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STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-FR901483

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Abstract – The total synthesis of potent immunosuppressant FR901483 (**1**) is reported. The remarkable feature of our convergent synthesis is the *p*-methoxybenzyl and methylamino groups are stereoselectively incorporated within the tri-cyclic core skeleton. The skeleton itself is constructed by an intramolecular aldol reaction on a symmetrical keto-aldehyde (**14**), which is readily derived by an eight-step sequence from nitromethane and methyl acrylate.

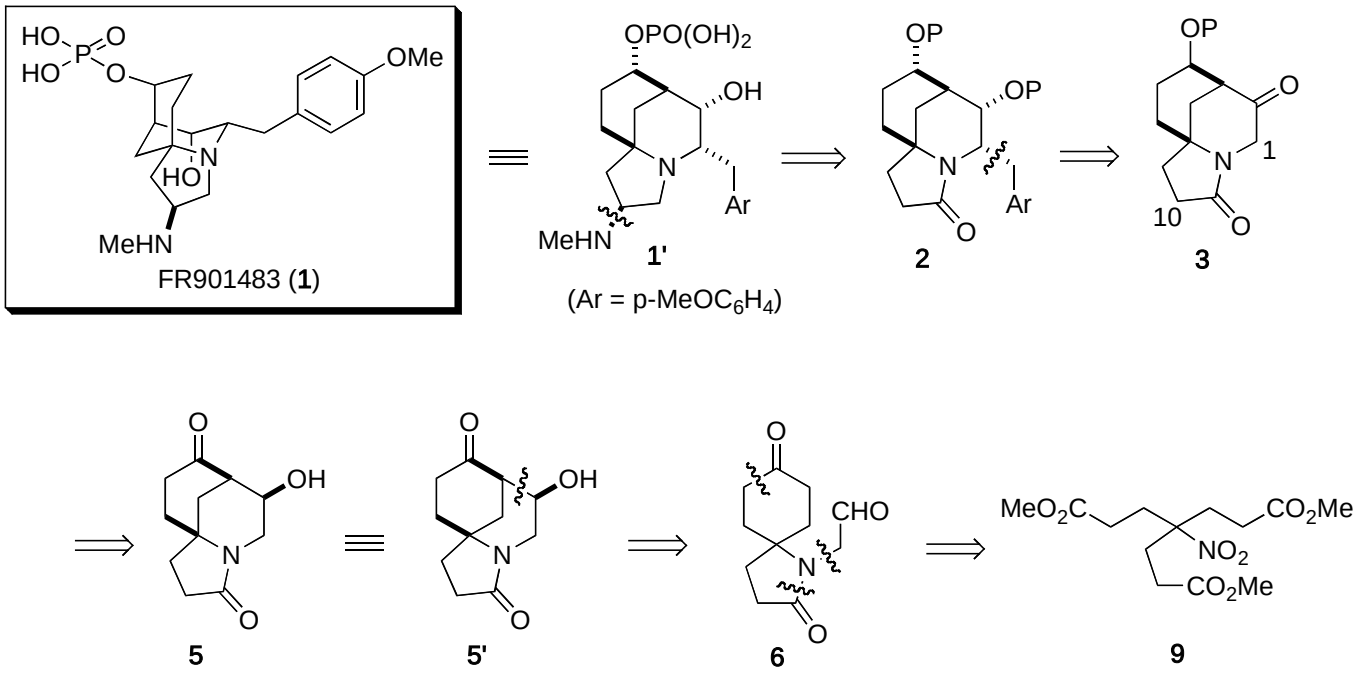
INTRODUCTION

FR901483 (1) is a novel immunosuppressant isolated from the fermentation broth of the Cladobotryum species.[1] The promising biological activity and intriguing structure of this compound have made it an attractive target for total synthesis.[2,3] Although several total syntheses and synthetic studies of 1 have been reported, there are few stereoselective syntheses.[4] Herein, we describe the details of our stereocontrolled total synthesis of racemic 1, which may lead to a plethora of diverse analogs.

