HETEROCYCLES, Vol. 86, No. 2, 2012, pp. 1071 - 1092. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 18th June, 2012, Accepted, 7th August, 2012, Published online, 28th August, 2012
DOI: 10.3987/COM-12-S(N)38

STEREOCONTROLLED TOTAL SYNTHESIS OF (–)-FR901483

Shigeru Ieda,[c] Akitaka Masuda,[b] Mami Kariyama,[b] Toshiyuki Wakimoto,[a,b] Tomohiro Asakawa,[b] Tohru Fukuyama,*[a] and Toshiyuki Kan*[b]

[a]Graduate School of Pharmaceutical Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-0033, Japan, E-mail: fukuyama@mol.f.u-tokyo.ac.jp
[b]School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka-shi, 422-8526, Japan E-mail: kant@u-shizuoka-ken.ac.jp
[c]Astellas Pharma Inc., 160-2, Akahama, Takahagi, Ibaraki 318-0001, Japan

Abstract – The total synthesis of a potent immunosuppressant (–)-FR901483 is accomplished. The skeleton itself is constructed by the Ugi 4CC reaction, subsequent intramolecular Dieckmann condensation, and a diastereoselective intramolecular aldol reaction. However, the remarkable feature is the stereoselective incorporation of the *p*-methoxybenzyl and methylamino groups within the tricyclic core skeleton.

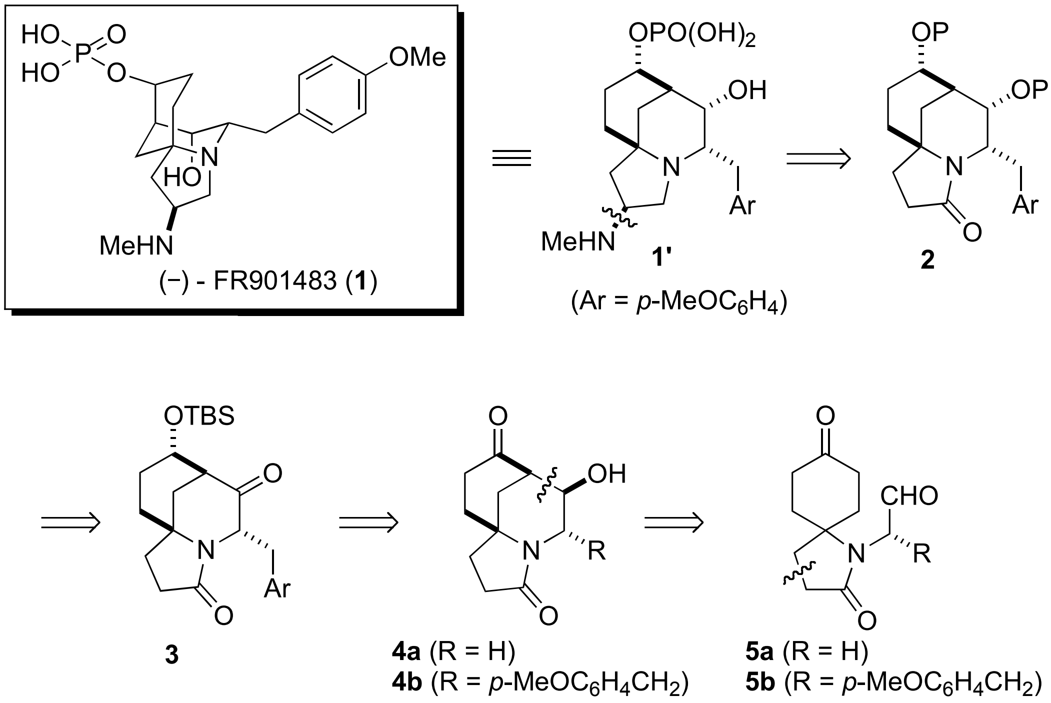
INTRODUCTION

(–)-FR901483 (**1**) is a novel immunosuppressant isolated from the fermentation broth of *Cladobotryum* sp. No. 11231.[1] Unlike Cyclosporin A and tacrolimus,[1] which are powerful, but have strong side effects, **1** has a different mode of action and is expected to replace or reduce their dosages. Moreover, **1** is an attractive total synthesis target due to its promising biological activity and unique tricyclic structure. Although several total syntheses and synthetic studies of **1** have been reported to date, few are stereoselective.[2-4] Previously, we reported the stereocontrolled synthesis of optically active key intermediate **3**.[31] Herein we describe a detailed stereocontrolled total synthesis of optically active **1**. This synthesis may realize diverse analogues.

RESULTS AND DISCUSSION

Scheme 1 illustrates our retrosynthetic analysis of **1**. Because the crucial step in our racemic synthesis is an intramolecular aldol reaction of keto-aldehyde **5a** to provide tricycle intermediate **4a**, we initially attempted an enantioselective intramolecular aldol reaction of **5a** by means of a chiral organocatalyst.

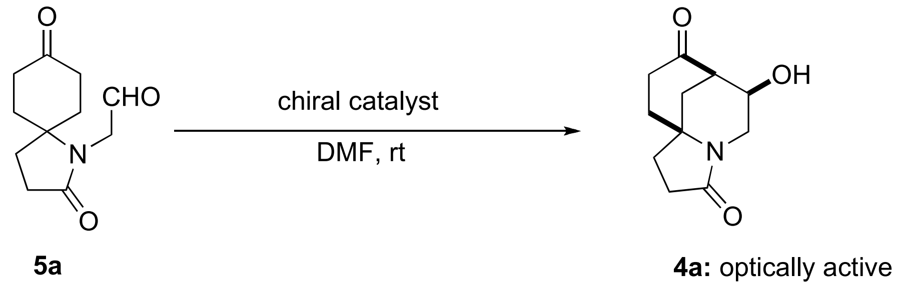
Dedicated to Prof. Ei-ichi Negishi on celebration of his 77th birthday.



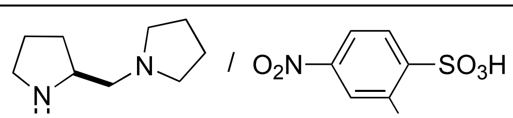
Scheme 1. Retrosynthetic analysis of (–)-FR901483

Organocatalytic mediated aldol reactions have received much attention.[5] Thus, we anticipated that **5a** would provide optically active **4a** and incorporate three stereocenters. Although we tested several catalysts for the enantioselective desymmetrization[6] of **5a**, the results were unsatisfactory. Table 1 shows typical reaction conditions.

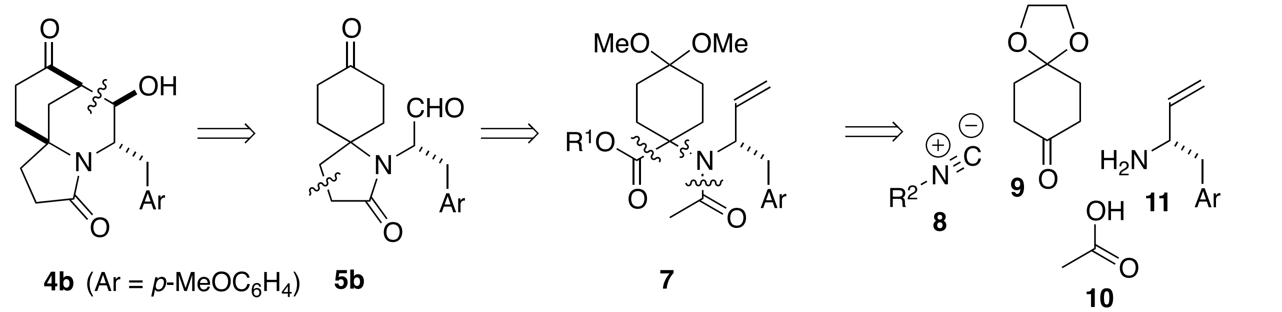
Table 1. Desymmetrization of**5a** by an intramolecular chiral aldol reaction



Entry	Catalyst	yield (%)	ee (%)
1	L-proline	24	0
2	L-phenylalanine	trace	18
3	L-phenylalanine/D-CSA	20	5
4	**6**[5a]	trace	18

6: 

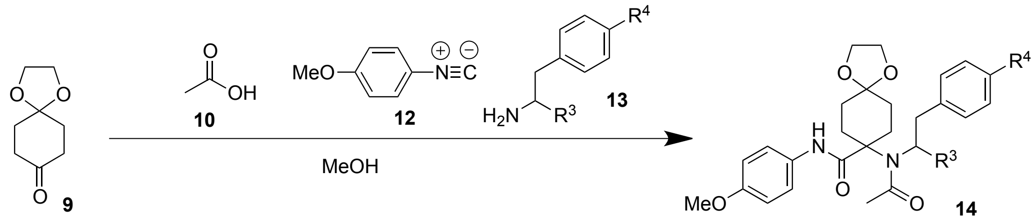
Next we examined a diastereoselective aldol reaction of **5b** to construct tricycle intermediate **4b**, which could easily be converted into intermediate **2** relying on our racemic synthesis. We envisioned the facile construction of optically pure azaspiro intermediate **5b** to be the crucial step. Although α-trisubstituted amines have been synthesized via numerous procedures, we opted to construct **7** using the Ugi 4CC reaction[7] because the Ugi reaction can assemble complex molecules from simple components (**Scheme 2**).



Scheme 2. Retrosynthetic analysis of **4b**

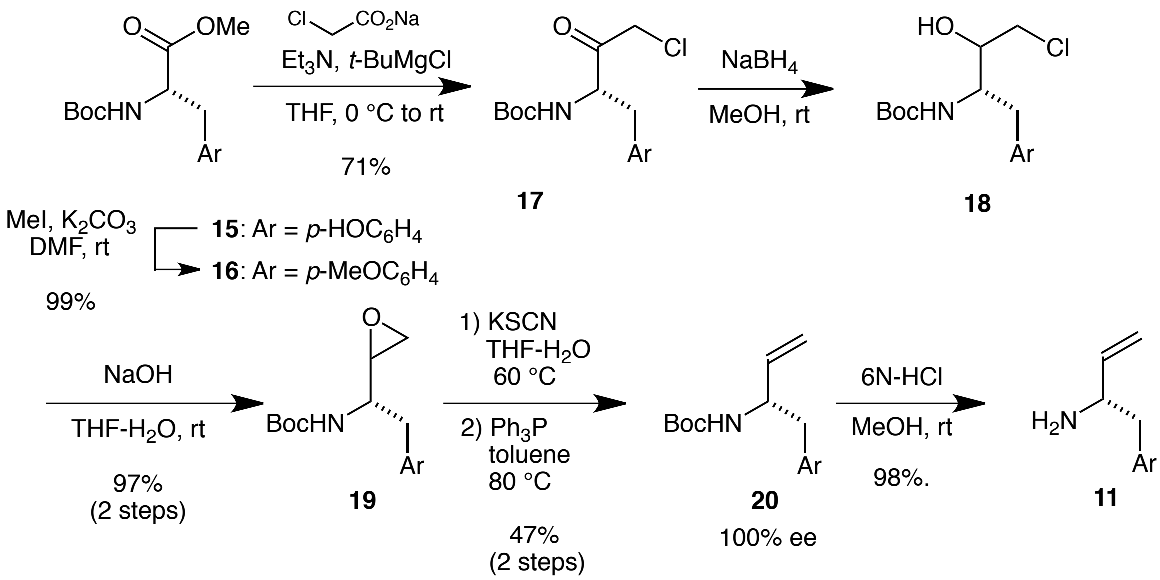
Due to the limited examples of the Ugi 4CC reaction with a ketone system, we initially explored suitable reaction conditions using commercially available cyclohexanedione monoethylene acetal **9**, acetic acid **10**, *p*-methoxyphenyl isocyanide **12**, and amine moieties **13**[8] in MeOH. As indicated in **Table 2**, the R^3 substituent in fragment **13** was essential, and the ethereal substituents in **12** were unsatisfactory, but an sp^2 carbon in R^3 accelerated the reaction rate. Consequently, we selected the vinyl group as an aldehyde equivalent.

