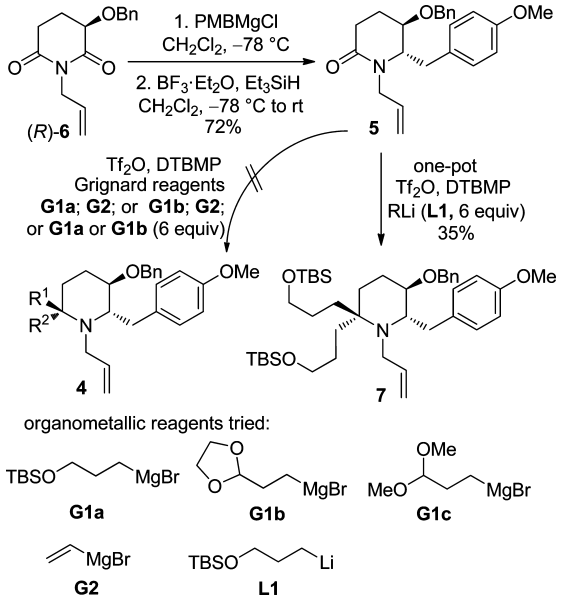
5. On the basis of our strategy for the construction of the tricyclic core, FR901483 (**1**) was envisioned to be available from compound **2** via lactam α-amination followed by selective phosphate esterification. The amination was envisioned to occur diastereoselectively from the more accessible convex face of the tricyclic core to establish the correct stereochemistry. Although the stereochemistry at C-8 was uncertain, either C-8 epimer could be convertible to the required phosphate ester with conversion[3a] or inversion[3b] of configuration. In addition, Sorensen and co-workers have demonstrated that the two hydroxyl groups are easily distinguishable.[3b] Compound **2**, in turn, could be obtainable from compound **3** via allylic oxidation and *cis*-diastereoselective reduction by the Fukuyama procedure.[4b] Retro-aldol reaction[3a−d,4b,c] and retro-RCM[11] disconnections of compound **3** suggested polysubstituted piperidine **4** as a precursor. In the light of our method for the one-pot reductive bis-alkylation of lactams/amides[7a] and that for the two-step reductive *trans*-diastereoselective alkylation of imides,[8,9] (*R*)-3-benzyloxyglutarimide **6** was deduced to be the starting material.

The synthesis commenced with the regio- and diastereoselective reductive alkylation of (*R*)-3-benzyloxyglutarimide **6** (Scheme 2). Treatment of imide **6** with *p*-methoxybenzyl

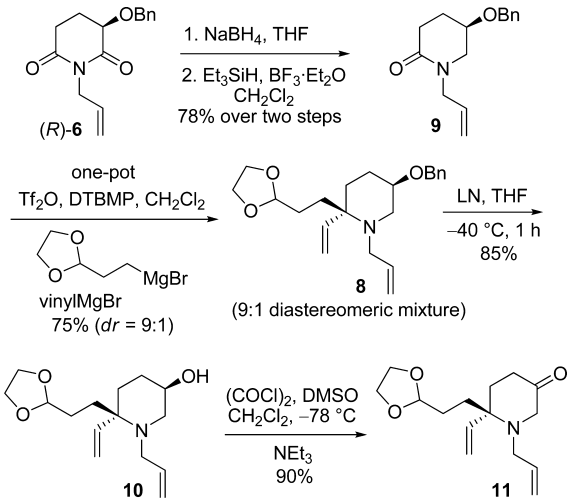
Scheme 2. Attempted Synthesis of 4 via Bisalkylation of 5



magnesium chloride in CH_2Cl_2 at −78 °C for 3 h, followed by a reductive dehydroxylation (Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C−rt, 12 h) of the resulting hemiaminal,[9] afforded lactam **5** in 72% yield as the sole observable diastereomer (determined by ^1H NMR). Next, we attempted to construct the quaternary carbon center by using the amide reductive bis-alkylation method developed in our laboratory.[7a] Lactam **5** was thus successively treated with triflic anhydride (Tf_2O, 1.1 equiv), DTBMP (1.0 equiv), Grignard reagent **G1a**, and vinyl magnesium bromide (**G2**) in CH_2Cl_2 at −78 °C. Unfortunately, no desired product **4** was observed. When more reactive Büchi Grignard reagent[12] (**G1b**) or 3,3-dimethoxypropyl magnesium bromide[13] (**G1c**) was used instead of **G1a**, no desired product was produced. To ascertain if the failure of this reaction was caused by the less nucleophilic vinyl magnesium bromide, the reductive bis-alkylation was undertaken with 6 equiv of Grignard reagents **G1a** (or more reactive **G1b**). Nevertheless, no desired product was observed. The sluggish reaction may thus be attributed to the steric hindrance of lactam **5**. The assumption was further confirmed by the reductive bis-alkylation of **5** with an even more reactive lithium reagent **L1** (6 equiv), in which the desired product **7** was produced in 35% yield.

In view of the unfavorable steric effect of *p*-methoxybenzyl group on the reductive bis-alkylation, this group had to be introduced at the late stage of our synthetic route. In the modified approach, piperidin-2-one **9** was first prepared from imide **6** by partial and regioselective reduction with $NaBH_4$ (−30 °C, 15 min) and the subsequent reductive dehydroxylation (Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C−rt, 12 h) of the resultant hemiaminal intermediate (Scheme 3). The observed

Scheme 3. Stereoselective Synthesis of the Key Intermediate 11



high regioselectivity in the reduction of **6** with $NaBH_4$ to give the corresponding hemiaminal intermediate is in agreement with the well documented malimide derivatives[14] and is attributable to the higher reactivity of the C-2 carbonyl as a result of the attractive inductive effect of the α-*O*-benzyl group,[14] although a chelation-promoted regioselective reduction could not be excluded.[15] The subsequent bis-alkylation of lactam **9** proceeded as planned to produce the desired amine **8** in 75% yield with a remarkable 9:1 diastereoselectivity (determined by ^1H NMR of the crude sample). The stereochemistry of the major diastereomer was deduced to be *trans* based on mechanistic consideration that the vinyl group would approach the *N*-acyliminium ion intermediate from the α-side opposing the benzyloxy group, which was confirmed at a later stage. It is worth mentioning that among various synthetic approaches developed for the synthesis of FR901483 (**1**), this is the first example utilizing the one-pot amide reductive bis-alkylation method to construct the quaternary chiral center.

For *O*-debenzylation of compound **8**, the standard hydrogenolytic conditions were obviously unsuitable due to the presence of two olefinic groups. Lithium naphthalenide (LN)[16] was chosen as the proper reagent for the selective *O*-debenzylation of piperidine **8** (diastereomeric mixture), which gave, after chromatographic separation, the piperidin-3-ol **10** as a pure diastereomer in 85% yield.

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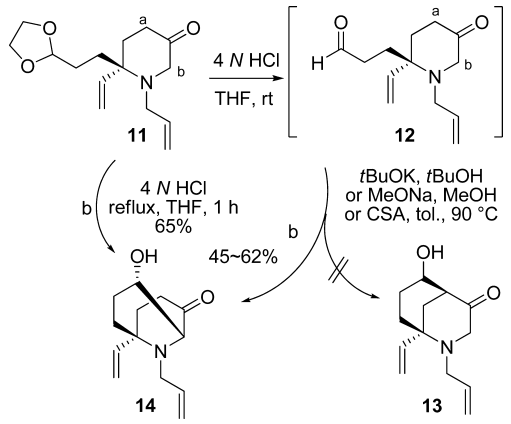
Before the key intramolecular aldol ring closure reaction was taken, the piperidin-3-ol **10** needed to be oxidized to the ketone **11**. The oxidation with the Dess–Martin periodinane failed to give the desired ketone, and the Ley oxidation gave only 35% of **11**, whereas the Swern oxidation was successful, which yielded ketone **11** in 90% yield in the presence of an extreme excess of triethylamine [6 equiv $(COCl)_2$, 12 equiv DMSO, CH_2Cl_2, −78 °C, 1 h; then 25 equiv NEt_3].