RESULTS AND DISCUSSION

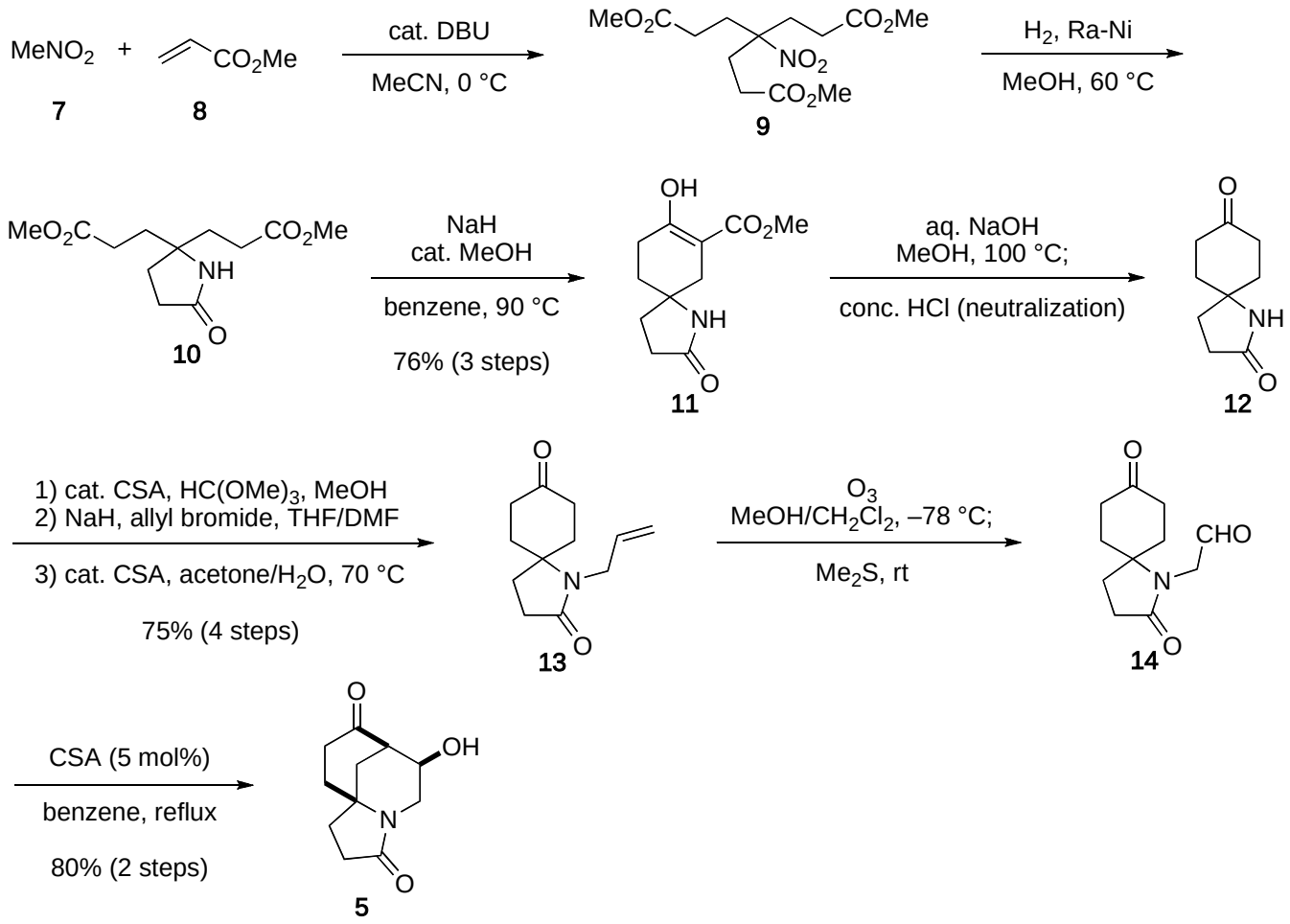
Scheme 1 illustrates our retrosynthetic analysis. Our synthesis features an intermediacy of tricycle **3** and uses multiple carbonyl groups to append the requisite *p*-methoxybenzyl and methylamino groups at C(1) and C(10), respectively. The synthesis of **3** would be accomplished using an intramolecular aldol reaction

on symmetrical keto-aldehyde **6** as a key step. The spiro-lactam would be derived from triester **9**, which would be obtained by a Michael addition with acryrates and nitromethane.



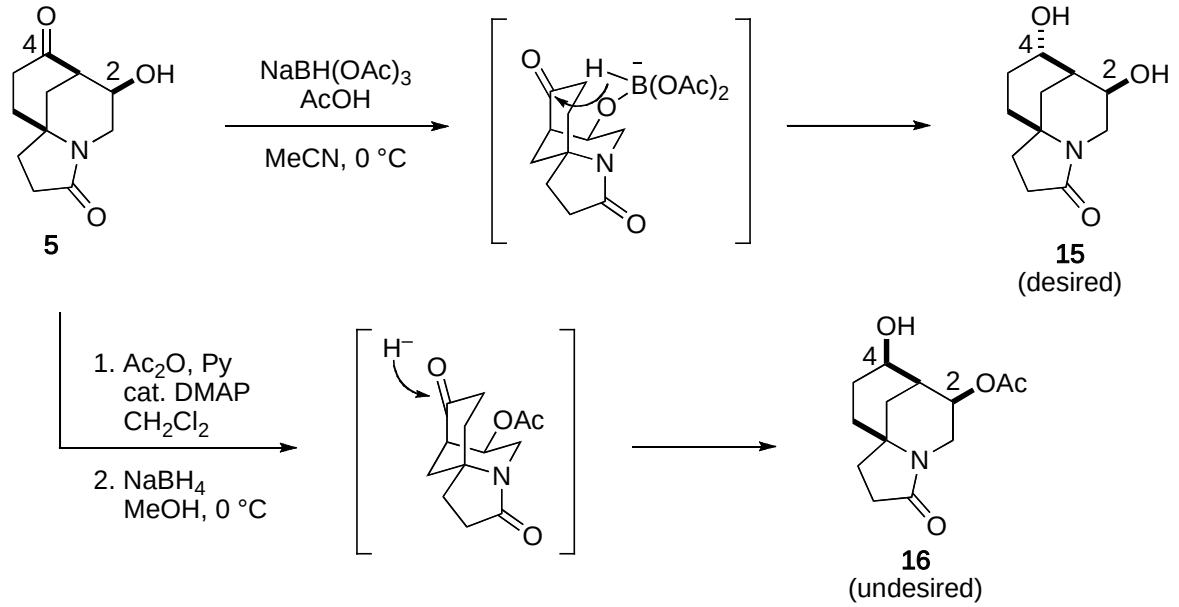
Scheme 1. Retrosynthetic Analysis.