Table 2. Screening of Ugi 4CC reaction conditions



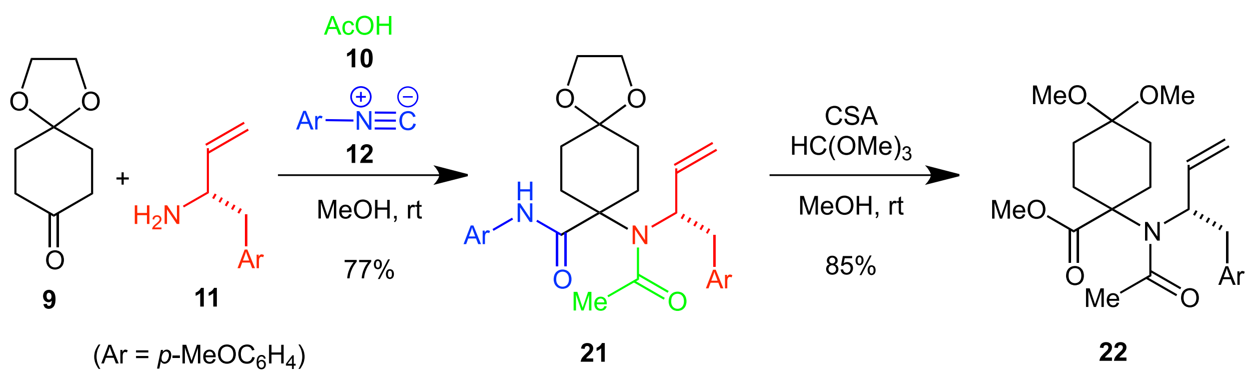
Entry	R^3	R^4	temp.	time (hour)	yield (%)
1	CH_2OTBS	H	rt	144	60
2	CH_2OTBS	H	50 ℃	96	25
3	CH_2OBn	H	rt	144	56
4	CO_2Me	H	rt	48	69
5	CO_2t-Bu	H	rt	96	73
6	$CH(OMe)_2$	MeO	rt	144	18
7	HC=CH_2	MeO	rt	**48**	**81**

Optically active amine **11** was prepared in seven steps from commercially available *N*-Boc-tyrosine methyl ester **15**,[9] while oxirane **19** was prepared in accordance with Kaneka's patent.[10] A classical reduction of oxirane via thiirane afforded desired compound **20**, and recrystallization improved its enantiomeric excess up to 100% ee.



Scheme 3. Preparation of amine **11**

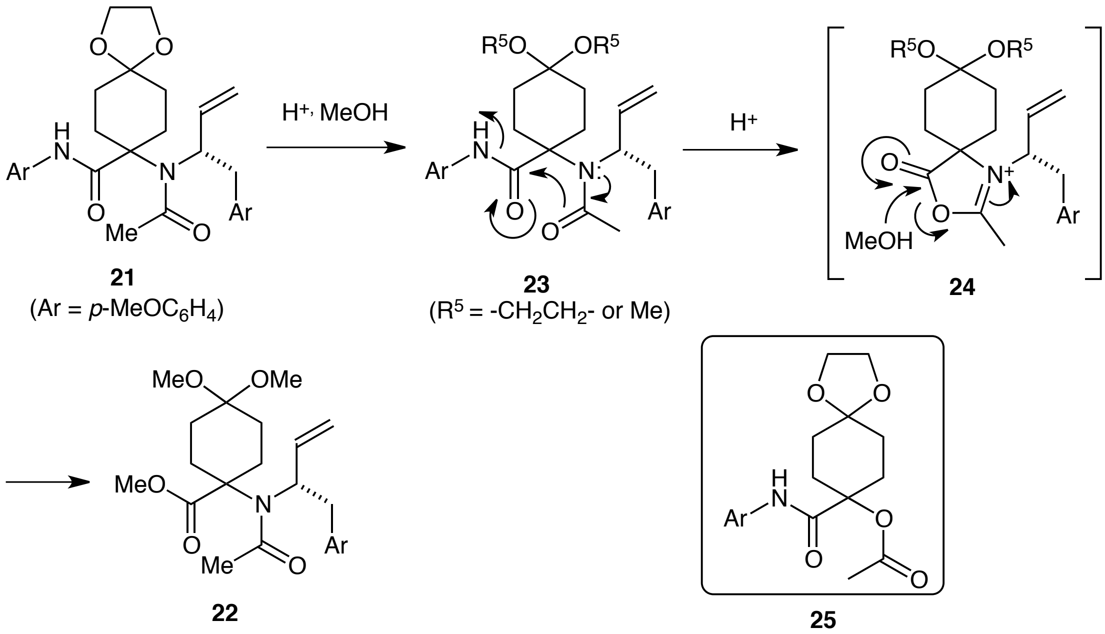
A mixture of cyclohexanedione monoethlyene acetal **9**, acetic acid **10**, optically active amine **11**, *p*-methoxyphenyl isocyanide **12**, in MeOH was allowed to stand at room temperature to afford **21**. This reaction efficiently assembled all the carbon atoms necessary to construct tricyclic key intermediate **3** in a single step. Although hydrolysis of the *C*-terminal amide bond in the Ugi adduct can be troublesome,[11] methanolysis of the *p*-methoxyphenyl amide in **21** proceeded smoothly with a concomitant acetal exchange to provide **22**.



Scheme 4. Ugi 4CC reaction and subsequent transformation

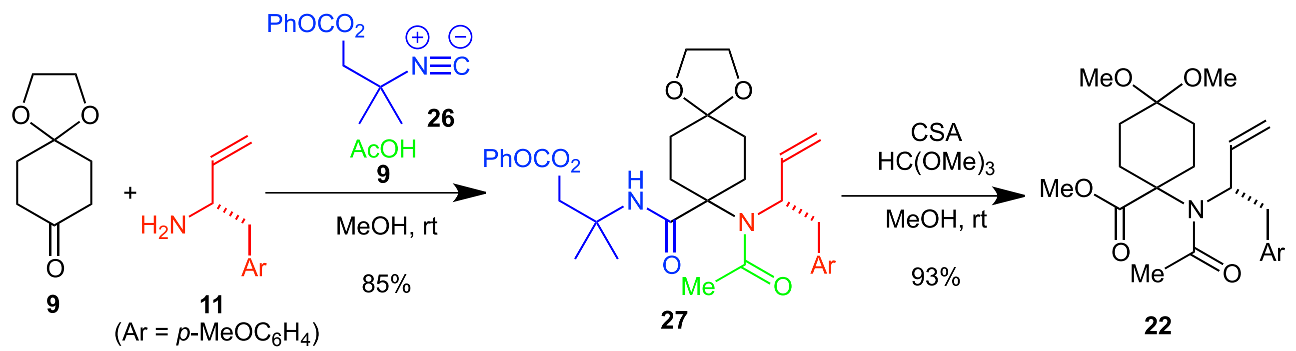
Presumably, this reaction proceeded via oxazolonium intermediate **24** through neighboring group participation. As shown in **Scheme 5**, the acetamide moiety should play a key role in this transformation;

this speculation is supported by the fact that the amide of Passerini compound **25**, which has an acetate instead of an acetamide moiety, is unaffected under the same methanolysis conditions. Additionally, trimethyl orthoformate should play a key role in dehydration and trapping of *p*-anisidine.



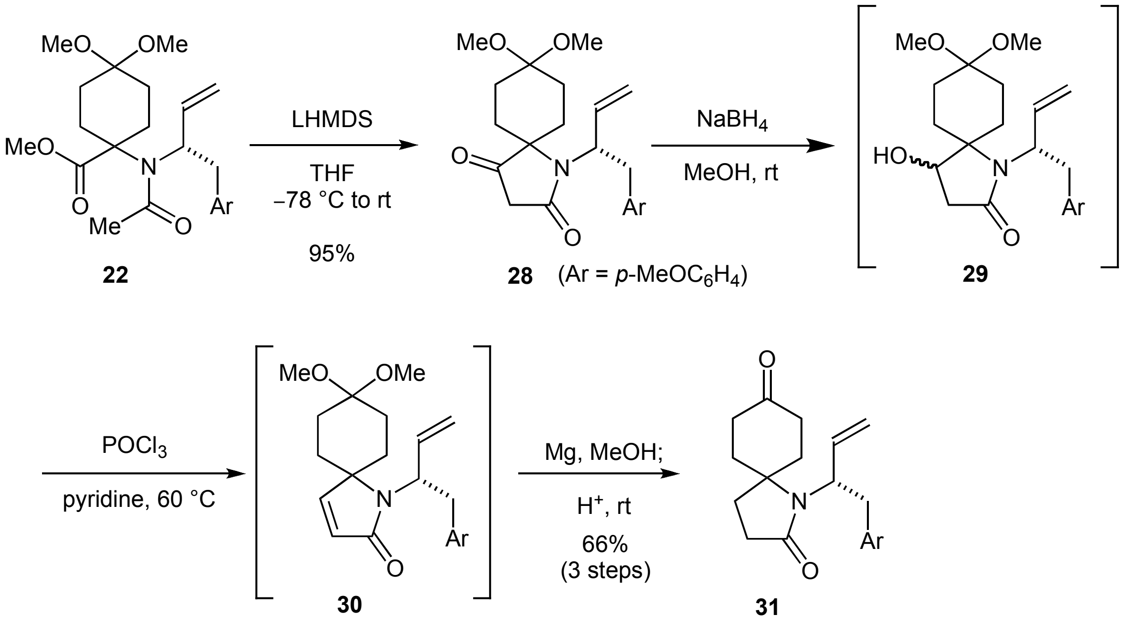
Scheme 5. Neighboring group participation in the methanolysis of **21**