Although the utilization of an intramolecular aldol reaction has been reported in the syntheses of FR901483,[3a−d,4b,c] this key step turned out to be a challenge in our case. After the acetal **11** was deprotected with a 4 N HCl solution (Scheme 4)

Scheme 4. Attempted Regioselective Deacetalization−Intramolecular Aldol Reaction



and neutralized with a saturated aqueous solution of $NaHCO_3$, the crude **12** was subjected to the aldol reaction under either basic (*t*BuOK/*t*BuOH, or MeONa/MeOH) or acidic (CSA, toluene, 90 °C) conditions. Unfortunately, only the regioisomer **14** was obtained in moderate yields (45−62%). The stereochemistries of the newly formed stereogenic centers of compound **14** were assigned as shown in Figure 2 by

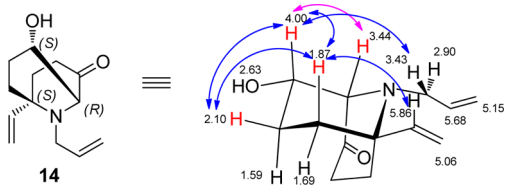
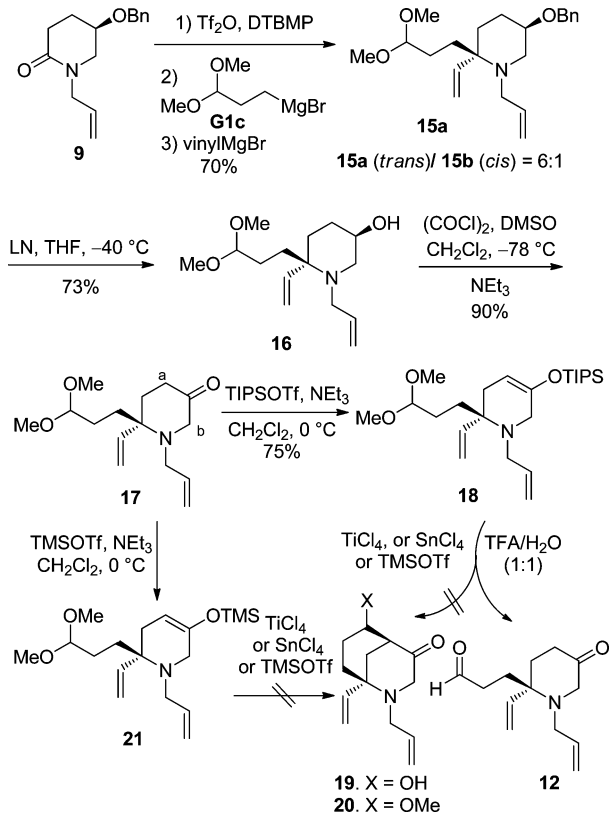


Figure 2. Observed key NOE correlations of compound **14**.

NOESY experiments, in which the NOE correlations between the carbinolic proton at δ 4.00 and the two β-face oriented methylenic protons at δ 1.87 and δ 2.10, as well as the carbonyl α-H appearing at δ 3.44, were observed, while no correlations were observed between the carbinolic proton (δ 4.00) and the two α-face oriented methylenic protons at δ 1.59 and δ 1.69. The one-pot deacetalization−aldol reaction (4 N HCl, THF, reflux, 1 h) was also attempted, but the undesired regioisomer **14** (yield 65%) was once again produced.

To tackle the problem of regioselectivity, the use of preformed silyl enol ether appeared attractive.[4a] To facilitate the deacetalization reaction, piperidin-3-one **17** was synthesized from **8** (Scheme 5) following the procedures described in Scheme 3. Silylation (TIPSOTf, NEt_3, CH_2Cl_2, 0 °C or TMSOTf, NEt_3, CH_2Cl_2, 0 °C) of ketone **17** produced

Scheme 5. Attempted Regioselective Intramolecular Mukaiyama Aldol Reaction



regioselectively the desired silyl enol ethers **18** and **21**. However, both of them failed to yield the desired Mukaiyama aldol product **19** (or **20**) under various Lewis acid mediated conditions (cf. Scheme 5). Treatment of compound **18** with a mixture of TFA/H_2O led to the formation of keto-aldehyde **12**.

The failure of the regioselective aldol reaction (Scheme 4) might be attributed to the influence of the basic amino group. To our surprise, when compound **11** was treated with a 4 N HCl solution and the resulting deacetalization product, in the form of its hydrochloride salt, was reacted with CSA (1.0 equiv), adduct **14** and concomitantly acetalized regioisomer **22** were obtained as a 1:1 ratio in a combined yield of 60%. Encourage by this result, compound **11** was treated with a 4 N HCl aqueous solution (6.0 equiv) in THF at rt for 1 h. After further reaction at 50 °C for 30 min, ethylene glycol (EG, 4.0 equiv) was added, and the resulting mixture was concentrated. The resultant residue, in the form of its hydrochloride salt, was reacted with CSA (0.3 equiv) in toluene at 90 °C for 10 min, which produced predominantly compound **22** as the sole observable diastereomer in 53% yield, along with 5% of the regioisomer **14** (Scheme 6). It was remarkable that the regioselectivity of the intramolecular aldol reaction was inversed just by changing the reaction conditions (cf. Scheme 4). The relative stereochemistry of **22** was established on the basis of the observed strong NOE correlations between the carbinolic proton at δ 3.83 and the four β-face methylenic protons at δ 1.41, 1.65, 2.12, and 2.24.

The regioselections of the intramolecular aldol reactions can be understood from the conformational analysis shown in Scheme 7. Under the HCl-only conditions (in THF at rt, cf. Scheme 4), among the four possible regio-conformers of the amino-enol hydrochloride salt **12a**−**12d**, only **12b** and **12d** can

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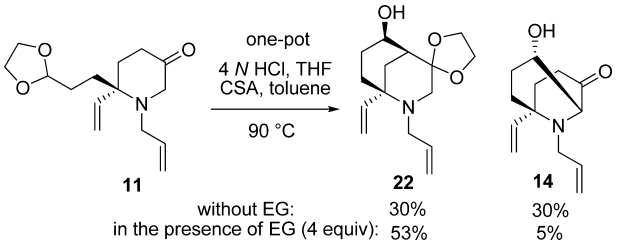
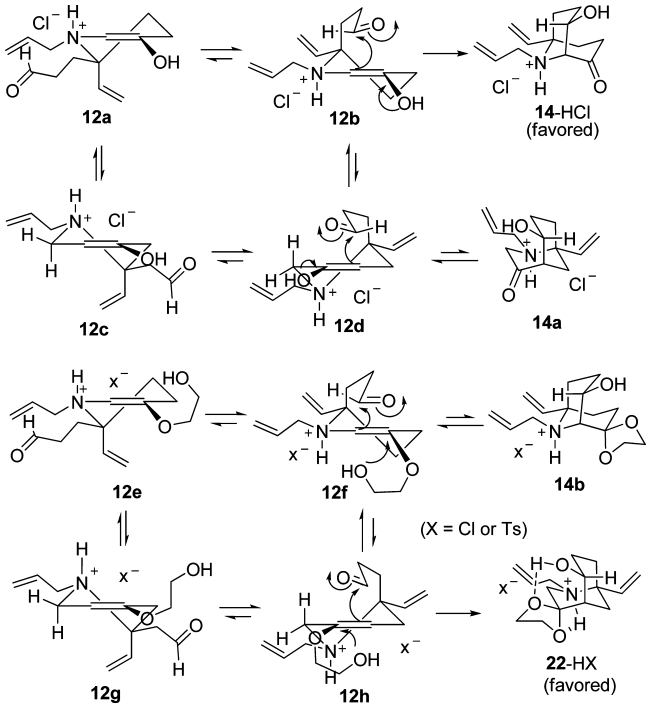
Scheme 6



Scheme 7

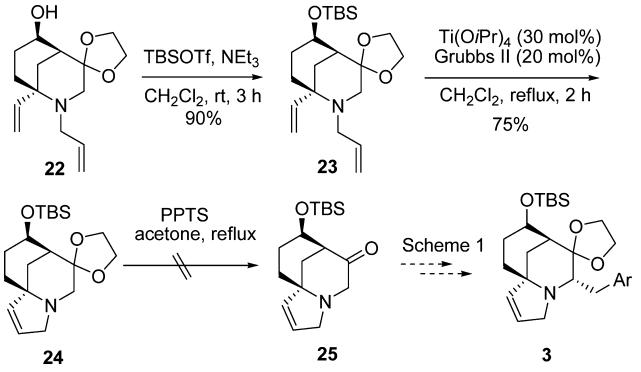


lead to the aldol products. The latter conformers are particular favored due to an overlap of orbitals of the quasi parallelly disposed carbonyl and enol. The aldol product **14a**-HCl is disfavored by the severe interaction between the *N*-allyl group and the cyclohexyl protion compared to the synclinal interaction between the vinyl and the allyl groups in **14**-HCl. Consequently, aldol product **14** was obtained as the sole observable regio- and diastereomer.

For the reaction of the hydrochloride salt of compound **11** in the presence of both CSA and ethylene glycol in toluene at 90 °C (cf. Scheme 6), as discussed above, among the four possible regio-conformers of the amino-enol hydrochloride salt **12e**–**12h**, only **12f** and **12h** can lead to the aldol products, and regio- and diastereomer **22**-HX is favored due to the stabilization effect of the hydrogen bonding between the axial acetal oxygen and N–H, and between the equatorial acetal oxygen and OH, in addition to a lack of an unfavorable synclinal interaction compared with that of **14b** (Scheme 7).