As shown in Scheme 2, cyclization precursor **14** was readily prepared by an eight-step sequence from inexpensive nitromethane **7** and methyl acrylate **8**. Upon treatment of **7** and three equivalents of **8** with 5 mol% DBU, the desired Michael reaction proceeded smoothly to afford triester **9**. Subsequent reduction of the nitro group and concomitant ester-amide exchange proceeded to provide **10**, which possessed the required tetra-substituted carbon. After Dieckmann condensation of diester **10**, basic hydrolysis of the corresponding methyl ester and neutralization with acid caused decarboxylation of the β-keto acid to afford spiro-lactam **12** in high yield. Cyclization precursor **14** was prepared from **12** by a four-step sequence involving the protection of the ketone as the dimethyl ketal, allylation of the amide, acidic hydrolysis of the dimethyl ketal, and oxidative cleavage of the double bond. Upon treatment of **14** in the presence of 5 mol% CSA, the crucial intramolecular aldol reaction furnished desired tricycle **5** as a single isomer. The synthesis of **5** from **7** and **8** could be readily scaled up because tedious chromatographic purifications were unnecessary during the synthetic process, which produced **5** as white crystals. A desymmetrizing aldol reaction of **14** could also potentially be used to prepare an optically active compound.[5]

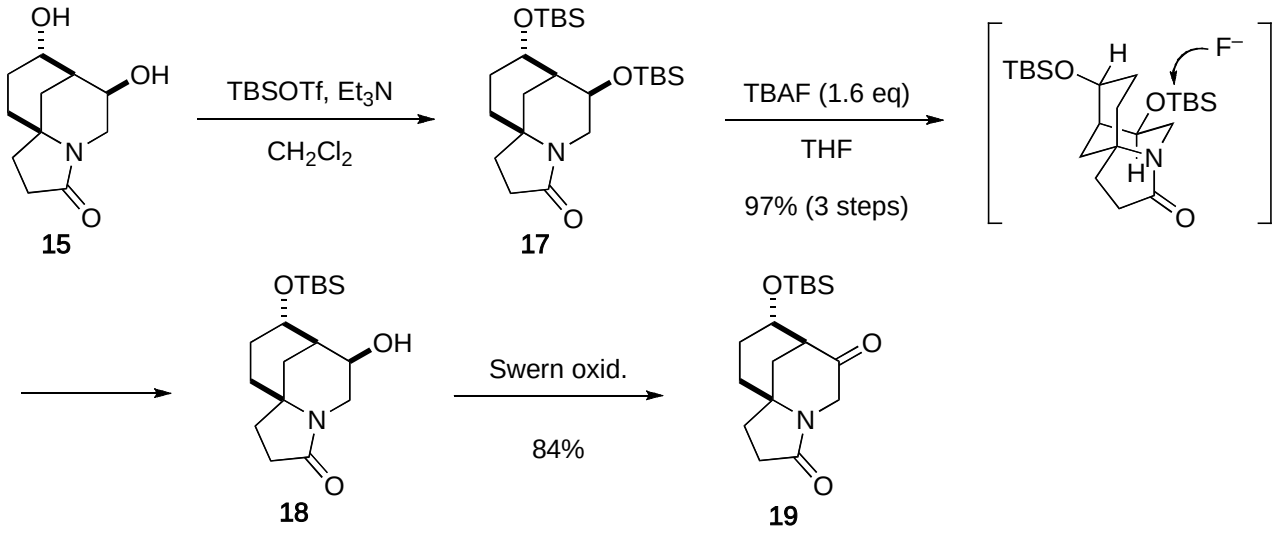


Scheme 2. Construction of tricyclic ketone **5**.

With desired tri-cyclic compound **5** in hand, we then focused our attention to the ketone of **5**. Reduction with $NaBH(OAc)_3$[6,7] gave the desired α-alcohol. The reaction of ketone **5** underwent hydroxyl group directed reduction to give diol **15**. Meanwhile, the reduction of the acetate derivatives of **5** mediated by $NaBH_4$ afforded undesired β-alcohol **16**, which is formed when the hydride attacks from the convex face of the molecule (Scheme 3). The stereochemistry of the alcohols in **15** and **16** could not be elucidated by the completion of this total synthesis because the difference of the coupling constants in the 4-position protons is not so significant, which were observed as broad singlets by NMR. Based on the well-known reaction mechanisms, we supposed that **15** have the desired stereochemistry. The two hydroxy groups of **15** were differentiated in a stepwise manner. After protection of **15** as the TBS ether, selective cleavage of the equatorial TBS ether **17** was carried out by treatment with TBAF. Subsequent oxidation of the resultant alcohol under Swern conditions provided key intermediate **19** (Scheme 4).[8]