Recently, we developed a novel, odorless isonitrile, which is advantageous for cleavage of the amide bond in the Ugi adduct (**Scheme 6**). Additionally, the Ugi 4CC reaction with isonitrile **26** yielded **22** after treatment under acidic conditions. These results are reasonable because the mechanism appears to be similar to the methanolysis of **21.**



Scheme 6. Ugi 4CC reaction using odorless isonitrile **26**

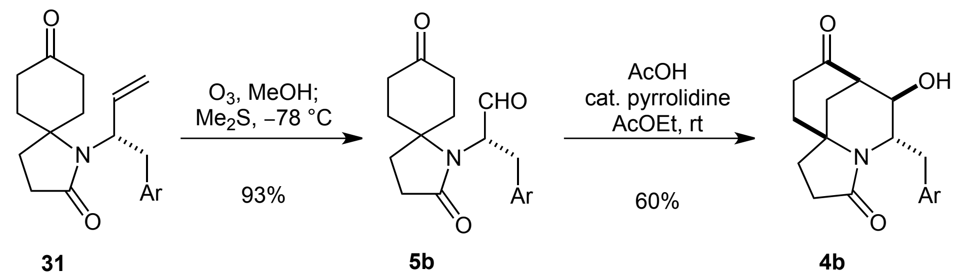
The subsequent intramolecular Dieckmann condensation effectively constructed the spiro-lactam ring. Thus, treatment with LHMDS caused **22** to cyclize, yielding **28**. The ensuing deoxygenation of the carbonyl group in **28** was performed via a three-step sequence to give desired lactam **31**: the reduction of the ketone with $NaBH_4$, dehydration with phosphoryl chloride, and a chemoselective one-electron reduction of the resultant unsaturated lactam. In addition, simultaneous hydrolysis of the dimethyl acetal occurred in the last step of the acidic work-up.



Scheme 7. Construction of the azaspiro[4.5]lactam system

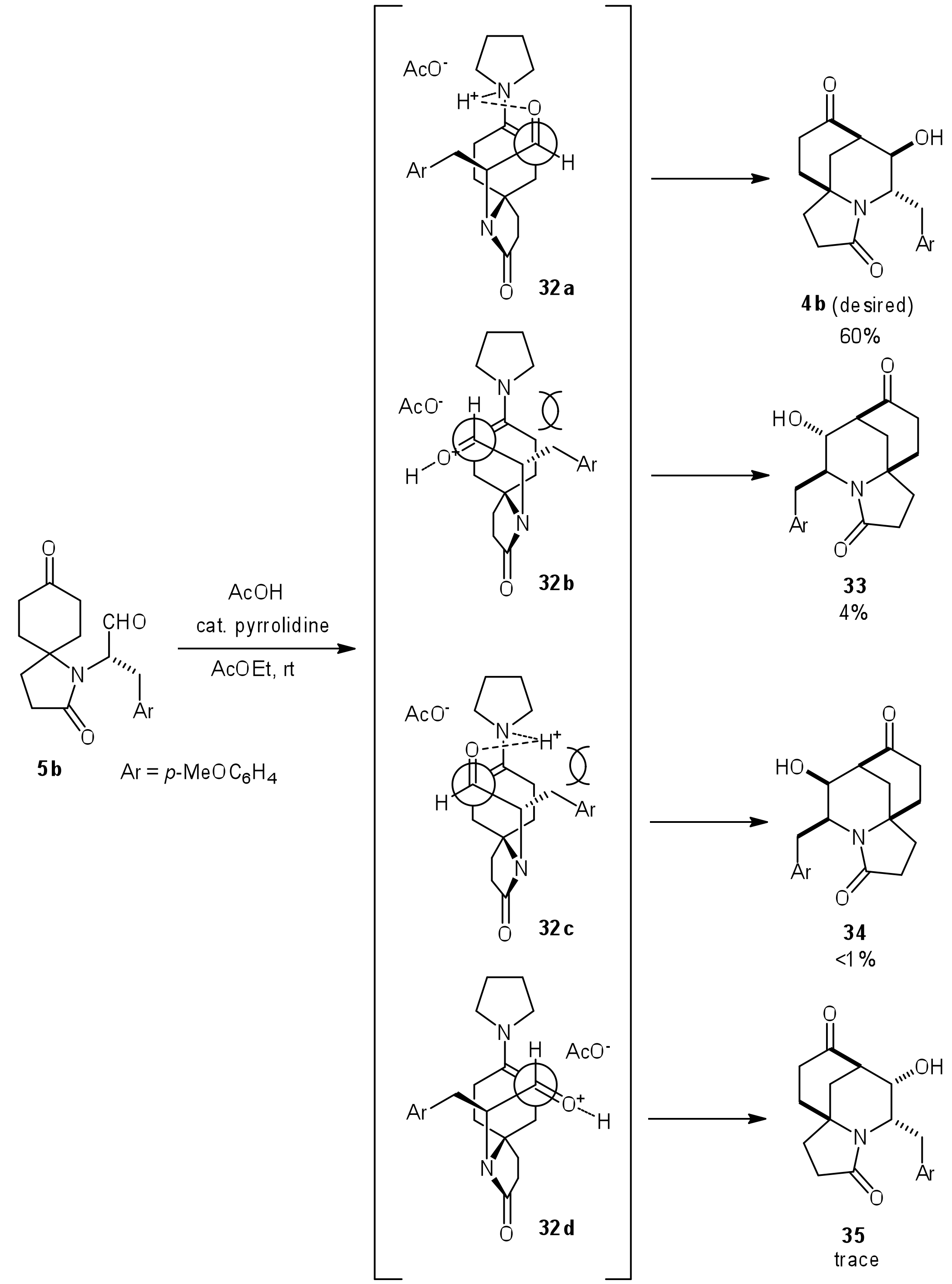
During the dehydration reaction with phosphoryl chloride, concomitant formation of methyl enol ethers occurred. After the mixture was reduced with magnesium metal in methanol without purification, hydrolysis of both the enol ether and dimethyl ketal in an acidic work up gave ketone **31**. At this stage, the oxidative cleavage of the terminal olefin in **31** was performed by ozonolysis to afford **5b**.

With desired optically active keto-aldehyde **5b** in hand, we then focused on the diasteroselective intramolecular aldol reaction. Although Snider has reported a similar intramolecular cyclization of **5b**, their reaction conditions could not be applied to our study because the cyclization reaction proceeded with a significant amount of racemization under basic conditions and the reproducibility was insufficient. Therefore, we selected acidic conditions at room temperature. Treatment of keto-aldehyde **5b** with acetic acid and a catalytic amont of pyrrolidine[12] afforded **4b** via the desired cyclization where the two chiral centers were generated in one step. Although the stereochemistry of the hydroxy group in **4b** was the opposite of the natural product,[13] it was necessary to control the endo-reduction of the ketone in **4b**.



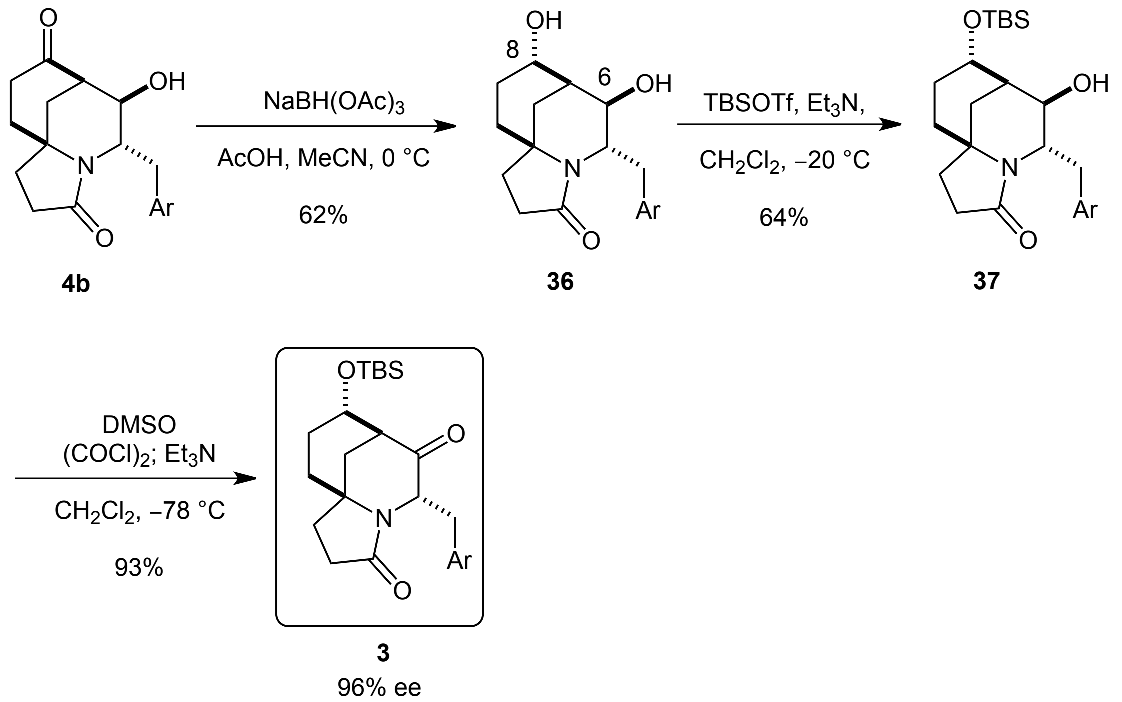
Scheme 8. Construction of tricyclic ketone **4b**

It is plausible that thermodynamic control is responsible for the stereochemistry of diequatorial aldol product **4b**. The ratio of the byproducts, which can analyze the selectivity of the intramolecular aldol reaction (**Scheme 9**), indicates that chelation with hydrogen bonding via a proton and steric hinderance of *p*-methoxybenzyl group contributed to the selectivity.