The hydroxyl group in **22** was then protected as TBS ether **23** (90%) by reaction with TBSOTf/NEt_3 in CH_2Cl_2 at 0 °C (Scheme 8). The ring-closing olefin metathesis (RCM)[11,6f] of **23** was undertaken using Grubbs second generation catalyst[17] in the presence of $Ti(OiPr)_4$[18] to give the cyclization product **24** in 75%. The construction of the azatricyclic core of FR901483 was thus accomplished. According to our synthetic

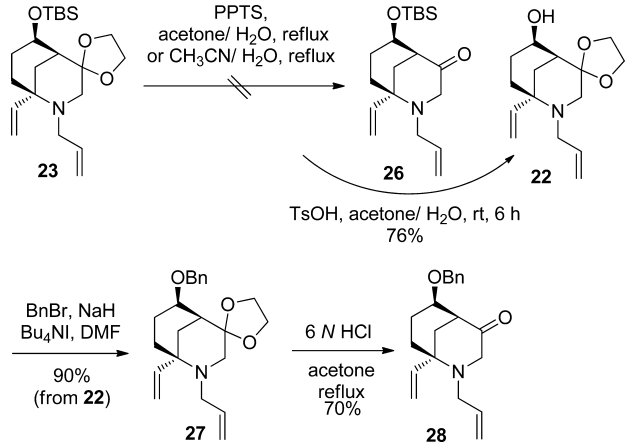
Scheme 8



plan, selective deacetalization of **24** and α-alkylation of the resulting ketone **25** followed by reacetalization would give compound **3**. However, we were unable to perform the selective deacetalization of **24**. The synthetic plan had to be modified.

Diene **23** was to be selectively deacetalized before the ring-closing olefin metathesis. However, treatment of **23** with PPTS in wet acetone or CH_3CN at reflux failed to give ketone **26**, while *p*-TsOH-catalyzed reaction (TsOH, acetone/H_2O, rt) led chemoselectively to desilylation, giving back hydroxy-acetal **22** in 76% yield (Scheme 9). We therefore selected benzyl group

Scheme 9. Synthesis of Piperidin-3-one 28



as a robust hydroxyl protecting group, which turned out to be successful. The deacetalization of *O*-benzylated acetal **27**, generated from *O*-benzylation of **22** (BnBr, NaH, *n*-Bu_4NI, DMF, rt, 18 h, yield 90%), went smoothly with 6 N HCl in refluxing acetone, producing the α-aminoketone **28** in 70% yield.

The regioselective *p*-methoxybenzylation of ketone **28** (KHMDS, THF, *p*-$MeOC_6H_4Br$, DMF) proceeded smoothly to give compound **29** as the sole isolable diastereomer in 80% yield (Scheme 10). The subsequent SmI_2-mediated diastereoselective reductions[4b,19] of ketone **29**, however, failed to give the desired piperidinol **30**. Enamine **31** was formed instead.

The unsuccessful transformation of α-aminoketone **29** to the desired β-amino alcohol **30** was attributed to the unfavorable effect of the amino group. In light of the successful transformation of a tricyclic keto lactam to the corresponding β-hydroxylactam by Fukuyama,[4b] tricyclic lactam **34** was then envisaged as a key intermediate in our synthesis (Scheme 11).

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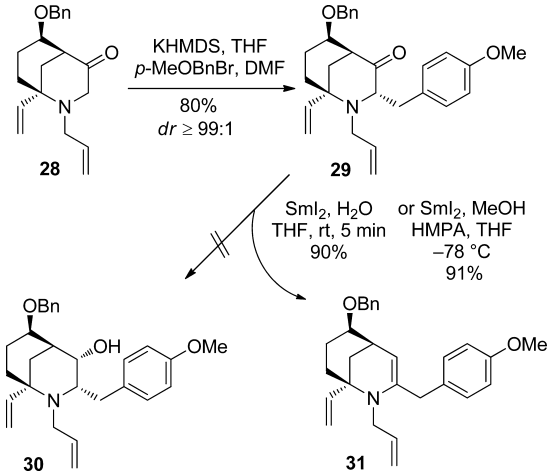
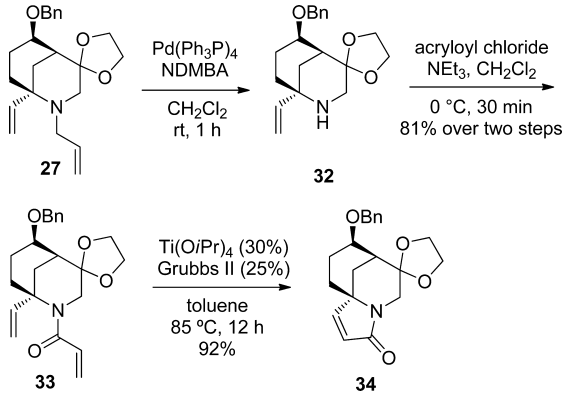
Scheme 10. Attempted Diastereoselective Reduction of α-Aminoketone 29



Scheme 11. Synthesis of Tricyclic Core 34

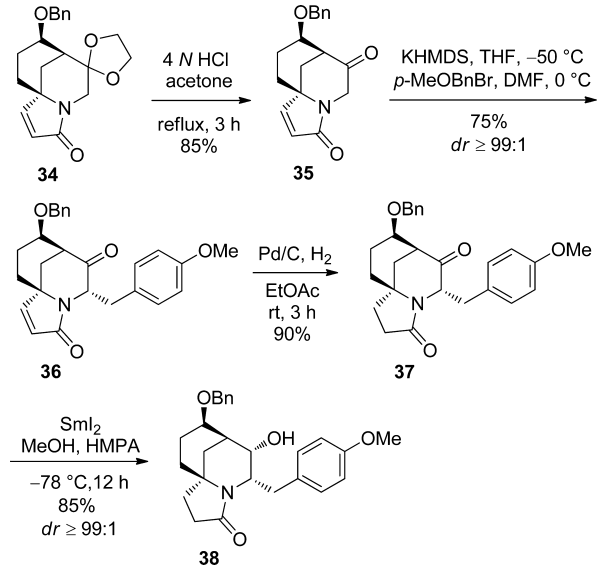


For this purpose, compound **27** was subjected to Pd-catalyzed *N*-deallylation[20] [$Pd(Ph_3P)_4$ (0.01 equiv), NDMBA (3 equiv), CH_2Cl_2, rt, 1 h], and the resulting amine **32** was acryloylated with acryloyl chloride and NEt_3 in CH_2Cl_2 at 0 °C to give acrylamide **33** in 81% yield over two steps.

The RCM reaction of diene **33** was investigated. Formation of α,β-unsaturated lactams by the RCM reaction of acrylamides using either Grubbs first or second generation catalyst have been well documented.[21] The reaction generally proceeded well in CH_2Cl_2.[6f,21] However, all attempts to perform the RCM reaction of **33** using the Grubbs first or second generation catalyst in CH_2Cl_2 were unsuccessful. Considering the steric hindrance of the substrate, it was envisioned that higher reaction temperature would favor the reaction. Indeed, when a toluene solution of acrylamide **33** was heated together with the Grubbs second generation catalyst (25 mol %) at 85 °C for 12 h, the desired cyclized product **34** was obtained in 30% yield, along with 60% of the recovered starting material. Remarkably, when the reaction (Grubbs II 25 mol %, toluene, 85 °C) was run in the presence of 30 mol % of $Ti(OiPr)_4$,[22] the desired tricyclic core **34** was obtained in 92% yield.

Acetal **34** was selectively deacetalized by treatment with 4 N HCl in refluxing acetone to give the keto-amide **35** in 85% yield (Scheme 12). Ketone **35** was deprotonated with KHMDS (1 equiv) in THF at −50 °C to give the enolate, which was added to *p*-methoxybenzyl bromide (3.0 equiv) in DMF at 0 °C to produce compound **36** as the only observable regio- and

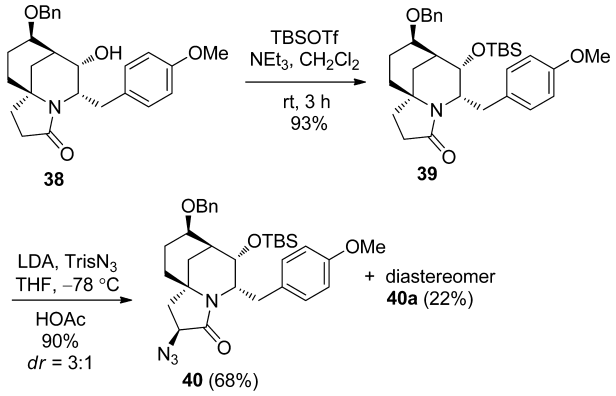
Scheme 12. Diastereoselective Synthesis of the Tricyclic Core 38



diastereomer in 75% yield. Selective hydrogenation of **36** on 10% Pd/C (30 wt %) under 1 atm of H_2 in EtOAc produced lactam **37** in 90% yield. The SmI_2-mediated reduction[4b,19] of ketone **37** (SmI_2 5 equiv, HMPA 25 equiv, MeOH 10 equiv, THF, −78 °C, 12 h) gave the desired *cis*-diastereomer **38** as the only observable diastereomer in 85% yield. The spectral data of **38** matched those reported for the racemic one.[6d] The relative stereochemistry of our synthetic product **38** was thus confirmed as shown in Scheme 12.