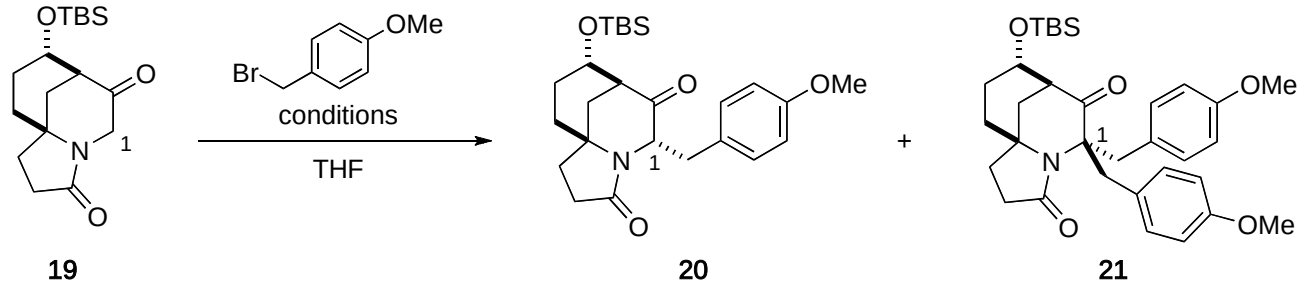


Scheme 3. Stereoselective reduction of tricyclic ketone **5**.



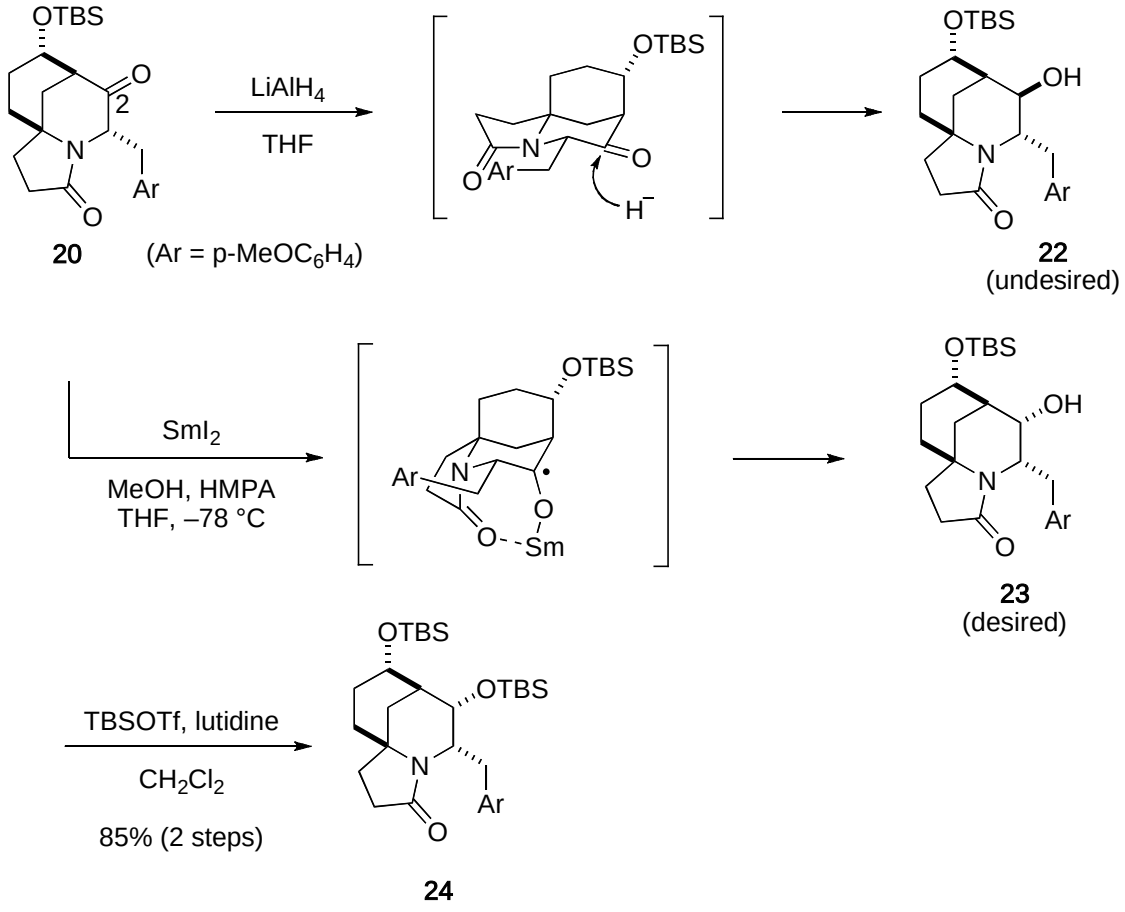
Scheme 4. Conversion of diol **15**.