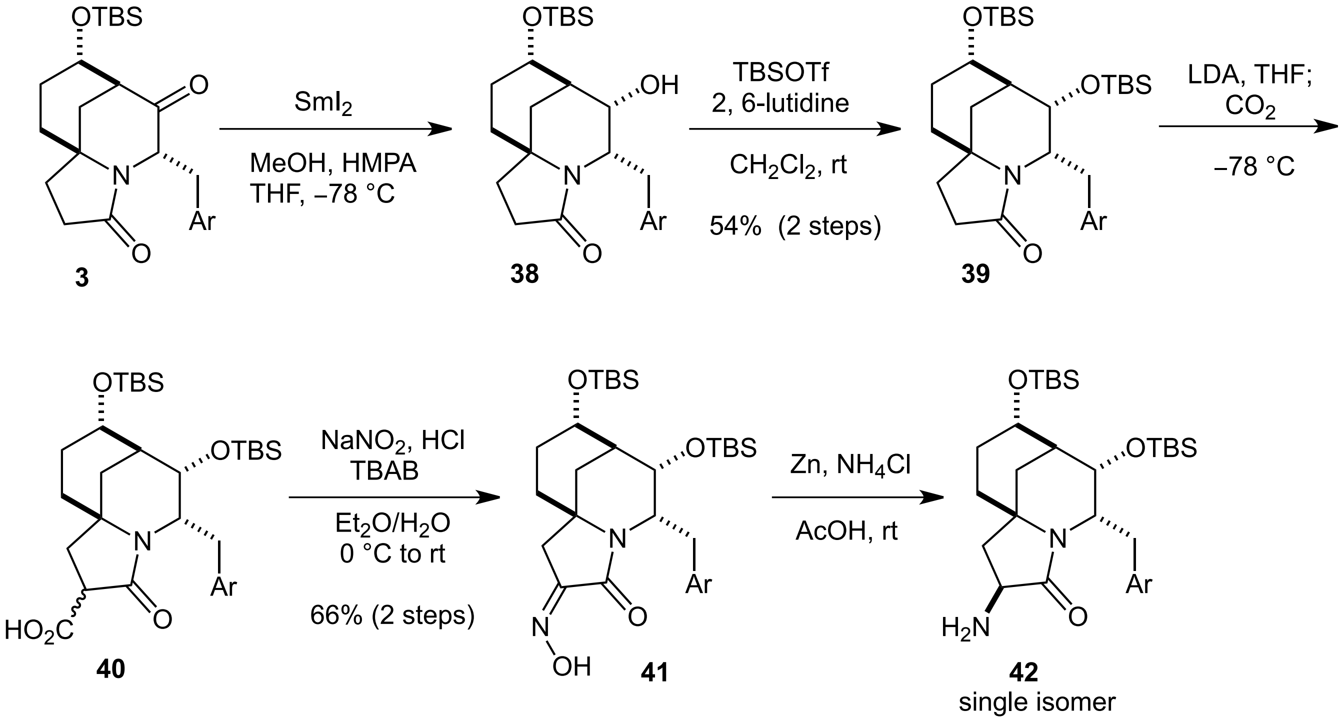
Scheme 9. Selectivity of the intramolecular aldol reaction in **5b**

Similar to the route established for **4b**, stereoselective reduction of **4b** was carried out by $NaBH(OAc)_3$,[14,15] through coordination with the hydroxyl group to give **36**. Selective protection of the *exo*-oriented hydroxy group of **36** as a TBS ether and a subsequent Swern oxidation of the remaining alcohol provided key intermediate **3**, whose enantiomeric excess (96% ee) was determined by chiral HPLC.



Scheme 10. Synthesis of key intermediate **3**

A one-electron reduction converted ketone **3** into the *exo*-oriented alcohol because the reduction with lithium aluminum hydride exclusively gave the undesired *endo*-alcohol. Because the hydride should attack from the convex face of **3**, a one-electron reduction with samarium (II) was investigated. Thus, treatment with samarium (II) diiodide (SmI_2)[16] in the presence of HMPA at –78 °C smoothly reduced ketone **3** to provide desired **38**. In this SmI_2 mediated reduction of **3**, the addition of HMPA was essential for high selectivity[17]. Subsequent protection of **38** with the TBS ether gave **39**. As shown in **Scheme 11**, an amine group was stereoselectively incorporated using a one-electron reduction as a key step. Upon treatment of **40** with sodium nitrite under acidic conditions in a biphasic medium, sequential nitrosylation and decarboxylation proceeded smoothly to provide oxime **41**. The addition of a phase transfer catalyst improved the reproducibility in the reaction. The crucial reduction of **41** was accomplished by treatment with zinc in acetic acid to provide desired amine **42** as a single isomer. As shown in **Figure 1**, the approach of the proton from the convex face of more stable intermediate **43** could explain the selectivity.



Scheme 11. Conversion of amine **42**

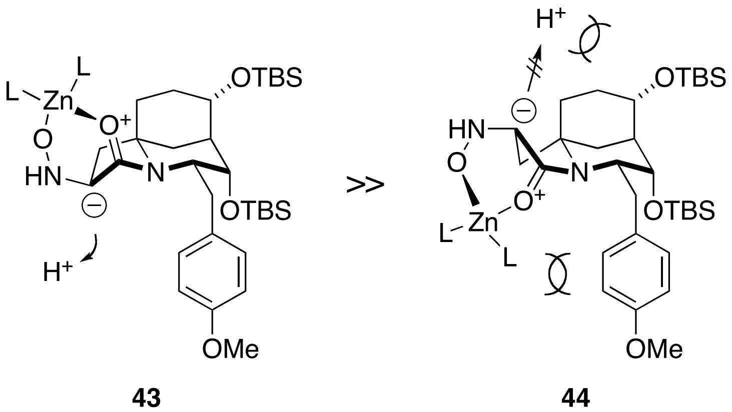
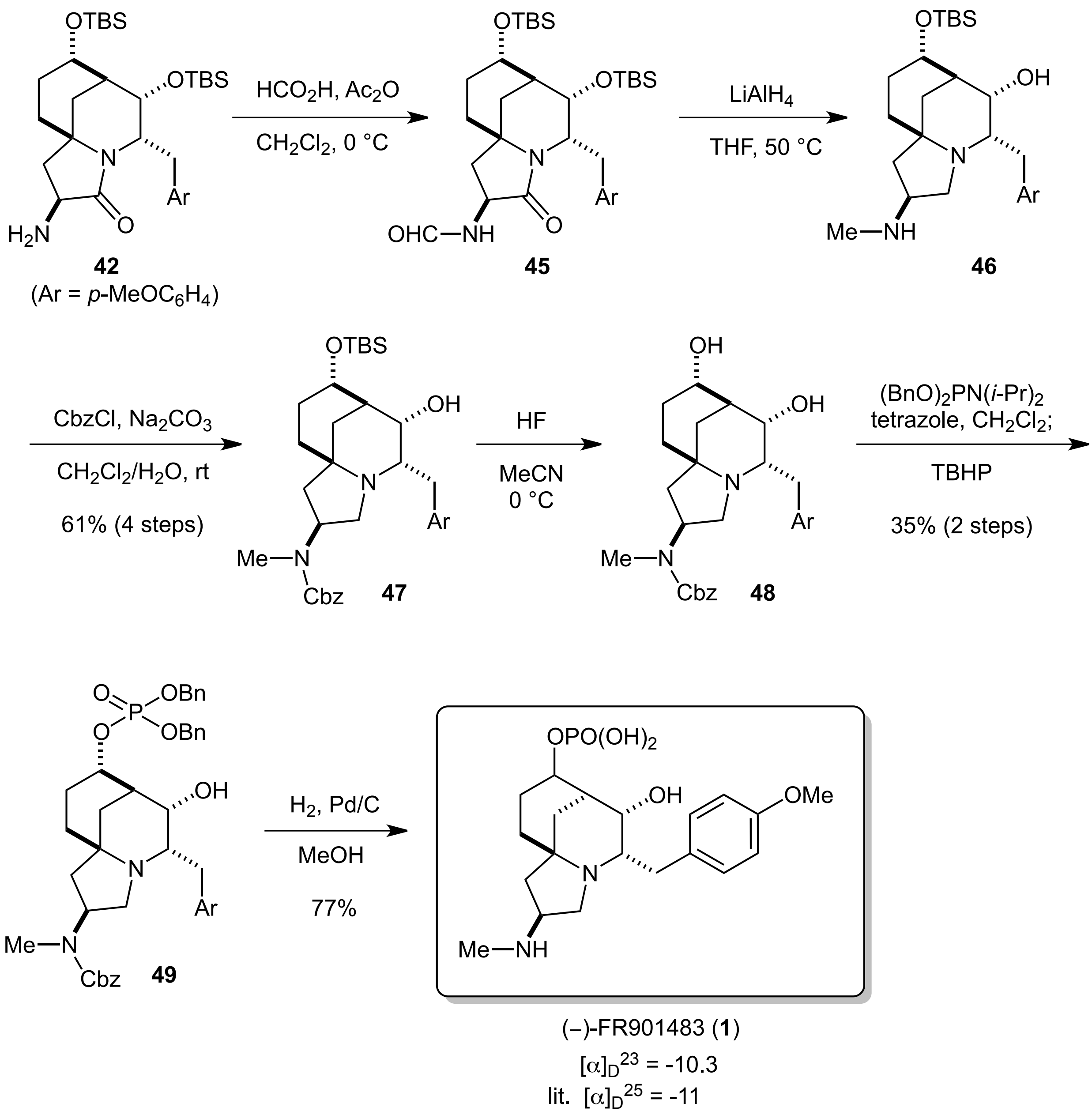


Figure 1. Selectivity of the reduction of **41** with zinc metal

Mono-*N*-methylation of primary amine **42** was achieved in a stepwise manner. After the conversion of **42** into formamide **45**, treatment with lithium aluminum hydride allowed the simultaneous reduction of both the lactam and formamide, while concomitant deprotection of one of the TBS groups provided corresponding methylamine derivative **46**, which was subsequently protected with a Cbz group to afford **47**.



Scheme 12. Total synthesis of (–)-FR901483 (**1**)

After the deprotection of the TBS ether, the phosphate ester was selectively incorporated via the phosphoramidite method[18] to give **49**.[19] Finally, simultaneous cleavage of Cbz and the benzyl ester groups under hydrogenolysis conditions yielded (–)-FR901483 (**1**). The spectral data (relative optical rotation, ^{1}H NMR, ^{13}C NMR, IR, and HRMS) of **1** fully agreed with those of the natural product (**Scheme 12**).

In conclusion, a highly stereoselective total synthesis of (–)-FR901483 (**1**) was achieved via the Ugi 4CC reaction, subsequent intramolecular Dieckmann condensation, and a diastereoselective intramolecular aldol reaction. Our synthesis stereoselectively constructed the *exo*-oriented alcohol by a SmI_2 mediated reduction. Finally, a one-electron reduction determined the amine stereochemistry at C(10). The versatility and flexibility of this total synthesis should contribute to future syntheses of FR901483 analogues.