We next turned our attention to the stereoselective α-amination of lactam **38**. Hydroxyl group in **38** was first protected (TBSOTf, NEt_3, CH_2Cl_2, 93%) as TBS ether **39** (Scheme 13). Successive treatment of **39** with LDA (3.0 equiv)

Scheme 13. Synthesis of Compound 40



and $TrisN_3$ (3 equiv) at −78 °C for 5 min, followed by quenching with HOAc, gave desired azide **40** as a separable diastereomeric mixture in a 3:1 ratio with a combined yield of 90%. The major diastereomer **40** was formed via the electrophilic addition from the less hindered β-face, the stereochemistry of which was determined by NOESY experiments.

To convert the azido group to the *N*-methylamino group, azido compound **40** was first hydrogenated (10% Pd/C 30 wt %, H_2 1 atm) in the presence of Boc_2O (1.2 equiv) to give the

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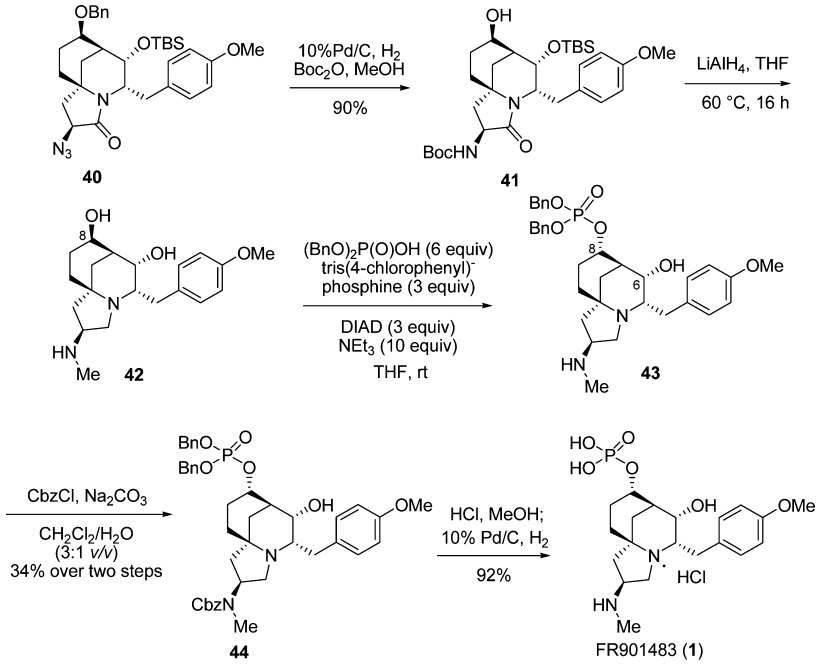
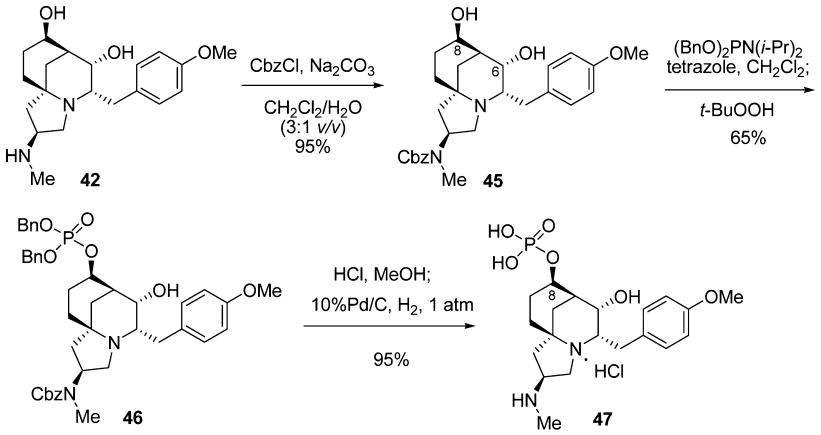
Scheme 14. Synthesis of FR901483 (1)



Scheme 15. Synthesis of 8-*epi*-FR901483 (47)



protected compound **41** in 90% yield (Scheme 14). Treatment of compound **41** with a large excess of $LiAlH_4$ (30 equiv) in THF at 60 °C for 16 h afforded the amino-diol **42** in 92% yield. The ^1H and ^{13}C NMR spectral data of compound **42** are in agreement with those reported by Ciufolini.[3d] It is worth noting that *N*-Boc reduction to the *N*-Me group, lactam reduction to pyrrolidine, and *O*-desilylation occurred sequentially in this scenario.

To complete the total synthesis of (−)-FR901483 (**1**), an inversion of the configuration at C-8 was necessary. In light of previous work by Sorensen[3b] and Ciufolini,[3d] compound **42** was converted to **43** by treatment with $(BnO)_2P(O)OH$ (6.0 equiv), tris(4-chlorophenyl)phosphine (3.0 equiv), DIAD (3.0 equiv), and Et_3N (10.0 equiv) at rt for 1 h. Without purification, the presumed crude product of **43** was dissolved in a mixed solvent system of CH_2Cl_2/H_2O (3:1 v/v) and treated with CbzCl (4.0 equiv) and Na_2CO_3 (10.0 equiv), giving compound **44** in 34% over two steps. Final hydrogenolysis (10% Pd/C 100 wt %, MeOH, H_2, 1 atm, rt, 6 h) of the monohydrochloride salt of **44** produced (−)-FR901483 (**1**) in 92% yield. The physical and ^1H and ^{13}C NMR spectral data of our synthetic compound **1** were in good agreement with those reported by Snider.[3a]

In view of the importance of stereoisomers and/or analogues in drug R & D, the synthesis of 8-*epi*-FR901483 (**47**) was envisioned. Thus, amino-diol **42** was treated with CbzCl [Na_2CO_3, CH_2Cl_2/H_2O (3:1 v/v), rt, 2 h] to give the chemoselectively *N*-protected product **45** in 95% yield (Scheme 15). The next task resided in the regioselective monophosphatation of the equatorial hydroxyl group at C-8. Since Sorensen has nicely demonstrated, during the synthesis of FR901483 (**1**), that the more accessible equatorial hydroxyl group at C-8 could undergo regioselective Mitsunobu reaction in the presence of the more hindered axial hydroxyl group at C-6,[3b] a direct regioselective monophosphatation of the diol **45** was envisaged. To our delight, treatment of **45** with $(BnO)_2PN(i\text{-}Pr)_2$ (1.8 equiv)/tetrazole (10 equiv) at 0 °C for 2 h, followed by oxidation of the presumed dibenzyl phosphite ester with *t*-BuOOH (3 equiv),[3a] produced phosphate **46** selectively in 65% yield. Hydrogenolysis (10%

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Pd/C, 50 wt %, H_2, 1 atm, MeOH, rt, 3 h) of the hydrochloride salt of **46** gave 8-*epi*-FR901483 (**47**) in 95% yield.

CONCLUSIONS

In summary, we have accomplished a novel enantioselective total synthesis of FR901483 (**1**) and 8-*epi*-FR901483 (**47**) starting from (*R*)-3-benzyloxyglutarimide **6** in 21 steps with overall yield of 1.3% and 2.4%, respectively. This novel route is based on two synthetic methodologies developed from our laboratory, namely, the use of chiron **6** as the starting material, and the one-pot amide reductive bis-alkylation method for the highly diastereoselective construction of quaternary α-carbon center in piperidine **8** from piperidin-2-one **9**.

EXPERIMENTAL SECTION

General Methods. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Silica gel (300−400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/hexane. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2. High-resolution mass spectra were obtained using electrospray ionization using an ICR analyzer (ESI-MS).