The next challenge in the synthesis was stereoselective incorporation of the *p*-methoxybenzyl groups into tricyclic ketone **19 (**Scheme 5). Diastereoselective alkylation proceeded smoothly upon treatment of **19** with LHMDS and *p*-methoxybenzyl bromide, although the yield was low. Changing from LHMDS to KHMDS increased the yield and provided concomitantly the dialkylated product. As shown in Scheme 5**,** alkylation was accomplished by treatment with KHMDS in the presence of TMEDA, which presumably plays a key role in the reaction,[9] to give desired ketone **20** as a single isomer.



entry	reagents	temp.	yield (%)
1	LHMDS (1.1 eq)	–45 °C	31
2	KHMDS (1.1 eq)	–45 °C	43
3	KHMDS (1.0 eq), TMEDA (5 eq)	–78 °C	64

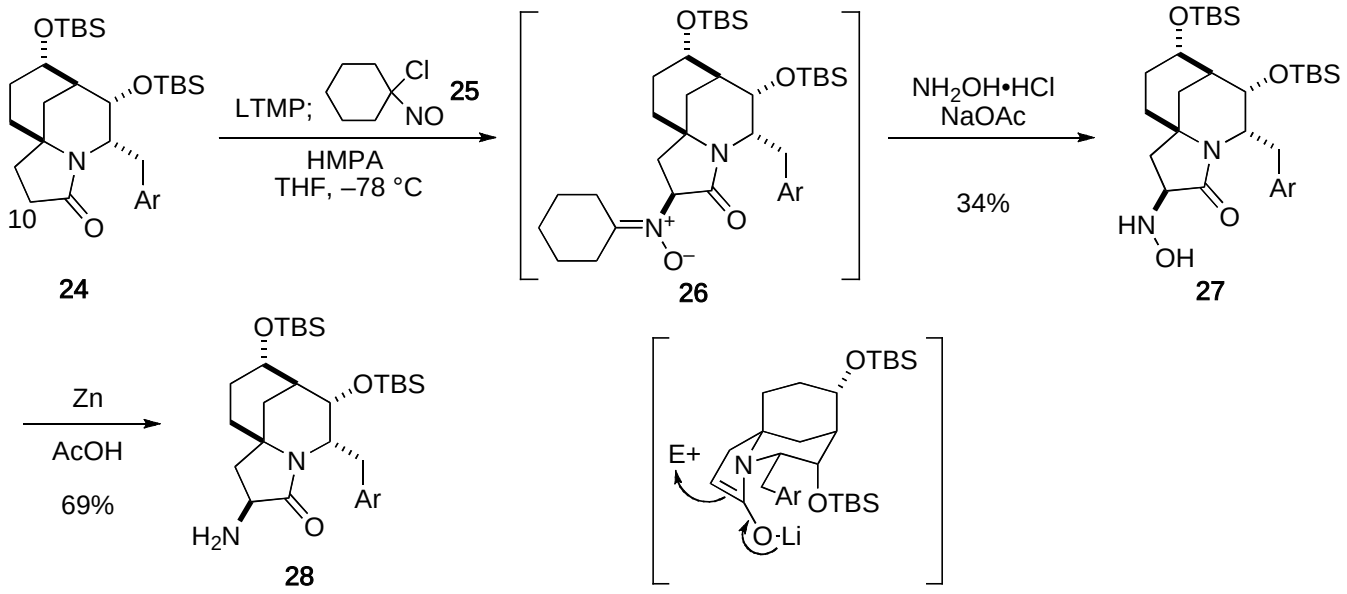
Scheme 5. Diastereoselective alkylation of **18**.



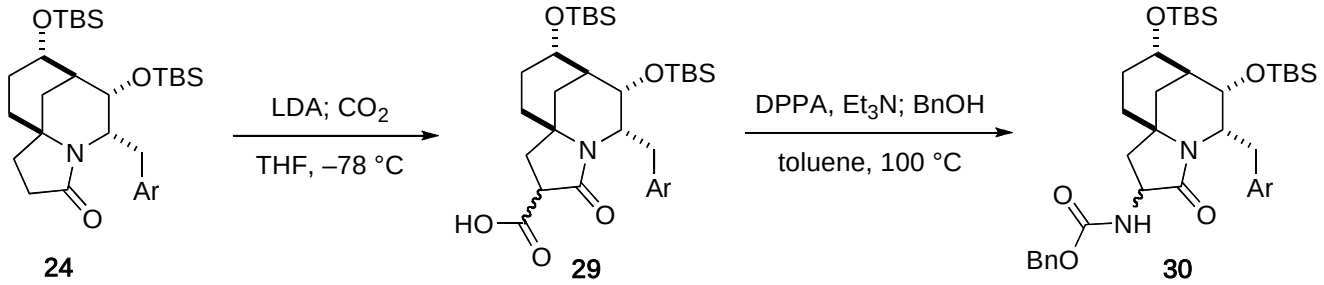
Scheme 6. Stereoselective reduction of **20**.