EXPERIMENTAL

General. Nuclear magnetic resonance [^{13}C NMR (68 MHz)] spectra were determined on a JEOL EX-270 instrument, [^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)] spectra were determined on a JEOL-LA400 instrument, and [^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz)] spectra were determined on a JEOL ECA 500 instrument and JEOL α–500 instrument. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (δ) in deuterochloroform ($CDCl_3$) or deuteromethanol (CD_3OD) as an internal standard or relative to the signal at 7.26 (3.31) ppm for deuterochloroform (deuteromethanol), while coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm relative to the centerline of the triplet at 77.0 ppm for deuterochloroform or the centerline of a septet at 118.2 (49.0) ppm for deuteroacetonitrile (CD_3CN) [deuteromethanol (CD_3OD)]. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Infrared spectra (IR), which are reported in wavenumbers (cm^{-1}), were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-GCmate MS-DIP20 with polyethylene glycol as the matrix or a JEOL MStation 700 using the Fast Atom Bombardment (FAB) method and 3-nitrobenzylalcohol as the matrix. Analytical thin layer chromatography (TLC) was performed on 0.25-mm thick Merck precoated analytical plates of silica gel 60 F254. Preparative TLC separations were conducted on 0.50-mm thick Merck precoated of silica gel 60 F254. Compounds were eluted from the adsorbent with 10% methanol (MeOH) in chloroform ($CHCl_3$). Flash column chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh). All non-aqueous reactions were carried out in oven-dried glass apparatuses under a slight positive pressure of argon. Prior to use, all solvents were dried over molecular sieves 3A or 4A. All other reagents were commercially available, and unless otherwise specified, were used without further purification.

***tert*-Butyl [(2*S*)-1-(4-methoxyphenyl)but-3-en-2-yl]carbamate (20).**

Potassium thiocyanate (22.0 g, 226 mmol) was added to a stirred suspension of **19** (22.1 g, 75.3 mmol) in EtOH (400 mL) and H_2O (300 mL) at room temperature. The mixture was heated to 60 °C and stirred for 24 h before cooling to room temperature. Then H_2O (400 mL) was added. The mixture was extracted with AcOEt twice. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then passed through a pad of silica gel. The solvent was removed under reduced pressure. The residual mixture was used in the next step without further purification.

To a stirred solution of the crude product in toluene (50 mL), PPh_3 (7.29 g, 27.8 mmol) was added at room temperature. The mixture was heated to 80 °C and stirred for 12 h before cooling to room temperature. The mixture was diluted with toluene (50 mL), and then H_2O (50 mL) was added. The resulting precipitate was filtered with a sintered glass filter. After the organic layer was separated, the aqueous layer was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residual mixture was purified by silica gel chromatography (toluene-AcOEt:*n*-hexane=1:20) to give **20** (10.9 g, 39.2 mmol) as a colorless crystal. The resulting crystal was recrystallized from toluene–*n*-heptane to afford purified **20** (9.81 g, 35.2 mmol, 47%, 100% ee[20]) as a colorless crystal. $[\alpha]_D^{26.4}$ 34.5 (*c* 1.01, $CHCl_3$); IR (firm) 3363, 2981, 1685, 1612, 1511, 1441, 1244, 1167 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.41 (9H, s), 2.77 (2H, br. d, *J* = 6.4 Hz), 3.78 (3H, s), 4.37 (1H, br. s), 4.52 (1H, br. s), 5.06-5.11 (2H, m), 5.78 (1H, ddd, *J* = 5.3, 10.3, 15.9 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 7.09 (2H, d, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 28.3, 40.4, 53.5, 55.1, 79.2, 113.6, 129.3, 130.4, 138.1, 144.6, 155.2, 158.1; HRMS (ESI) calculated for $C_{16}H_{23}NNaO_3$ 300.1576 [$(M+Na)^+$], found 300.1563.

(2*S*)-1-(4-Methoxyphenyl)but-3-en-2-amine (11).

6N-HCl (13 mL) was added to a solution of **20** (1.30 g, 4.69 mmol) in MeOH (26 mL) at room temperature and stirred for 24 h. Then the reaction mixture was washed with toluene. The addition of 12% aqueous sodium hydroxide created basic conditions. The mixture was extracted with Et_2O three times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. Resulting colorless oil **11** (819 mg, 4.60 mmol, 98%) was used in the next step without further purification.

^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.84 (2H, br, s), 2.57 (1H, dd, *J* = 7.8, 13.2 Hz), 2.78 (1H, dd, *J* = 6.2, 13.2 Hz), 3.56 (1H, dd, *J* = 6.2, 13.2 Hz), 3.79 (3H, s), 5.05 (1H, d, *J* = 10.4 Hz), 5.14 (1H, d, *J* = 17.0 Hz), 5.88 (1H, ddd, *J* = 6.2, 10.4, 17.0 Hz), 6.84 (2H, d, *J* = 8.6 Hz), 7.12 (2H, d, *J* = 8.6 Hz).

8-{Acetyl[(2*R*)-1-(4-methoxyphenyl)but-3-en-2-yl]amino}-*N*-(4-methoxyphenyl)-1,4-dioxaspiro[4.5]-decane-8-carboxamide (21).

Acetic acid **10** (0.48 mL, 8.32 mmol) was added to a solution of ketone **9** (1.08 g, 6.92 mmol), amine **11** (1.47 g, 8.29 mmol), and isonitrile **12** (1.39 g, 10.4 mmol) in MeOH (30 mL) at room temperature. The solution stood at room temperature for 3.5 days. The mixture was concentrated under reduced pressure, and then the residual mixture was purified by silica gel chromatography (AcOEt:*n*-hexane=1:2 to 1:1) to give **21** (2.70 g, 53.6 mmol, 77% from ketone **9**) as a thick, pale brown amorphous solid. $[a]_D^{20.5}$ –17.1 (*c* 0.46, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.64 - 1.67 (3H, m), 1.86 (1H, quint, *J* = 7.4 Hz), 2.06 - 2.16 (4H, m), 2.20 (3H, s), 2.54 (1H, br. s), 3.06 (1H, dd, *J* = 7.4, 13.1 Hz), 3.32 (1H, br. s), 3.67 (3H, s), 3.77 (3H, s), 3.92 (4H, s), 4.48 (1H, br. s), 5.24 (2H, dd, *J* = 11.4, 15.1 Hz), 6.15 - 6.29 (1H, m), 6.80 (2H, d, *J* = 8.9 Hz), 6.82 (2H, d, *J* = 8.9 Hz), 7.14 (4H, d, *J* = 8.9 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 14.0, 20.9, 25.6, 31.4, 31.8, 39.5, 54.9, 55.3, 60.2, 64.0, 64.1, 66.3, 107.5, 113.7, 114.1, 116.8, 122.9, 130.1, 138.1, 156.4, 158.3, 171.0, 174.2; IR (firm) 3379, 2935, 2247, 1649, 1513, 1248, 1107, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{36}N_2NaO_6$ 531.2478 [(M+Na)$^+$], found 531.2473.

Methyl 1-{acetyl[(2*R*)-1-(4-methoxyphenyl)but-3-en-2-yl]amino}-4,4-dimethoxycyclohexane carboxylate (22).

Racemic camphor sulfonic acid (1.20 g, 5.31 mmol) was added to a stirred solution of **21** (2.70 g, 5.31 mmol) in MeOH (20 mL) and trimethyl orthoformate (20 mL) at room temperature. After a stirring for 16 h, the solvent was removed under reduced pressure. Aqueous $NaHCO_3$ was added to the residual mixture, and then the mixture was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The resulting mixture was purified by silica gel chromatography (AcOEt:*n*-hexane=1:2) to give **22** (1.90 g, 4.53 mmol, 85%) as a colorless crystal. mp 107 °C; $[\alpha]_D^{25.6}$ 3.28 (*c* 1.04, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.31 (1H, m), 1.66 (1H, m), 2.00-2.20 (4H, m), 2.15 (3H, s), 3.00-3.30 (2H, m), 3.10 (3H, br. s), 3.71 (3H, s), 3.80 (3H, s), 4.41 (1H, br. s), 5.28 (1H, m), 6.02 (1H, m), 6.88 (2H, d, *J* = 8.36 Hz), 7.15 (2H, d, *J* = 8.36 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 25.0, 28.4, 28.6, 28.8, 28.8, 40.3, 47.2, 47.6, 51.6, 51.9, 57.5, 65.0, 98.6, 114.0, 113.9, 115.9, 129.9, 130.0, 130.4, 137.5, 158.2, 172.2, 173.7; IR (firm) 2950, 2832, 1739, 1641, 1514, 1249, 1107 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{33}NNaO_6$ 442.2206 [(M+Na)$^+$], found 442.2206.

8,8-Dimethoxy-1-[(2*S*)-1-(4-methoxyphenyl)but-3-en-2-yl]-1-azaspiro[4.5]decane-2,4-dione (28).

1.6 M Lithium hexamethyldisilazide in THF (2.81 mL, 4.50 mmol) was added to a solution of **22** (629 mg, 1.50 mmol) in THF (7 mL) at –78 °C under argon atmosphere, and was stirred for 2 h before being allowed to warm to room temperature. Then aqueous NH_4Cl was added. The mixture was extracted with AcOEt three times. From the combined organic layer, the solvent was removed under reduced pressure. The residual mixture was purified by silica gel chromatography (AcOEt:*n*-hexane=1:2) to give **28** (552 mg, 1.43 mmol, 95%) as a yellow oil. $[\alpha]_D^{26.4}$ 6.67 (*c* 1.33, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.62 (1H, br. d, *J* = 14.0 Hz), 1.23 (1H, m), 1.52 (1H, br. d, *J* = 13.3 Hz), 1.74-1.89 (3H, m), 3.03 (2H, s), 3.13 (3H, s), 3.16 (3H, s), 3.55-3.78 (2H, m), 3.78 (3H, s), 5.09-5.30 (2H, m), 6.34 (1H, ddd, *J* = 6.9, 10.3, 17.2 Hz), 6.82 (2H, d, *J* = 8.48 Hz), 7.11 (2H, d, *J* = 8.48 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.6, 27.4, 27.5, 27.9, 37.2, 40.4, 47.2, 47.6, 54.9, 58.9, 69.1, 98.1, 114.0, 113.5, 116.0, 130.3, 130.3, 136.5, 158.1, 167.8, 208.3; IR (firm) 2949, 2832, 1477, 1758, 1691, 1513, 1307, 1248 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{29}NNaO_5$ 410.1943 [(M+Na)$^+$], found 410.1941.

1-[(2*S*)-1-(4-Methoxyphenyl)but-3-en-2-yl]-1-azaspiro[4.5]decane-2,8-dione (31).

Sodium borohydride (2.00 g, 52.9 mmol) was added to a stirred solution of **28** (4.10 g, 10.6 mmol) in MeOH (100 mL) at room temperature. After stirring for 24 h, aqueous NH_4Cl was added, and the resulting mixture was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solution was removed under reduced pressure. The resulting crude product was used in the next step without further purification.

To a stirred solution of the crude product from the previous step, phosphoryl chloride (3.30 g, 21.6 mmol) in pyridine was added at room temperature. The mixture was heated at 60 °C, and stirred for 2 h. The mixture was allowed to cool to room temperature, aqueous $NaHCO_3$ was added, and then the mixture was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The resulting crude product was used in the next step without further purification.