(5*R*,6*S*)-1-Allyl-5-(benzyloxy)-6-(4-methoxybenzyl)piperidin-2-one (5). To a solution of the known (*R*)-3-benzyloxyglutarimide **6**[9a] (7.20 g, 27.8 mmol) in CH_2Cl_2 (278 mL) at −78 °C was added dropwise a solution of freshly prepared *p*-$MeOC_6H_4MgCl$ in THF (1.0 M, 83.4 mL, 83.4 mmol). The mixture was stirred at −78 °C for 3 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. After extraction with ethyl acetate (5 × 100 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, ethyl acetate/hexane = 1:2) to give the hemiaminal as a diastereomeric mixture (10.3 g, yield 97%), which was used in the next step without further separation. To a cooled (−78 °C) solution of the above diastereomeric mixture of hemiaminal (10.3 g, 27.0 mmol) in CH_2Cl_2 (270 mL) were added dropwise Et_3SiH (42.7 mL, 270 mmol) and $BF_3{\cdot}OEt_2$ (10.0 mL, 81.0 mmol) successively. The mixture was stirred at −78 °C for 1 h, then allowed to warm up slowly, and stirred at room temperature overnight. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:1) to give compound **5** (7.30 g, yield 72% over two steps) as a colorless oil. $[\alpha]^{20}_D$ −56.1 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3075, 3017, 2951, 1675, 1520, 1462, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93−2.08 (m, 2H), 2.36 (ddd, *J* = 17.8, 6.6, 2.4 Hz, 1H), 2.49 (dd, *J* = 14.1, 10.0 Hz, 1H), 2.63 (ddd, *J* = 17.8, 11.4, 7.5 Hz, 1H), 3.02 (dd, *J* = 14.1, 4.6 Hz, 1H), 3.42 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.55 (dt, *J* = 4.4, 2.3 Hz, 1H), 3.71 (ddt, *J* = 10.0, 4.4, 1.7 Hz, 1H), 3.80 (s, 3H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.71 (ddt, *J* = 15.6, 4.4, 1.7 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.79 (dddd, *J* = 17.2, 10.2, 7.0, 4.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.08−7.17 (m, 2H), 7.20−7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 26.9, 37.9, 47.5, 55.2, 61.0, 69.8, 71.1, 114.1 (2C), 117.1, 127.3 (2C), 127.4, 128.2 (2C), 129.2, 129.7 (2C), 133.3, 137.9, 158.4, 169.5; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2064, found 366.2068.

(5*R*,6*S*)-1-Allyl-5-(benzyloxy)-2,2-bis[3-(*tert*-butyldimethylsilyloxy)propyl]-6-(4-methoxybenzyl)piperidine (7). To a solution of lactam **5** (254 mg, 0.70 mmol) and DTBMP (157 mg, 0.77 mmol) in anhydrous CH_2Cl_2 (7.0 mL) at −78 °C was added Tf_2O (0.13 mL, 0.77 mmol) dropwise. After 3 h of stirring at −78 °C, a solution of 3-TBSOPrLi (0.45 M in Et_2O, 9.3 mL, 4.2 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (5 × 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:20) to give compound **7** (170 mg, yield 35%) as a colorless oil. $[\alpha]^{20}_D$ −22.9 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3062, 3037, 2952, 2856, 1611, 1511, 1462, 1248, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.09 (s, 6H), 0.93 (s, 9H), 0.94 (s, 9H), 1.39−1.74 (m, 10H), 1.79−1.90 (m, 1H), 1.91−2.01 (m, 1H), 2.56 (dd, *J* = 13.8, 8.5 Hz, 1H), 3.05 (dd, *J* = 13.8, 2.2 Hz, 1H), 3.26−3.34 (m, 2H), 3.39 (dd, *J* = 15.7, 7.4 Hz, 1H), 3.45−3.53 (m, 1H), 3.56−3.68 (m, 4H), 3.82 (s, 3H), 4.24 (d, *J* = 12.1 Hz, 1H), 4.29 (d, *J* = 12.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.78−5.93 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.16−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (4C), 18.29, 18.32, 22.6, 25.96 (3C), 25.97 (3C), 26.8, 27.9, 29.7, 32.4, 32.8, 33.7, 48.0, 55.2, 57.5, 59.4, 63.8, 63.9, 69.5, 73.6, 113.6 (2C), 115.1, 127.0, 127.4 (2C), 128.1 (2C), 130.1 (2C), 133.2, 139.2, 139.6, 157.6; HRMS (ESI, *m*/*z*) calcd for $C_{41}H_{70}NO_4Si_2$ $[M + H]^+$ 696.4838, found 696.4840.

(1*R*,5*S*,8*S*)-9-Allyl-8-hydroxy-5-vinyl-9-azabicyclo[3.3.1]-nonan-2-one (14). A solution of piperidin-3-one **11** (230 mg, 0.87 mmol) in THF (8.7 mL) and 4 N HCl (3.2 mL) was refluxed for 1 h. The cooled reaction mixture was neutralized with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc (5 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 3:2) to give compound **14** (125 mg, yield 65%) as a white solid. mp 40−42 °C (EtOAc/hexane); $[\alpha]^{20}_D$ −31.5 (*c* 0.5, $CHCl_3$); IR (film) ν_{max} 3259, 3081, 2934, 1710, 1641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52−1.65 (m, 1H), 1.70 (ddd, *J* = 13.8, 5.2, 2.0 Hz, 1H), 1.87 (ddt, *J* = 13.8, 5.4, 1.7 Hz, 1H), 1.99−2.15 (m, 2H), 2.27−2.41 (m, 1H), 2.47−2.57 (m, 1H), 2.63 (br s, 1H, OH, D_2O exchangeable), 2.67 (dddd, *J* = 18.4, 9.6, 3.5, 1.0 Hz, 1H), 2.90 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.32−3.52 (m, 2H), 4.02 (dt, *J* = 11.0, 5.2 Hz, 1H), 5.00−5.21 (m, 4H), 5.69 (dddd, *J* = 17.5, 10.1, 7.2, 4.8 Hz, 1H), 5.86 (dd, *J* = 17.5, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 29.3, 36.0, 37.6, 52.2, 55.6, 67.3, 67.9, 113.7, 117.4, 135.4, 146.0, 215.5; HRMS (ESI, *m*/*z*) calcd for $C_{13}H_{19}NO_2Na$ $[M + H]^+$ 244.1308, found 244.1310.

(2*R*,5*R*)-1-Allyl-5-(benzyloxy)-2-(3,3-dimethoxypropyl)-2-vinylpiperidine (15). To a solution of lactam **9** (1.20 g, 4.90 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.00 g, 4.90 mmol) in anhydrous CH_2Cl_2 (49 mL) at −78 °C was added Tf_2O (0.91 mL, 5.39 mmol) dropwise. After 3 h of stirring at −78 °C, a solution of 3,3-dimethoxypropyl magnesium bromide[13] (**G1c**) (0.5 M in THF, 9.8 mL, 4.90 mmol) was added over 1 h, and then vinylMgBr (0.7 M in THF, 21.0 mL, 14.7 mmol) was added dropwise. After being stirred at rt for 3 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:4) to give compound **15** (1.23 g, yield 70%) as a diastereomeric mixture (dr = 6:1, determined by ^{1}H NMR) as a colorless oil. $[\alpha]^{20}_D$ −8.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3076, 2938, 2871, 1640, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) data of the major diastereomer read from the mixture spectrum of diastereomers δ 1.32−1.43 (m, 2H), 1.52−1.65 (m, 4H), 1.72−1.85 (m, 2H), 1.85−1.95 (m, 1H), 2.49 (dd, *J* = 12.1, 8.5 Hz, 1H), 2.84 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.90 (ddd, *J* = 12.1, 4.1, 1.1 Hz, 1H), 3.22 (ddt, *J* = 14.2, 5.3, 1.5 Hz, 1H), 3.31 (s, 3H), 3.32 (s, 3H), 3.44−3.55 (m, 1H), 4.33 (t, *J* = 5.4 Hz, 1H), 4.54 (s, 2H), 5.05 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.10−5.14 (m, 1H), 5.14−5.19 (m, 2H), 5.72 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.69−5.80 (m, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 26.4, 27.5, 31.0, 32.4, 49.6, 52.9, 53.0, 59.7, 70.1, 73.8, 104.4, 114.7, 116.1, 127.4, 127.5 (2C), 128.3 (2C), 137.3, 138.9, 142.7; HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{34}NO_3$ $[M + H]^+$ 360.2533, found 360.2536.