Conversion of ketone **20** into the *exo*-oriented alcohol was accomplished by a one-electron reduction because reduction with LAH gave exclusively undesired *endo*-alcohol **22**. Because the hydride should attack from the convex face of **20**, a one-electron reduction with samarium (II) was investigated. Thus, upon treatment with samarium (II) diiodide (SmI_2)[10] in the presence of HMPA, ketone **20** was smoothly reduced at –78 °C to provide desired **23**. In this SmI_2 mediated reaction of **20**, the addition of HMPA was essential for high selectivity. A similar reduction of **20** without HMPA did not proceed at –78 °C, and the selectivity resulted in approximately 5:1 to 7:1 ratio. As shown in Scheme 6, chelation between the radical anion and the neighboring carbonyl group with the samarium cation should play a key role in the high selectivity.[11] Subsequent protection of **23** with the TBS ether gave **24**.

The next challenge was the incorporation of a nitrogen atom into amide **24**. Initially, we selected Oppolzer's protocol, as shown in Scheme 7.[12] Although the trapping of chloronitroso compound **25** with the lithium enolate of **24** and subsequent reduction afforded desired amine **28** as a single isomer, the yield was unsatisfactory. However, as shown in Scheme 8, Curtius rearrangement of **29** was investigated because carboxylation of **24** with solid CO_2 proceeded smoothly. **29** easily underwent the desired rearrangement upon treatment with DPPA and Et_3N, and addition of BnOH to the isocyanate intermediate gave Cbz protected **30** as a 1:1 mixture.

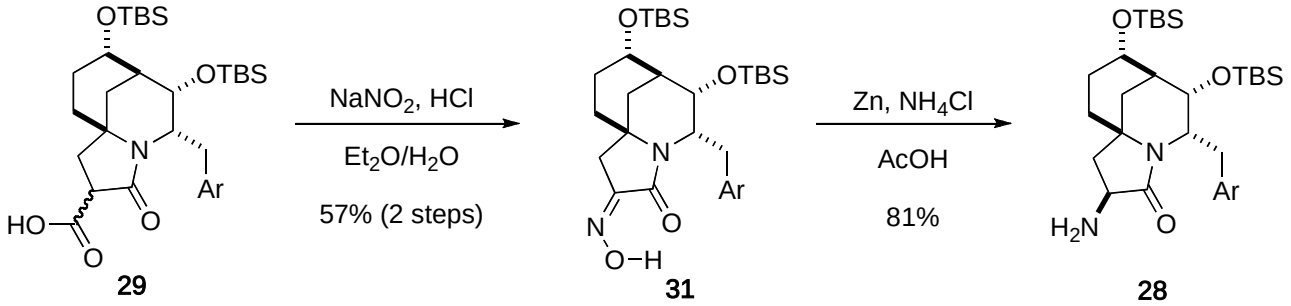


Scheme 7. Incorporation of a nitrogen atom by Oppolzer's protocol.[12]



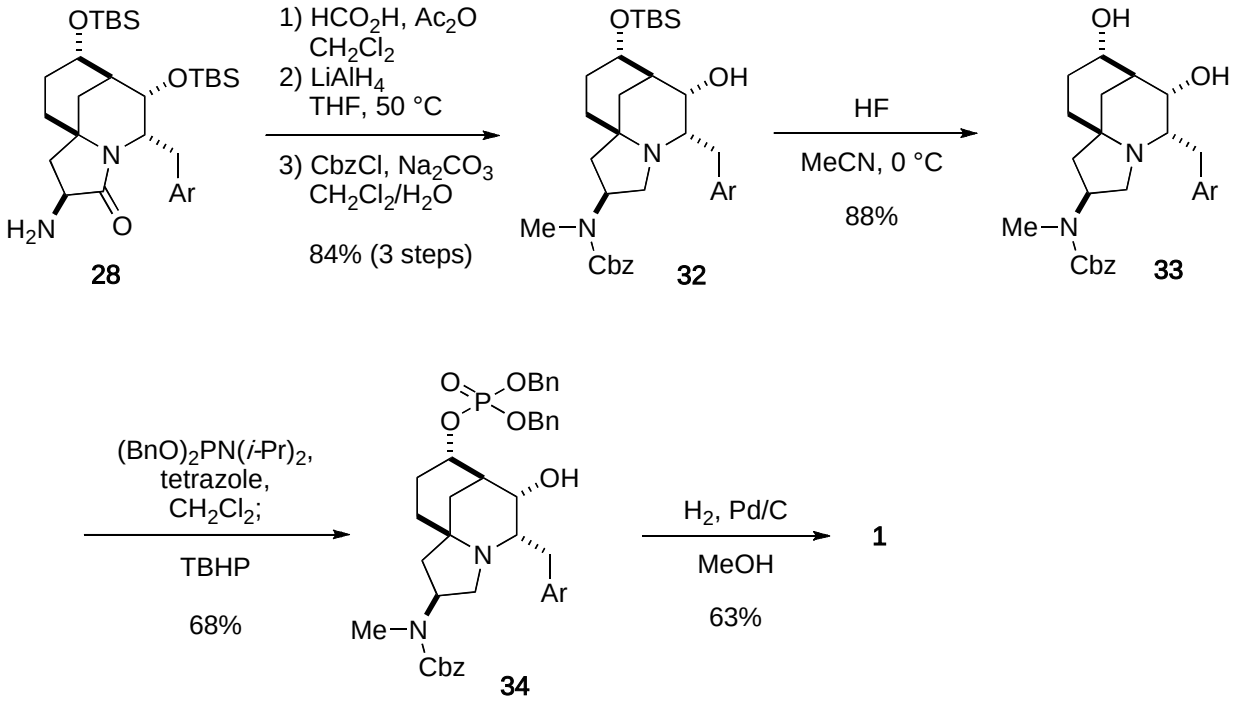
Scheme 8. Incorporation of a nitrogen atom by Curtius rearrangement.