Mg metal (4.20 g, 173 mmol) was added to a stirred solution of the crude product in MeOH (100 mL) at room temperature. Until hydrogen gas was generated, the suspension was heated with a heat gun. After stirring for 5 h and confirming the metal tips disappeared, 3 N HCl was added at 0 °C. After stirring at room temperature for 2 h, the mixture was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The resulting mixture was purified by silica gel chromatography (AcOEt:*n*-hexane=1:1 to 2:1) to give **31** (2.27 g, 6.91 mmol, 66%) as a colorless oil. $[\alpha]_D^{25.6}$ 4.26 (*c* 0.99, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.76 (1H, dq, *J* = 3.2, 13.5 Hz), 1.47 (1H, dt, *J* = 4.8, 13.8 Hz), 1.72-1.78 (2H, m), 1.93-1.98 (2H, m), 2.19-2.12 (2H, m), 2.24-2.44 (4H, m), 2.81 (2H, s), 2.90 (1H, m), 3.55-3.63 (1H, m), 3.78 (3H, s), 5.03-5.11 (1H, m), 6.34 (1H, ddd, *J* = 7.2, 10.3, 17.4 Hz), 6.81 (2H, d, *J* = 11.6 Hz), 7.07 (2H, d, *J* = 11.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.3, 29.5, 33.3, 34.2, 37.1, 37.5, 51.1, 55.1, 58.9, 63.0, 113.5, 115.7, 130.4, 130.8, 137.0, 158.1, 174.3, 208.9; IR (firm) 2936, 1716, 1679, 1666, 1513, 1410, 1246 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}NNaO_3$ 350.1732 [$(M+Na)^+$], found 350.1745.

(2*S*)-2-(2,8-Dioxo-1-azaspiro[4.5]dec-1-yl)-3-(4-methoxyphenyl)propanal (5b).

Ozone gas was passed through a stirred solution of **31** (2.26 g, 6.90 mmol) in MeOH (40 mL) at –78 °C. After starting material **31** was no longer detected by TLC, argon gas was passed through the solution for a few minutes before Me_2S (858 mg, 13.8 mmol) was added. The mixture was allowed to warm to room temperature, and then the solvent was removed under reduced pressure. Brine was added to the residual mixture, which was extracted with AcOEt twice. The solvent was removed under reduced pressure. The resulting crude product **5b** (2.11 g, 6.41 mmol, 93%) was used in the next step without further purification. $[\alpha]_D^{24.8}$ –48.9 (*c* 1.16, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.71 (1H, m), 1.27 (1H, dt, *J* = 5.0, 18.8 Hz), 1.81 (2H, dt, *J* = 5.4, 13.3 Hz), 2.13 (1H, m), 2.26 (1H, dd, *J* = 6.0, 14.7 Hz), 2.35-2.60 (5H, m), 3.30-3.50 (3H, m), 4.97 (3H, s), 6.83 (2H, d, *J* = 8.7 Hz), 7.08 (2H, d, *J* = 8.7 Hz), 9.65 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.7, 32.4, 33.7, 34.4, 34.5, 37.4, 37.5, 55.3, 62.1, 62.8, 114.0, 128.2, 129.0, 129.5, 130.6, 158.5, 175.1, 198.7, 208.3; IR (firm) 3382, 2934, 1477, 1666, 1511, 1248 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}NNaO_4$ 352.1525 [$(M+Na)^+$], found 352.1528.

(5*S*,6*R*,7*R*,10a*R*)-6-Hydroxy-5-(4-methoxybenzyl)tetrahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-

3,8(2*H*,5*H*)-dione (4b).

Pyrrolidine (149 mg, 2.09 mmol) and acetic acid (503 mg, 8.38 mmol) were added to a stirred solution of **5b** (2.30 g, 6.98 mmol) in AcOEt at 0 °C. The mixture was warmed to 20 °C, and stirred for 24 h. The solvent was removed under reduced pressure, and the residual mixture was purified by silica gel chromatography (AcOEt:*n*-hexane=2:1) to give **4b** (1.38 g, 4.20 mmol, 60%) as a colorless crystal. mp 156.3 °C; $[\alpha]_D^{23.7}$ –93.2 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (1H, br. d, *J* = 13.5 Hz), 1.72-1.87 (6H, m), 2.05 (1H, dd, *J* = 3.6, 13.2 Hz), 2.18 (1H, m), 2.48-2.55 (4H, m), 2.81 (1H, s), 3.56 (1H, dd, *J* = 4.4, 14.0 Hz), 3.78 (3H, s), 3.71-3.80 (1H, m), 3.95 (1H, dd, *J* = 6.2, 8.5 Hz), 6.82 (2H, d, *J* = 8.5 Hz), 7.18 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.2, 32.2, 33.4, 35.2, 35.8, 38.1, 51.1, 55.1, 59.5, 59.6, 70.4, 113.7, 129.4, 131.0, 158.1, 175.5, 211.1; IR (firm) 3382, 2934, 1666, 1511, 1248 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NNaO_4$ 352.1525 [$(M+Na)^+$], found 352.1538.

(5*S*,6*R*,7*S*,10a*R*)-6,8-Dihydroxy-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]-azocin-3-one (36).

Sodium triacetoxyborohydride (45.9 mg, 217 μmol) was added to a stirred solution of **4b** (23.8 mg, 72.3 μmol) in MeCN (2 mL) and acetic acid (1 mL) at 0 °C. After stirring for 1 h, brine was added. The mixture was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residual mixture was purified by silica gel thin layer chromatography (AcOEt:MeOH=10:1) to give **36** (14.9 mg, 45.0 μmol, 62%) as a colorless crystal. mp 197.9 °C; $[\alpha]_D^{22.7}$ 75.3 (*c* 0.75, MeOH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.02 (1H, br. d, *J* = 13.0 Hz), 1.57 (1H, m), 1.73-1.80 (8H, m), 2.16 (1H, dd, *J* = 4.1, 13.0 Hz), 2.24 (1H, br. s), 2.36 (1H, dd, *J* = 9.4, 17.4 Hz), 2.51 (1H, m), 3.10 (1H, m), 3.78 (3H, s), 3.75-3.90 (1H, m), 3.86-4.00 (2H, m), 4.26 (1H, br. s), 6.84 (2H, d, *J* = 8.5 Hz), 7.18 (2H, d, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.6, 31.2, 31.3, 31.6, 33.4, 36.6, 41.2, 44.6, 55.2, 59.9, 60.4, 60.7, 64.1, 72.0, 114.1, 129.5, 130.9, 158.3, 175.4; IR (firm) 3372, 2932, 1658, 1511, 1406, 1250 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{26}NNaO_4$ 354.1681 [$(M+Na)^+$], found 354.1670.

(5*S*,6*R*,7*R*,10a*R*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (37).

Triethylamine (103 mg, 1.02 μmol) and TBS triflate (134 mg, 508 μmol) were added to a solution of **36** (112 mg, 339 μmol) in CH_2Cl_2 at –20 °C, which was stirred for 24 h. Aqueous NH_4Cl was added. The mixture was allowed to warm to room temperature, and was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residual mixture was purified by silica gel thin layer chromatography (AcOEt:*n*-hexane=1:2) to give **37** (96.7 mg, 216 μmol, 64%) as a colorless oil. $[\alpha]_D^{20.4}$ 32.7 (*c* 1.02, $CHCl_3$); IR (firm) 2930, 1660, 1551, 1251, 1031 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ -0.03 (3H, s), -0.02

(3H, s), 0.84 (9H, s), 1.10 (1H, d, J = 12.8 Hz), 1.51-1.70 (7H, m), 1.76 (1H, dd, J = 8.2, 11.9 Hz), 2.13 (1H, br. s), 2.18 (1H, dd, J = 4.1, 12.8 Hz), 2.33 (1H, dd, J = 9.6, 17.4 Hz), 2.49 (1H, m), 2.80 (1H, m), 3.75 (3H, s), 3.70-3.85 (1H, m), 4.13 (1H, d, J = 3.2 Hz), 4.16 (1H, br. s), 6.83 (2H, d, J = 7.6 Hz), 7.18 (2H, d, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ -5.1, -4.9, 18.0, 25.7, 29.1, 31.2, 31.6, 31.7, 33.5, 37.6, 41.7, 55.1, 60.3, 60.8, 64.6, 72.8, 114.2, 129.7, 130.8, 158.4, 175.4; IR (firm) 2930, 1660, 1551, 1251, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{39}NNaO_4Si$ 468.2546 [$(M+Na)^+$], found 468.2532.

(5*S*,7*S*,10a*R*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)tetrahydro-1*H*-7,10a-methano-pyrrolo[1,2-*a*]azocine-3,6(2*H*,5*H*)-dione (3).

Oxalyl chloride (281 mg, 2.21 mmol) was added to a solution of DMSO (230 mg, 2.94 mmol) at –78 °C, which was stirred for 20 min. Then a solution of **37** (98.5 mg, 221 μmol) and triethylamine (816 mg, 8.07 mmol) was added. The mixture was warmed to 0 °C and stirred for an additional 10 min before aqueous NH_4Cl was added. The mixture was allowed to warm to room temperature, and was extracted with AcOEt twice. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residual mixture was purified by silica gel thin layer chromatography (CH_2Cl_2:MeOH=10:1) to give **3** (91.6 mg, 206 μmol, 93%, 96.4% ee) as a colorless oil. $[\alpha]_D^{23.6}$ 32.6 (c 0.91, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.00 (3H, s), 0.00 (3H, s), 0.12 (1H, br. d, J = 8.5 Hz), 0.81 (9H, s), 1.27 (1H, m), 1.51 (2H, m), 1.69-1.86 (5H, m), 2.18 (1H, m), 2.24 (1H, br. s), 2.40 (1H, dd, J = 9.2, 17.4 Hz), 2.60 (1H, ddd, J = 8.2, 12.4, 17.0 Hz), 3.08 (1H, dd, J = 2.8, 13.7 Hz), 3.75 (3H, s), 3.80-3.75 (1H, m), 3.96 (1H, m), 4.52 (1H, br. s), 6.76 (2H, d, J = 8.5 Hz), 6.86 (2H, d, J = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -5.1, -5.1, 17.9, 25.6, 26.9, 28.9, 30.9, 31.5, 34.1, 34.1, 35.2, 51.7, 55.2, 59.4, 64.2, 68.0, 113.8, 128.7, 131.0, 158.7, 174.5, 210.1; IR (firm) 2934, 1687, 1512, 1396, 1251, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{37}NNaO_4Si$ 466.2390 [$(M+Na)^+$], found 466.2401.

(5*S*,6*S*,7*R*,10a*R*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (38).

Diiodomethane (0.57 mL, 7.1 mmol) was added to a suspension of Sm^0 (1.28 g, 8.52 mmol) in THF (71 mL) at –78 °C. After stirring at room temperature for 16 h, a degassed mixture of MeOH (0.58 mL, 14.2 mmol), HMPA (6.2 mL, 35.5 mmol), and THF (30 mL) was added. Then key intermediate **3** (630 mg, 1.42 mmol) in degassed THF (9 mL) was added dropwise at –78 °C, and the reaction was stirred overnight. Saturated aqueous sodium bicarbonate was added at room temperature, and the mixture was extracted with AcOEt (three times). The combined organic layer was washed with brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt:n-hexane=4:1-1:1) to afford crude alcohol **38** (553 mg) containing inseparable HMPA, which was used in the next reaction without further purification.