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(3*R*,6*R*)-1-Allyl-6-(3,3-dimethoxypropyl)-6-vinylpiperidin-3-ol (16). To a solution of piperidine **15** (268 mg, 0.746 mmol) in THF (7.5 mL) at −40 °C was added a solution of lithium naphthalenide (1.0 M in THF, 2.98 mL, 2.98 mmol) dropwise. After being stirred at −40 °C for 1 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, MeOH/CH_2Cl_2 = 1:30) to give compound **16** (146 mg, yield 73%) as a colorless oil. $[\alpha]^{20}_D$ +15.7 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3440, 3079, 2934, 1640, 1452, 1126, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41−1.56 (m, 2H), 1.58−1.77 (m, 5H), 1.84 (ddd, *J* = 13.4, 11.8, 4.7 Hz, 1H), 2.57 (dd, *J* = 12.1, 2.0 Hz, 1H), 2.69 (ddd, *J* = 12.1, 4.7, 1.4 Hz, 1H), 2.80 (dd, *J* = 14.0, 7.5 Hz, 2H), 3.31 (s, 3H), 3.32 (s, 3H), 3.34−3.39 (m, 1H), 3.75 (br s, 1H, OH, D_2O exchangeable), 4.33 (t, *J* = 5.4 Hz, 1H), 5.05−5.18 (m, 3H), 5.25 (dd, *J* = 11.2, 1.2 Hz, 1H), 5.72 (dddd, *J* = 17.7, 10.1, 7.5, 4.7 Hz, 1H), 5.86 (dd, *J* = 17.7, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.5, 28.2, 31.0, 51.5, 52.4, 52.76, 52.81, 59.9, 65.3, 104.9, 115.7, 116.7, 136.9, 138.2; HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{28}NO_3$ $[M + H]^+$ 270.2064, found 270.2068.

(*S*)-1-Allyl-6-(3,3-dimethoxypropyl)-6-vinylpiperidin-3-one (17). To a solution of oxalyl chloride (2.0 M in CH_2Cl_2, 1.6 mL, 3.16 mmol) in CH_2Cl_2 (22 mL) at −78 °C was added DMSO (0.45 mL, 6.32 mmol) slowly. After the mixture was stirred for 30 min, a solution of **16** (118 mg, 0.439 mmol) in CH_2Cl_2 (2.0 mL) was added slowly. After 3 h of stirring at −78 °C, Et_3N (1.8 mL, 13.2 mmol) was added slowly. The mixture was stirred at −78 °C for 1 h and then at 0 °C for 1 h. The reaction was quenched with water and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:4) to give compound **17** (105 mg, yield 90%) as a colorless oil. $[\alpha]^{20}_D$ +5.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3079, 2954, 2829, 1725, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62−1.75 (m, 4H), 1.91−2.02 (m, 2H), 2.33−2.42 (m, 1H), 2.42−2.54 (m, 1H), 3.06 (dd, *J* = 14.1, 6.1 Hz, 1H), 3.15 (d, *J* = 17.1 Hz, 1H), 3.13−3.21 (m, 1H), 3.25 (d, *J* = 17.1 Hz, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 4.30−4.38 (m, 1H), 5.10 (dq, *J* = 10.1, 1.6 Hz, 1H), 5.16 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.23 (dd, *J* = 17.7, 1.1 Hz, 1H), 5.28 (dd, *J* = 11.0, 1.1 Hz, 1H), 5.62−5.77 (m, 1H), 5.88 (dd, *J* = 17.7, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 30.2, 30.6, 35.8, 51.7, 52.87, 52.93, 56.4, 59.0, 104.8, 115.4, 117.1, 135.8, 140.1, 210.0; HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{26}NO_3$ $[M + H]^+$ 268.1907, found 268.1908.

(*S*)-1-Allyl-2-(3,3-dimethoxypropyl)-5-(triisopropylsilyloxy)-2-vinyl-1,2,3,6-tetrahydropyridine (18). To a solution of compound **17** (240 mg, 0.899 mmol) in CH_2Cl_2 (9.0 mL) at 0 °C were added successively Et_3N (0.44 mL, 3.15 mmol) and TIPSOTf (0.74 mL, 2.70 mmol). After being stirred at 0 °C for 30 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 6 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:10) to give compound **18** (285 mg, yield 75%) as a colorless oil. $[\alpha]^{20}_D$ +18.7 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3074, 2943, 2866, 1671, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J* = 5.2 Hz, 18H), 1.09−1.17 (m, 3H), 1.50−1.72 (m, 4H), 2.05 (dt, *J* = 16.7, 2.0 Hz, 1H), 2.17 (dt, *J* = 16.7, 1.9 Hz, 1H), 2.82−2.99 (m, 2H), 3.14 (d, *J* = 17.2 Hz, 1H), 3.25 (d, *J* = 5.0 Hz, 1H), 3.28 (s, 3H), 3.29 (s, 3H), 4.31 (t, *J* = 5.3 Hz, 1H), 4.80 (t, *J* = 3.9 Hz, 1H), 5.00−5.11 (m, 2H), 5.12−5.21 (m, 2H), 5.73−5.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6 (2C), 18.0, (6C), 26.8, 29.1, 31.7, 49.2, 52.0, 52.5, 52.7, 58.7, 98.5, 104.9, 114.6, 116.2, 137.3, 141.7, 147.6; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{46}NO_3Si$ $[M + H]^+$ 424.3241, found 424.3250.

(1*S*,5*R*,6*R*)-2-Allyl-1-vinyl-2-azaspiro[bicyclo[3.3.1]nonane-4,2′-[1,3]dioxolan]-6-ol (22). To a solution of piperidin-3-one **11** (1.53 g, 5.8 mmol) in THF (58.0 mL) was added an aqueous solution of 4 N HCl (8.7 mL, 34.8 mmol), and the mixture was stirred for 1 h at rt. After further reaction at 50 °C for 30 min, ethylene glycol (1.50 mL, 23.2 mmol) was added, and the resulting mixture was concentrated under reduced pressure. The residue was used in the next reaction without further purification.

To a solution of the foregoing residue (5.8 mmol estimated on a 100% yield) in toluene (58 mL) at rt was added CSA (0.40 g, 1.7 mmol), and the mixture was heated to 90 °C for 10 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:1) to give compound **22** (0.81 g, yield 53%), and compound **14** (64 mg, yield 5%). Compound **22**: colorless oil; $[\alpha]^{20}_D$ −12.5 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3514, 3080, 2918, 1639, 1075 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (dd, *J* = 13.1, 2.9 Hz, 1H), 1.65 (dt, *J* = 13.9, 6.3 Hz, 1H), 1.70−1.83 (m, 1H), 2.17−2.02 (m, 3H), 2.24 (d, *J* = 2.9 Hz, 1H), 2.76 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.86 (d, *J* = 13.0 Hz, 1H), 3.01 (d, *J* = 13.0 Hz, 1H), 3.52 (dt, *J* = 13.5, 2.1 Hz, 1H), 3.86 (br s, 1H, OH, D_2O exchangeable), 3.77−3.85 (m, 1H), 3.93−3.99 (m, 2H), 3.99−4.06 (m, 2H), 5.00−5.12 (m, 3H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.70−5.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 31.4, 38.8, 41.5, 55.0, 55.2, 57.4, 63.9, 64.9, 71.4, 109.3, 113.7, 116.7, 136.7, 146.4; HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{24}NO_3$ $[M + H]^+$ 266.1751, found 266.1760.

(1*S*,5*S*,6*R*)-2-Allyl-6-(*tert*-butyldimethylsilyloxy)-1-vinyl-2-azaspiro{bicyclo[3.3.1]nonane-4,2′-[1,3]dioxolane} (23). To a solution of compound **22** (35 mg, 0.132 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C were added successively Et_3N (73 μL, 0.528 mmol) and TBSOTf (61 μL, 0.061 mmol). After being stirred at rt for 3 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:10) to give compound **23** (45 mg, yield 90%) as a colorless oil. $[\alpha]^{20}_D$ +16.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3073, 2925, 2866, 1637, 1604, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.92 (s, 9H), 1.38 (dd, *J* = 14.2, 4.1 Hz, 1H), 1.64 (dt, *J* = 13.5, 7.0 Hz, 1H), 1.83−1.97 (m, 2H), 2.02−2.16 (m, 3H), 2.76 (dd, *J* = 13.5, 8.7 Hz, 1H), 2.90 (d, *J* = 12.8 Hz, 1H), 2.97 (d, *J* = 12.8 Hz, 1H), 3.50 (ddt, *J* = 13.5, 4.3, 2.2 Hz, 1H), 3.82−4.07 (m, 5H), 4.99−5.08 (m, 3H), 5.15 (d, *J* = 17.1 Hz, 1H), 5.74−5.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, 18.3, 25.9 (3C), 27.6, 30.9, 39.2, 42.7, 55.0, 55.3, 57.3, 63.6, 64.7, 72.5, 108.4, 113.3, 116.7, 136.9, 146.9; HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{38}NO_3Si$ $[M + H]^+$ 380.2615, found 380.2616.