As shown in Scheme 9, an amine group was stereoselectively incorporated using a one-electron reduction as a key step. Upon treatment of **29** with sodium nitrite under acidic conditions a sequential nitrosylation and decarboxylation proceeded smoothly to provide oxime **31**. The crucial reduction of **31** was accomplished by treatment with zinc in acetic acid to provide desired amine **28** as a single isomer.



Scheme 9. Successful incorporation of a nitrogen atom.

Mono-*N*-methylation of primary amine **28** was achieved in a stepwise manner. After conversion of **28** into the formamide, treatment with lithium aluminum hydride allowed the simultaneous reduction of both the lactam and the formamide, while concomitant deprotection of one of the TBS groups provided the corresponding methylamine derivative, which was then protected with a Cbz group to afford **32**. After deprotection of the TBS ether, regioselective incorporation of the phosphate ester was achieved via the phosphoramidite method[13] to give **34**.[14] Finally, simultaneous cleavage of Cbz and the benzyl ester groups by hydrogenolysis conditions yielded racemic FR901483 (**1**), which had spectral data (^{1}H NMR, ^{13}C NMR, IR and HRMS) that fully agreed with those of the natural product (Scheme 10).



Scheme 10. Total synthesis of FR901483 (**1**).

In conclusion, a highly stereoselective total synthesis of FR901483 (**1**) was accomplished by alkylation of key intermediate **5**, which itself was obtained by an intramolecular aldol reaction. Our synthesis features the stereoselective construction of the *exo*-oriented alcohol by a SmI_2 mediated reduction. Finally, the amine stereochemistry at C(10) is set by a one-electron reduction.

EXPERIMENTAL

General. Nuclear magnetic resonance (^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)) spectra were determined on a JEOL-LA400 instrument. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (δ) in deuterochloroform as the internal standard, 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 a triplet at 77.0 ppm for deuterochloroform ($CDCl_3$). 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. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Preparative TLC separations were made on Merck precoated analytical plates, 0.50 mm thick, 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. All solvents were dried over molecular sieves 3A or 4A before use. All other reagents were commercially available, and used without further purification, unless otherwise specified.

4-(2-Methoxycarbonyl-ethyl)-4-nitro-heptanedioic acid dimethyl ester (9).

To a stirred solution of $MeNO_2$ **7** (20.0 g, 328 mmol) in MeCN (400 mL) at 0 °C were added methyl acrylate **8** (118 mL, 1.32 mol) and DBU (5.40 mL, 36.2 mmol). After stirring at 0 °C for 30 min, saturated aqueous ammonium chloride was added and the mixture was extracted with Et_2O. The combined organic layer was washed with brine then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting oil **9** (107 g) was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.24-2.35 (12H, m), 3.70 (9H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.4, 30.2, 52.0, 91.8, 172.1; IR (film) 1738, 1538, 1438, 1176 cm^{-1}.

3-[2-(2-Methoxycarbonyl-ethyl)-5-oxo-pyrrolidin-2-yl]-propionic acid methyl ester (10).

To a stirred solution of foregoing crude product **9** (50.0 g) in MeOH (250 mL) at rt was added Ra-Ni (W_2) (5.00 g). After stirring at 60 °C under hydrogen gas atmosphere (5 kgw/cm^2) for 6 h, the mixture was filtered through a pad of Celite and washed with MeOH. The solvent was removed under reduced pressure and the resulting crude product of **10** (40.8 g) was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.82-1.96 (6H, m), 2.30-2.47 (6H, m), 3.69 (6H, s), 6.85 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.7, 30.2, 34.6, 51.9, 60.6, 173.5, 177.3; IR (film) 3213, 3086, 2953, 1731, 1696, 1436 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{20}NO_5$ 258.1336 [$(M+H)^+$], found 258.1326.

8-Hydroxy-2-oxo-1-aza-spiro[4.5]dec-7-ene-7-carboxylic acid methyl ester (11).

To a stirred solution of foregoing crude product of **10** (20.0 g) in benzene (150 mL) at 0 °C was added MeOH (315 mL, 7.77 mmol) followed by NaH (7.77 g, 194 mmol). After stirring at 90 °C for 30 min, aqueous 3 N HCl was added and the mixture was extracted with AcOEt. The combined organic layer was washed with saturated aqueous sodium hydrogen bicarbonate and brine then dried over $MgSO_4$. The solvent was removed under reduced pressure. Resulting solid residue was triturated with hexane to afford **11** (12.8 g, 56.8 mmol, 76% for 3 steps) as a white solid: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.71-2.05 (4H, m), 2.35-2.51 (6H, m), 3.76 (3H, s), 6.73 (1H, br), 12.16 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.4, 29.7, 32.2, 32.8, 35.1, 51.6, 57.2, 95.2, 170.7, 172.3, 177.2; IR (film) 3203, 3084, 2951, 1745, 1695, 1620, 1443, 1361 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{16}NO_4$ 226.1074 [$(M+H)^+$], found 226.1069.