(5*S*,6*S*,7*S*,10a*R*)-6,8-bis{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-

methanopyrrolo[1,2-*a*]azocin-3-one (39).

2,6-Lutidine (0.4 mL, 3.7 mmol) followed by TBSOTf (0.6 mL, 2.5 mmol) were added to a stirred solution of the crude product of **38** (554 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at room temperature. After stirring at room temperature for 5 h, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2 (three times). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt:*n*-hexane=5:95) to afford pure product **39** (360 mg, 0.664 mmol, 54% for 2 steps) as a pale yellow oil. $[\alpha]_D^{22.0}$ 18.3 (*c* 1.03, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.00 (3H, s), 0.01 (3H, s), 0.02 (1H, s), 0.02 (1H, s), 0.87 (9H, s), 0.92 (9H, s), 1.59-1.83 (7H, m), 1.86-1.94 (1H, m), 2.28-2.42 (2H, m), 3.11 (1H, dd, *J* = 7.9, 14.7 Hz), 3.62-3.65 (1H, m), 3.75-3.78 (1H, m), 3.79 (3H, s), 3.85 (1H, dd, *J* = 5.1, 14.2 Hz), 4.04-4.09 (1H, m), 6.82 (2H, d, *J* = 8.5 Hz), 7.21 (2H, d, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz): δ –4.9, –4.8, –4.7, –4.1, 18.0, 18.3, 25.7, 26.0, 27.3, 29.5, 31.1, 32.1, 33.7, 34.0, 45.4, 55.2, 58.6, 60.6, 67.5, 69.4, 113.6, 130.2, 132.6, 157.7, 176.1; IR (firm) 2953, 2930, 2857, 1693, 1513, 1250, 1077, 1053 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{53}NO_4Si_2$ 559.3513 (M^+), found 559.3528.

(5*S*,6*S*,7*S*,10a*S*)-6,8-bis{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)-3-oxooctahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-2-carboxylic acid (40).

n-BuLi (2.0 M in hexane)(4.8 mL, 12.9 mmol) was added to a solution of diisopropylamine (2.3 mL, 16.1 mmol) in THF (15 mL) at –78 °C. The resulting solution was stirred at 0 °C for 20 min before cooling to –78 °C. Then a solution of **39** (600 mg, 1.07 mmol) in THF (5 mL) was added dropwise. After stirring for 1 h at –78 °C, crushed dry-ice blocks were added until dry-ice solids were observed. After stirring at –78 °C for 20 min, saturated aqueous ammonium chloride was added, and the mixture was extracted with AcOEt (six times). The combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was washed with hexane and filtered over a pad of Celite. The filtrate was concentrated under reduced pressure to give the crude product of **40** (672 mg), which was used in the next reaction without further purification.

(2*Z*,5*S*,6*S*,7*S*,10a*S*)-6,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-(hydroxyimino)-5-(4-methoxybenzyl)-octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (41).

$NaNO_2$ (1.2 g, 17.0 mmol) was added to a stirred solution of the crude product of **40** (100 mg) and tetra-n-butylammonium bromide in 5:1 Et_2O:H_2O (2.4 mL) at 0 °C, and then conc. HCl (0.25 mL, 3.00 mmol) was added cautiously in four portions over 9 h. Saturated aqueous ammonium chloride was added. The mixture was stirred for an additional 1 h before extracting with AcOEt (four times). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt:*n*-hexane=7:1 to 4:1) to afford pure oxime **41** (64 mg, 115 μmol, 66% for 2 steps) as a pale orange solid. $[\alpha]_D^{24.0}$ 16.8 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.01-0.04 (12H, m), 0.86 (9H, s), 0.92 (9H, s), 1.60-2.08 (7H, m), 2.56 (2H, q, J = 18.0 Hz), 3.12 (1H, dd, J = 9.2, 15.6 Hz), 3.65 (1H, s), 3.78 (3H, s), 4.11-4.18 (2H, m), 6.82 (2H, d, J = 8.2 Hz), 7.20 (2H, d, J = 8.2 Hz), 9.42 (1H, br. s) ^{13}C-NMR ($CDCl_3$, 100 MHz): δ –5.0, –4.9, –4.8, –4.1, 18.0, 18.3, 25.7, 26.0, 28.8, 30.2, 32.7, 33.5, 37.1, 45.2, 55.2, 57.9, 60.1, 66.7, 68.9, 113.7, 130.0, 131.9, 152.8, 157.8, 163.9; IR (firm) 3269, 2953, 2930, 2857, 1708, 1660, 1513, 1251 cm^{-1} ; HRMS (FAB) calcd for $C_{31}H_{52}N_2O_5Si_2$ 588.3415 (M^+), found 588.3410.

(2*S*,5*S*,6*S*,7*S*,10a*S*)-2-Amino-6,8-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (42).

Activated zinc dust (1.30 g, 19.4 mmol) and NH_4Cl (520 mg, 9.7 mmol) were added to a stirred solution of oxime **41** (285 mg, 0.510 mmol) in AcOH (12 mL) at room temperature. After stirring at 50 °C overnight, the mixture was filtered over a pad of Celite, and the filtrate was concentrated under reduced pressure. To the resulting residue, saturated aqueous sodium bicarbonate was added, and the mixture was extracted with CH_2Cl_2 (three times). The combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product of **42** (297 mg), which was used in the next reaction without further purification. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ –0.02-0.06 (12H, m), 0.85 (9H, s), 0.93 (9H, s), 1.61-2.07 (10H, m), 2.21 (1H, m), 3.13 (1H, dd, J = 7.3, 14.6 Hz), 3.46 (1H, dd, J = 8.7, 10.5 Hz), 3.51 (1H, s), 3.70 (1H, br), 3.79 (3H, s), 3.87 (1H, t, J = 6.9 Hz), 3.98 (2H, dd, J = 6.4, 14.7 Hz), 6.83 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ –5.0, –4.9, –4.8, –4.0, 18.0, 18.1, 25.7, 25.8, 26.4, 30.2, 32.6, 33.5, 42.7, 45.4, 52.6, 55.2, 57.2, 59.3, 67.2, 69.5, 113.7, 129.7, 132.4, 157.8, 176.7.

***N*-[(2*S*,5*S*,6*S*,7*S*,10a*S*)-6,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)-3-oxooctahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]formamide (45).**

A mixture (3.8 mL) of HCOOH (6.0 mL, 157 mmol) and Ac_2O (3.8 mL, 40 mmol) were added to a stirred solution of amine **42** (297 mg) in CH_2Cl_2 (15 mL) at 0 °C dropwise, and the solution was stirred for 10 min at 0 °C. Then the reaction mixture was warmed to room temperature, and a small amount of toluene was added. The solvent was removed under reduced pressure to give the crude product of **45** (323 mg). This unstable product was used immediately in the next reaction without further purification.

(2*S*,5*S*,6*S*,7*R*,10a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)-2-(methylamino)octa-hydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-6-ol (46).

Lithium aluminum hydride (405 mg, 11 mmol) was added to a stirred solution of the crude product of **45** (323 mg) in THF (15 mL) at 0 °C. After stirring at 50 °C for 16 h, water (0.4 mL), 15% aqueous sodium hydroxide (0.4 mL), water (1.2 mL), and a sufficient amount of Et_2O were added successively at room temperature. After stirring for 30 min, the mixture was filtered over a pad of Celite. The filtrate was concentrated under reduced pressure to give crude methylamine **46** (259 mg). This polar product was used in the next reaction without further purification.

Benzyl [(2*S*,5*S*,6*S*,7*R*,10a*S*)-8-{[*tert*-butyl(dimethyl)silyl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]methylcarbamate (47).

Na_2CO_3 (488 mg, 4.6 mmol) followed by CbzCl (0.32 mL, 2.3 mmol) were added to a stirred solution of crude methylamine **46** (259 mg) in 3:1 CH_2Cl_2:H_2O (16 mL) at room temperature. After stirring for 3 h, saturated aqueous ammonium chloride was added, and the mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt:*n*-hexane=1:9 to 1:1) to afford pure alcohol **47** (174 mg, 0.293 mmol, 61% for 4 steps) as a pale yellow oil. $[\alpha]_D^{24.0}$ 7.65 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz): δ -0.02 (3H, s), -0.01 (3H, s), 0.86 (9H, s), 1.47 (1H, dd, *J* = 6.2, 13.6 Hz), 1.52 – 2.12 (9H, m), 2.71 – 2.89 (6H, m), 3.19 – 3.29 (1H, m), 3.35 – 3.57 (2H, m), 3.72 (1H, br. s), 3.79 (3H, s), 4.83 (1H, br. s), 5.12 (2H, s), 6.84 (2H, d, *J* = 8.5 Hz), 7.21 (2H, d, *J* = 8.5 Hz), 7.28 - 7.39 (5H, m,); ^{13}C-NMR ($CDCl_3$, 68 MHz): δ -4.8, -4.7, 18.1, 25.9, 29.1, 29.8, 31.1, 35.9, 42.9, 45.9, 50.1, 52.1, 55.3, 59.0, 59.3, 67.2, 67.4, 67.7, 113.9, 128.0, 128.0, 128.6, 130.3, 131.0, 137.0, 156.5, 158.0; IR (firm) 3448, 2952, 2931, 1698, 1512, 1329, 1249, 1161, 1041 cm^{-1}; HRMS (FAB) calcd for $C_{34}H_{51}N_2O_5Si$ 595.3562 [$(M+H)^+$], found 595.3531.

Benzyl [(2*S*,5*S*,6*S*,7*S*,10a*S*)-6,8-dihydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]methylcarbamate (48).

Aqueous HF (48%, 1.6 mL) was added to a stirred solution of alcohol **47** (174 mg, 0.293 mmol) in MeCN (9 mL) at 0 °C. After stirring at 0 °C for 5 h, the reaction mixture was diluted with CH_2Cl_2 and saturated aqueous sodium bicarbonate was added. The mixture was extracted with $CHCl_3$ (six times), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product of **48** (150 mg), which was used in the next reaction without further purification.

Benzyl[(2*S*,5*S*,6*S*,7*R*,10a*S*)-8-{[bis(benzyloxy)phosphoryl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]methylcarbamate (49).