(7*S*,8*R*,10a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5,7,8,9,10-hexahydrospiro[7,10*a*-methanopyrrolo[1,2-*a*]azocine-6,2′-[1,3]dioxolane] (24). To a solution of compound **23** (25 mg, 0.066 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt was added $Ti(OiPr)_4$ (5.7 μL, 0.020 mmol). After being stirred at rt for 30 min, a solution of the Grubbs II catalyst (17 mg, 0.020 mmol) in anhydrous CH_2Cl_2 (2 mL) was added. The mixture was refluxed for 2 h, until TLC analysis showed complete consumption of the starting material. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:1) to give compound **24** (16 mg, yield 70%) as a colorless oil. $[\alpha]^{20}_D$ −3.5 (*c* 0.5, $CHCl_3$); IR (film) ν_{max} 2927, 2854, 1593, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.42 (dd, *J* = 13.3, 2.9 Hz, 1H), 1.60 (dt, *J* = 13.3, 5.8 Hz, 1H), 1.65−1.72 (m, 1H), 1.72−1.80 (m, 1H), 2.03 (dt, *J* = 13.2, 3.3 Hz, 1H), 2.10 (dd, *J* = 6.8, 3.3 Hz, 1H), 2.16−2.29 (m, 1H), 2.93 (d, *J* = 13.6 Hz, 1H), 3.20 (d, *J* = 13.6 Hz, 1H), 3.66 (dt, *J* = 14.2, 2.0 Hz, 1H), 3.81−4.00 (m, 6H), 5.55 (dt, *J* = 6.1, 2.0 Hz, 1H), 5.71 (dt, *J* = 6.1, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (2C), 18.3, 25.9 (3C), 29.7, 33.1, 36.5, 44.8, 56.3, 60.6, 63.3, 63.8, 64.8, 72.9, 109.2, 126.2, 136.4; HRMS (ESI, *m*/*z*) calcd for $C_{19}H_{34}NO_3Si$ $[M + H]^+$ 352.2302, found 352.2302.

(1*S*,5*S*,6*R*)-2-Allyl-6-(benzyloxy)-1-vinyl-2-azabicyclo[3.3.1]-nonan-4-one (28). The mixture of acetal **27** (180 mg, 0.51 mmol)

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and HCl (6 N, 1.3 mL) in acetone (10 mL) was refluxed for 24 h. The reaction mixture was cooled and neutralized with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with ether (5 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:4) to give compound **28** (110 mg, yield 75%) as a pale yellow oil. $[\alpha]^{20}_D$ +30.5 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3086, 2931, 2859, 1712, 1658, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53−1.75 (m, 3H), 2.03 (dt, *J* = 13.8, 3.6 Hz, 1H), 2.06−2.20 (m, 2H), 2.85 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.08−3.15 (m, 1H), 3.24 (d, *J* = 19.7 Hz, 1H), 3.52 (ddt, *J* = 13.8, 4.5, 1.9 Hz, 1H), 3.67 (dt, *J* = 11.3, 5.4 Hz, 1H), 3.80 (d, *J* = 19.7 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.81 (d, *J* = 11.8 Hz, 1H), 5.06−5.20 (m, 4H), 5.66−5.79 (m, 2H), 7.24−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 29.0, 37.5, 47.6, 54.6, 55.3, 61.8, 69.9, 76.3, 114.1, 116.8, 127.6, 127.8 (2C), 128.4 (2C), 136.0, 138.2, 145.6, 207.4; HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{25}NO_2Na$ $[M + Na]^+$ 334.1778, found 334.1784.

(1*S*,3*S*,5*S*,6*R*)-2-Allyl-6-(benzyloxy)-3-(4-methoxybenzyl)-1-vinyl-2-azabicyclo[3.3.1]nonan-4-one (29). To a solution of ketone **28** (43 mg, 0.14 mmol) in THF (1.4 mL) at −78 °C were added TMEDA (100 μL, 0.69 mmol) and KHMDS (0.7 M in toluene, 200 μL, 0.14 mmol). After being stirred at −78 °C for 30 min, a solution of *p*-methoxybenzylbromide (61 μL, 0.42 mmol) in THF (1.4 mL) was added over 40 min. The mixture was allowed to warm to 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the mixture was extracted with EtOAc (1 × 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, EtOAc/hexane = 1:10) to give compound **29** (48 mg, yield 80%) as a colorless oil. $[\alpha]^{20}_D$ +73.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3061, 3037, 2935, 2864, 1709, 1659, 1610, 1511, 1247, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (dt, *J* = 13.9, 3.7 Hz, 1H), 1.13 (dd, *J* = 13.9, 2.4 Hz, 1H), 1.30−1.43 (m, 1H), 1.52 (dt, *J* = 13.8, 3.8 Hz, 1H), 1.90−1.98 (m, 1H), 2.04 (ddd, *J* = 13.8, 6.8, 3.5 Hz, 1H), 2.68−2.74 (m, 1H), 2.83 (dd, *J* = 13.4, 5.3 Hz, 1H), 3.13 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.25 (dd, *J* = 14.6, 7.3 Hz, 1H), 3.42−3.50 (m, 2H), 3.78 (s, 3H), 3.83 (t, *J* = 4.3 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.99−5.19 (m, 4H), 5.65 (dd, *J* = 18.0, 10.5 Hz, 1H), 5.88 (ddt, *J* = 17.0, 9.9, 7.1 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.23−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 30.3, 34.0, 39.6, 45.8, 52.9, 55.2, 55.7, 69.5, 69.8, 77.7, 113.0, 113.3 (2C), 117.5, 127.5, 127.8 (2C), 128.4 (2C), 130.7, 131.5 (2C), 137.7, 138.3, 146.4, 158.2, 210.9; HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{33}NO_3Na$ $[M + Na]^+$ 454.2353, found 454.2351.

(1*S*,5*R*,6*R*)-2-Allyl-6-(benzyloxy)-3-(4-methoxybenzyl)-1-vinyl-2-azabicyclo[3.3.1]non-3-ene (31). To a mixture of ketone **29** (20 mg, 0.046 mmol) and water (10 μL, 0.56 mmol) in THF (2.0 mL) was added a solution of SmI_2 (0.1 M in THF, 1.86 mL, 0.19 mmol). After being stirred at rt for 5 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, MeOH/CH_2Cl_2 = 1:20) to give compound **31** (18 mg, yield 94%) as a colorless oil. $[\alpha]^{20}_D$ +96.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3058, 3032, 2931, 2855, 1693, 1659, 1642, 1607, 1511, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38−1.52 (m, 2H), 1.59 (dt, *J* = 13.0, 5.2 Hz, 1H), 1.83−2.01 (m, 3H), 3.32 (d, *J* = 5.3 Hz, 1H), 3.40−3.54 (m, 4H), 3.77 (s, 3H), 4.32 (t, *J* = 7.3 Hz, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.10 (dd, *J* = 14.3, 2.6 Hz, 2H), 5.17 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.78−5.89 (m, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.21−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 28.8, 33.8, 40.4, 42.8, 46.8, 55.2, 65.2, 70.3, 79.0, 91.4, 113.4 (2C), 114.8 (2C), 127.3 (2C), 127.4 (2C), 128.2, 129.1 (2C), 136.3, 136.5, 138.9, 142.9, 147.9, 157.4; HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{34}NO_2$ $[M + H]^+$ 416.2584, found 416.2589.

(2*S*,5*S*,6*S*,7*R*,8*S*,10a*S*)-2-[(Benzyloxycarbonyl)methylamino]-octahydro-6-hydroxy-5-[(4-methoxyphenyl)methyl]-1*H*-7,10*a*-methanopyrrolo[1,2-*a*]azocin-8-yl Dibenzyl Phosphate (44). To a solution of compound **42** (50 mg, 0.068 mmol) in THF (2.0 mL) at rt were added successively dibenzyl phosphate (30 mg, 0.40 mmol, in 0.5 mL THF), tris(4-chlorophenyl)phosphine (73 mg, 0.20 mmol, in 0.5 mL THF), DIAD (40 μL, 0.20 mmol), and Et_3N (94 μL, 0.68 mmol). After being stirred at rt for 1 h, the reaction mixture was concentrated, and the residue was taken up with EtOAc. The combined organic layers were concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2/ H_2O (3:1 v/v) (8 mL). To the resulting solution were added Na_2CO_3 (72 mg, 0.68 mmol) and CbzCl (48 μL, 0.34 mmol). After being stirred at rt for 1 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl, and the resulting mixture was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, MeOH/CH_2Cl_2 = 1:10) to give compound **44** (36 mg, yield 34% over two steps) as a colorless oil. $[\alpha]^{20}_D$ +7.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3420, 2958, 2924, 1694, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (dd, *J* = 13.4, 6.4 Hz, 1H), 1.48 (br d, *J* = 13.4 Hz, 1H), 1.55−1.67 (m, 1H), 1.73 (d, *J* = 5.6 Hz, 1H), 1.76−1.96 (m, 5H), 1.98−2.09 (m, 1H), 2.15 (br s, 1H), 2.74 (dd, *J* = 9.8, 5.6 Hz, 1H), 2.78 (s, 3H), 2.80 (br s, 1H), 3.16 (br s, 1H), 3.23−3.36 (m, 1H), 3.44 (br s, 1H), 3.78 (s, 3H), 4.34 (br s, 1H), 4.78 (br s, 1H), 4.93−5.06 (m, 4H), 5.11 (s, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.21−7.48 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 29.0, 29.8, 35.6, 43.0, 43.5, 50.2, 51.9, 55.2, 58.3, 58.4, 67.0, 67.1, 69.17, 69.22, 75.0, 113.8 (2C), 127.82, 127.87 (2C), 127.90 (3C), 128.43 (2C), 128.47 (3C), 128.52 (4C), 130.0 (2C), 130.8, 135.9 (2C), 136.9, 156.3, 158.1; HRMS (ESI, *m*/*z*) calcd for $C_{42}H_{50}N_2O_8P$ $[M + H]^+$ 741.3299, found 741.3299.