1-*H*-tetrazole (21 mg, 0.30 mmol) was added to a stirred solution of diol **48** (50 mg) in CH_2Cl_2 (4 mL) at 0 °C, and the mixture was stirred for 20 min. Then dibenzyl(*N*,*N*-diisopropyl)phosphoramidite (90%)(ca. 58 μL, 0.20 mmol) was added slowly until the starting material was no longer detected by TLC analysis. Then the reaction mixture was cooled to –78 °C, and TBHP (5.5 M in decane) (40 μL) was added. Prior to the addition of saturated aqueous Na_2SO_3, the mixture was stirred for 1 h at –78 °C. Then the mixture was extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt:*n*-hexane=2:3 to 5:1) and silica gel thin layer chromatography (AcOEt:*n*-hexane=3:1) to afford pure dibenzyl phosphate **49** (25 mg, 34 μmol, 35% for 2 steps) as a colorless oil. $[\alpha]_D^{23.0}$ 6.69 (*c* 1.70,

$CHCl_3$); IR (firm) 3408, 2935, 1695, 1512, 1454, 1248, 1009 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.22 – 1.52 (2H, m), 1.61 - 2.11 (6H, m), 2.26 (1H, br. s), 2.70 (3H, s), 2.75 – 2.98 (3H, m), 3.26 (1H, br. s), 3.38 (1H, br. s), 3.54 – 3.72 (1H, m), 3.74 (3H, s), 4.31 (1H, br. s), 4.72 (1H, br. s), 4.96 – 5.04 (4H, m), 5.08 (2H, s), 6.84 (2H, d, J = 8.6 Hz), 7.21 (2H, d, *J* = 8.6 Hz), 7.27 - 7.40 (m, 15H); ^{13}C-NMR (CD_3OD, 68 MHz) δ 23.0, 29.3, 29.6, 31.3, 36.3, 44.1, 44.8, 51.7, 53.4, 55.7, 59.5, 68.0, 68.3, 70.8 (d, *J* = 6.0 Hz), 77.1, 114.7, 128.8, 129.1, 129.2, 129.6, 129.8, 131.2, 132.4, 137.2 (d, *J* = 6.0 Hz), 137.2 (d, *J* = 6.0 Hz), 138.2, 158.0, 159.6; HRMS (FAB) calcd for $C_{42}H_{50}N_2O_8P$ 741.3299 [$(M+H)^+$] found 741.3298.

(–)-FR901483 (1).

Aqueous 1 N HCl (18 μL) was added to a solution of dibenzyl phosphate **49** (34 mg, 46 μmol) in MeOH (3 mL), and the solvent was removed under reduced pressure giving **1**·HCl. Pd/C (5%, wet) (30 mg) and MeOH (4 mL) were added. The mixture was stirred at room temperature under 1 atm of hydrogen gas for 6 h and filtered. The residue was washed with MeOH. The combined filtrate was concentrated under reduced pressure to give FR901483 (**1**) (15 mg, 35.2 mmol, 77%) as a white solid. $[\alpha]_D^{23.0}$ -10.3 (*c* 0.68, $CHCl_3$); ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.84 - 1.92 (1H, m), 2.01 - 2.28 (6H, m), 2.43 (1H, br. s), 2.51 - 2.59 (1H, m), 2.68 (3H, s), 2.97 - 3.06 (1H, m), 3.21 - 3.28 (1H, m), 3.57 (1H, br. s), 3.73 - 3.84 (2H, m), 3.78 (3H, s), 4.09 - 4.24 (2H, m), 4.42 (1H, dd, *J* = 9.7, 13.2 Hz), 6.88 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz); ^{13}C-NMR (CD_3OD, 68 MHz) δ 22.5, 28.1, 28.5, 32.3, 34.1, 42.0, 43.0, 51.8, 55.0, 55.7, 61.5, 64.3, 67.8, 70.6 (d, *J* = 6.0 Hz), 115.2, 128.9, 131.7, 160.3; IR (firm) 3336, 2933, 1612, 1514, 1458, 1248, 1180, 1009 cm^{-1}; HRMS (FAB) calculated for $C_{20}H_{32}N_2O_6P$ 427.1992 [$(M+H)^+$] found 427.1996.

ACKNOWLEDGEMENTS

The authors thank Mr. Koji Nagao (Astellas Pharma Inc.) for the sample of natural product **1**. This work was financially supported by CREST, JST, and a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture and Technology of Japan.

REFERENCES AND NOTES

1. K. Sakamoto, E. Tsujii, F. Abe, T. Nakanishi, M. Yamashita, N. Shigematsu, S. Izumi, and M. Okuhara, *J. Antibiot.*, 1996, **49**, 37.
2. For a review of biomimetic syntheses of this family compounds, see: H. Takayama, *J. Synth. Org. Chem. Jpn.*, 2002, **60**, 350.
3. For synthetic studies, see: (a) T. Fujimoto, H. Kitaoka, S. Ieda, T. Kan, and T. Fukuyama, *Abstract of papers,* 79th Symposium on Organic Synthesis, Japan; The Society of Synthetic Organic Chemistry, Japan: Tokyo, June 2001, 17; (b) H. Suzuki, N. Yamazaki, and C. Kibayashi, *Tetrahedron Lett.*, 2001, **42**, 3013; (c) K. M. Brummond and J. L. Lu, *Org. Lett.*, 2001, **3**, 1347; (d)

D. J. Wardrop and W. M. Zhang, *Org. Lett.*, 2001, **3**, 2001; (e) G. Puigbo, F. Diaba, and J. Bonjoch, *Tetrahedron,* 2003, **59**, 2657; (f) J. Bonjoch, F. Diaba, G. Puigbo, E. Peidro, and D. Sole, *Tetrahedron Lett.*, 2003, **44**, 8387; (g) J. E. Kropf, I. C. Meigh, M. W. P. Bebbington, and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**, 2046; (h) S. Kaden and H.-U. Reissig, *Org. Lett.*, 2006, **8**, 4763; (i) D. B. Gotchev and D. L. Comins, *J. Org. Chem.*, 2006, **71**, 9393; (j) F. Diaba, E. Ricou, D. Sole, E. Teixido, N, Valls, and J. Bonjoch, *ARKIVOC,* 2007, **iv**, 320; (k) A. Asari, P. Angelov, J. M. Auty, and C. J. Hayes, *Tetrahedron Lett.*, 2007, **48**, 2631; (l) S. T. Simila and S. F. Martin, *J. Org. Chem.*, 2007, **72**, 5342; (m) H. Seike and E. J. Sorensen, *Synlett*, 2008, 695; (n) S. Ieda, T. Kan, and T. Fukuyama, *Tetrahedron Lett.*, 2010, **51**, 4027.

4. For total syntheses, see: (a) B. B. Snider and H. Lin, *J. Am. Chem. Soc.*, 1999, **121**, 7778; (b) G. Scheffler, H. Seike, and E. J. Sorensen, *Angew. Chem. Int. Ed.*, 2000, **39**, 4593; (c) M. Ousmer, N. A. Braun, C. Bavoux, M. Perrin, and M. A. Ciufolini, *J. Am. Chem. Soc.*, 2001, **123**, 7543; (d) J. Maeng and R. L. Funk, *Org. Lett.*, 2001, **3**, 1125; (e) T. Kan, T. Fujimoto, S. Ieda, Y. Asoh, H. Kitaoka, and T. Fukuyama, *Org. Lett.*, 2004, **6**, 2729; (f) K. M. Brummond and S. Hong, *J. Org. Chem.*, 2005, **70**, 907; (g) C. A. Carson and M. A. Kerr, *Org. Lett.*, 2009, **11**, 777; (h) S. Ieda, Y. Asoh, T. Fujimoto, H. Kitaoka, T. Kan, and T. Fukuyama, *Heterocycles,* 2009, **79**, 721.
5. For a review of organo-catalyst mediated aldol reactions, see: (a) S. Saito and H. Yamamoto, *Acc. Chem. Res.,* 2004, **37**, 570. Some examples in intramolecular aldol reactions, see: (b) Y. Hayashi, H. Sekizawa, and J. Yamaguchi, *J. Org. Chem.*, 2007, **72**, 6493; (c) N. Itagaki, M. Kimura, T. Sugawara, and Y. Iwabuchi, *Org. Lett.*, 2005, **7**, 4185.
6. For a review of enantioselective desymmetrization, see: M. C. Willis, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, **13**, 1765.
7. For reviews of multicomponent reactions with isonitriles, see: (a) C. Hulme and V. Gore, *Curr. Med. Chem.,* 2003, **10**, 51; (b) A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.,* 2000, **39**, 3168; (c) G. Gokel, G. Lüdke, and I. Ugi, 'Isonitrile Chemistry' ed. by I. Ugi, Academic Press, Inc., New York, 1971, 145; (d) 'Multicomponent Reactions' ed. by J. Zhu, H. Bienaymé, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 2005.
8. G. W. Gokel, R. P. Widera, and W. P. Weber, *Org. Synth., Coll. Vol. VI*, 1988, 232.
9. The conversion of **15** to **22** by DIBAL reduction and the subsequent Wittig olefination resulted in racemic **11**. Instead of a Wittig olefination, a Nozaki-Takai olefination (Zn, CH_2I_2, $AlMe_3$ in THF) was effectively conducted without racemization. However, the Nozaki-Takai olefination was unsuited for large-scale preparation due to its uncontrollable exothermic behavior.
10. US patent 5929284, 1997.
11. (a) K. Rikimaru, A. Yanagisawa, T. Kan, and T. Fukuyama, *Heterocycles*, 2007, **73**, 403; (b) K.

Rikimaru, A. Yanagisawa, T. Kan, and T. Fukuyama, *Synlett*, 2004, 41.

12. T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Am. Chem. Soc.*, 1963, **85**, 3785. This well-known classic condition was rediscovered in Solensen's work,[3m] although it exclusively gave the "undesired" stereoisomer in their synthetic studies.
13. Similar stereochemistry of the aldol product was observed with **4a**. Both the hydroxy groups of **3a** and **3b** were equatorially oriented and *syn* to the carbonyl groups.
14. D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
15. Synthetic protocol based on $NaBH(OAc)_3$ reduction, and selective deprotection of the TBS ether has already been reported in ref 4d. However, the transformation of **5** to **18** was developed independently in our laboratory, see ref 3a.
16. For a recent review of SmI_2, see: (a) G. A. Molander and C. R. Harris, *Chem. Rev.*, 1996, **96**, 307; (b) G. A. Molander, *Chem. Rev.*, 1992, **92**, 29.
17. Enhancement of the reduction potency of SmI_2 by the addition of HMPA has been reported, see: J. Inanaga and M. Yamaguchi, *J. Synth. Org. Chem. Jpn.*, 1989, **47**, 200.
18. For a review of the phosphoramidite method, see: R. P. Iyer, *Tetrahedron,* 1992, **48**, 2223.
19. For a similar regioselective phosphitylation, see ref 4a.
20. Eluted with 1% EtOH-*n*-hexane at flow rate of 1.0 mL/min on Daicel Chemical Ind., Ltd. CHIRALCEL OJ column (0.46 cm × 25 cm). Retention time: (–)- = 9.7 min, (+)- = 10.5 min.