(−)-FR901483 (1). To a solution of compound **44** (18 mg, 0.024 mmol) in MeOH (2.0 mL) was added 1 N HCl (29 μL, 0.029 mmol). The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (2.0 mL). 10% Pd/C (18 mg) was added, and the mixture was stirred at rt for 6 h under 1 atm of H_2. The resulting mixture was filtered through Celite and washed with MeOH. The combined filtrates were concentrated under reduced pressure and then rinsed with CH_3CN to give (−)-FR901483 (**1**) (11 mg, yield 92%) as a white solid. Mp 215−220 °C (MeOH/Et_2O) (lit.[2] mp 210−213 °C); $[\alpha]^{20}_D$ −10.2 (*c* 0.5, MeOH) {lit.[2] $[\alpha]^{20}_D$ −11.0 (*c* 0.74, MeOH)}; IR (film) ν_{max} 3396, 2960, 1626, 1248, 1010 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 1.87 (br d, *J* = 11.6 Hz, 1H), 2.04−2.25 (m, 6H), 2.44 (br s, 1H), 2.53 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.67 (s, 3H), 3.03 (br d, *J* = 9.4 Hz, 1H), 3.25 (dd, *J* = 11.8, 9.4 Hz, 1H), 3.57 (br s, 1H), 3.78 (s, 3H), 3.71−3.84 (m, 2H), 4.08−4.14 (m, 1H), 4.20 (br d, *J* = 8.0 Hz, 1H), 4.39 (dd, *J* = 13.1, 9.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 22.6, 28.2, 28.7, 32.3, 34.2, 42.2, 43.1, 51.8, 55.1, 55.8, 61.4, 64.5, 67.6, 70.6, 115.2, 129.1, 131.7, 160.3; HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{32}N_2O_6P$ $[M + H]^+$ 427.1992, found 427.1995.

Benzyl [(2*S*,5*S*,6*S*,7*S*,8*S*,10a*S*)-6,8-Dihydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10*a*-methanopyrrolo[1,2-*a*]azocin-2-yl](methyl)carbamate (45). To a solution of compound **42** (196 mg, 0.568 mmol) in CH_2Cl_2/ H_2O (3: 1) (56 mL) at rt were added successively Na_2CO_3 (602 mg, 5.68 mmol) and CbzCl (0.40 mL, 2.84 mmol). After being stirred at rt for 1 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, MeOH/CH_2Cl_2 = 1:20) to give compound **45** (259 mg, yield 95%) as a white foam. $[\alpha]^{20}_D$ −3.6 (*c* 0.6, $CHCl_3$); IR (film) ν_{max} 3435, 2934, 1703, 1512, 1246 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 0.98 (d, *J* = 11.9 Hz, 1H), 1.45 (br s, 1H), 1.57−1.69 (m, 1H), 1.71−1.91 (m, 4H), 2.09−2.22 (m, 2H), 2.67 (s, 3H), 2.76−3.20 (m, 5H), 3.58 (br s, 2H), 3.64 (br s, 1H), 3.72 (s, 3H), 3.83−3.92 (m, 1H), 4.50−4.76 (m, 1H), 5.05 (s, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.34 (s, 5H); ^{13}C NMR (125 MHz, CD_3CN) δ 28.6, 29.7, 31.6, 34.7, 36.4, 43.4, 45.0, 51.7, 53.0, 55.8, 60.4, 66.2, 67.5, 70.4, 114.5 (2C), 128.6 (2C), 128.8, 129.5 (2C), 131.2 (2C), 132.7 138.5, 157.0, 159.0;

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HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{37}N_2O_5$ $[M + H]^+$ 481.2697, found 481.2696.

Benzyl [(2*S*,5*S*,6*S*,7*S*,8*S*,10*aS*)-8-[[Bis(benzyloxy)phosphoryl]oxy]-6-hydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10*a*-methanopyrrolo[1,2-*a*]azocin-2-yl](methyl)carbamate (46). To a solution of diol **45** (62 mg, 0.129 mmol) and 1-*H*-tetrazole (90 mg, 1.29 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dibenzyl(*N*,*N*-diisopropyl)phosphoramidite (86 μL, 0.26 mmol, in 5 mL of CH_2Cl_2) over 60 min. The reaction mixture was cooled to −78 °C before addition of TBHP (5.5 M in decane, 70 μL, 0.39 mmol). The reaction was allowed to warm to −10 °C slowly, quenched with a saturated aqueous solution of Na_2SO_3 and extracted with CH_2Cl_2 (15 × 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, MeOH/CH_2Cl_2 = 1:20) to give compound **46** (62 mg, yield 65%) as a colorless oil. $[\alpha]^{20}_D$ +1.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3420, 2956, 2919, 2850, 1699, 1512, 1013 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.03 (d, *J* = 13.1 Hz, 1H), 1.26−1.36 (m, 2H), 1.50 (dd, *J* = 12.6, 6.9 Hz, 1H), 1.58−1.74 (m, 1H), 1.76−2.12 (m, 4H), 2.26 (br d, *J* = 12.2 Hz, 1H), 2.39 (br s, 1H), 2.73 (s, 3H), 2.82 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.86−3.03 (m, 2H), 3.56 (br s, 1H), 3.60 (s, 3H), 3.65 (br s, 1H), 4.56−4.66 (m, 1H), 4.67−4.77 (m, 1H), 4.84−4.91 (m, 4H), 5.08 (s, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.33 (s, 10H), 7.34 (s, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 28.0, 29.6, 30.2 30.7, 34.6, 36.5, 43.1, 43.4, 51.7, 53.4, 55.5, 60.9, 65.6, 68.3, 70.7, 79.2, 114.7, 128.8, 129.1, 129.2, 129.5, 129.66, 129.71, 131.2, 132.6, 137.1, 138.2, 158.0, 159.4; HRMS (ESI, *m*/*z*) calcd for $C_{42}H_{50}N_2O_8P$ $[M + H]^+$ 741.3299, found 741.3295.

(+)-8-*epi*-FR901483 (47). To a solution of compound **46** (30 mg, 0.040 mmol) in MeOH (2.0 mL) was added an aqueous solution of 2 N HCl (21 μL, 0.042 mmol). The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (2.0 mL). 10% Pd/C (30 mg) was added, and the mixture was stirred at rt for 6 h under 1 atm of H_2. The resulting mixture was filtered through Celite and washed with MeOH. The combined filtrates were concentrated under reduced pressure and then rinsed with CH_3CN to give 8-*epi*-FR901483 (**47**) (16 mg, yield 95%) as a white solid. Mp 215−218 °C (MeOH/Et_2O); $[\alpha]^{20}_D$ +8.0 (*c* 1.0, MeOH); IR (film) ν_{max} 3395, 2960, 1620, 1248, 1010 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.56 (br d, *J* = 12.6 Hz, 1H), 1.93 (br s, 1H), 2.07−2.41 (m, 3H), 2.44−2.70 (m, 4H), 2.79 (s, 2H), 2.90 (s, 1H), 3.01 (br s, 1H), 3.08−3.17 (m, 1H), 3.35 (s, 3H), 3.78 (s, 3H), 3.87−4.07 (m, 3H), 4.17−4.36 (m, 1H), 4.51 (dd, *J* = 13.0, 9.5 Hz, 1H), 4.62 (br s, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 26.8, 28.3, 31.0, 32.4, 34.2, 41.0, 41.2, 52.0, 55.1, 55.7, 61.8, 63.3, 68.0, 74.6, 115.3, 128.5, 131.6, 160.4; HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{32}N_2O_6P$ $[M + H]^+$ 427.1992, found 427.1994.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all new compounds; NOESY spectra of compounds **14**, **40**, and **40a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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