1-Aza-spiro[4.5]decane-2,8-dione (12).

To a stirred solution of **11** (1.66 g, 7.37 mmol) in MeOH (15 mL) at rt was added aqueous 4 N NaOH

(3.67 mL, 14.7 mmol). The reaction mixture was stirred at 100 °C for 3.5 h. After the reaction mixture was cooled to rt, small amount of methyl orange was added, and was neutralized with aqueous 12 N HCl carefully. The solvent was removed under reduced pressure and the resulting crude product of **12** was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.93-2.10 (6H, m), 2.36-2.61 (6H, m), 8.34 (1H, br); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.0, 32.3, 37.7, 37.8, 58.4, 178.2, 209.6; IR (film) 3202, 1705, 1652, 1323, 1268 cm^{-1}; HRMS (FAB) calcd for $C_9H_{13}NO_2$ 167.0946 (M^+), found 167.0962.

1-Allyl-1-aza-spiro[4.5]decane-2,8-dione (13).

To a stirred solution of **12** (7.37 mmol as theoretical amount) in MeOH (15 mL) at rt was added $HC(OMe)_3$ (0.964 mL, 8.81 mmol) followed by CSA (85.3 mg, 0.367 mmol). After stirring at rt for 30 min, the mixture was neutralized with Et_3N. The solvent was removed under reduced pressure and the resulting crude product of the dimethyl acetal was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.62-1.73 (8H, m), 1.96 (2H, t, *J* = 8.2 Hz), 2.40 (2H, t, *J* = 8.2 Hz), 3.18 (6H, s), 6.36 (1H, br); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.1, 29.7, 34.3, 34.4, 47.7, 58.6, 98.8, 177.1; IR (film) 3207, 2952, 1737, 1692, 1439, 1105, 1056 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{16}NO_2$ 182.1181 [$(M\text{-}OMe)^+$], found 182.1197.

To a stirred solution of the above dimethyl acetal (7.37 mmol as theoretical amount) in 3:1 THF/DMF (15 mL) at rt was added NaH (861 mg, 21.5 mmol). The mixture was stirred at rt for 10 min then allyl bromide (1.40 mL, 16.2 mmol) was added. After stirring at rt for 3.5 h, saturated aqueous ammonium chloride was added and the mixture was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude product of the lactam was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.37 (2H, d, *J* = 13.6 Hz), 1.48 (2H, dt, *J* = 4.0, 13.6 Hz), 1.84 (2H, dt, *J* = 4.0, 13.6 Hz), 1.96 (2H, t, *J* = 4.0 Hz), 2.03 (2H, d, *J* = 13.6 Hz), 2.40 (2H, t, *J* = 4.0 Hz), 3.18 (3H, s), 3.21 (3H, s), 3.82 (2H, d, *J* = 4.8 Hz), 5.10 (1H, d, *J* = 9.6 Hz), 5.17 (1H, d, *J* = 15.6 Hz), 5.80 (1H, ddd, *J* = 4.8, 9.6, 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.9, 29.0, 29.1, 31.2, 41.7, 47.6, 47.9, 63.5, 98.5, 116.1, 134.7, 173.6.

To a stirred solution of the above lactam (7.37 mmol as theoretical amount) in 2:1 acetone/H_2O (15 mL) at rt was added a catalytic amount of CSA (85.3 mg, 0.368 mmol). The reaction mixture was stirred at 70 °C for 30 min. After the reaction mixture was cooled to rt, Et_3N (0.15 mL, 1.08 mmol) was added. The solvent was removed under reduced pressure to afford **13** (1.14 g, 5.50 mmol, 75% for 4 steps) as a white solid: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.80-1.85 (2H, m), 2.10-2.23 (4H, m), 2.40-2.57 (6H, m), 3.85 (2H, d, *J* = 5.6 Hz), 5.12 (1H, d, *J* = 10.0 Hz), 5.17 (1H, d, *J* = 18.4 Hz), 5.79 (1H, ddd, *J* = 5.6, 10.0, 22.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.8, 28.9, 34.1, 37.6, 41.9, 62.5, 116.6, 134.5, 174.0, 208.6; IR (film)

2938, 1717, 1685, 1404, 1324, 1226, 1151 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{17}NO_2$ 207.1259 (M^+), found 207.1249.

(2,8-Dioxo-1-aza-spiro[4.5]dec-1-yl)-acetaldehyde (14).

Through a stirred solution of **13** (5.30 g, 25.6 mmol) in 1:1 MeOH/CH_2Cl_2 (50 mL) at –78 °C was bubbled ozone gas. After the disappearance of starting material monitored by TLC, argon gas was bubbled and to this solution at –78 °C was added Me_2S (18.8 mL, 256 mmol). After stirring for 30 min, the solvent was removed under reduced pressure and the resulting crude product of **14** was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.89-1.93 (4H, m), 2.32 (2H, t, *J* = 8.0 Hz), 2.42-2.62 (6H, m), 3.96 (2H, s), 9.56 (1H, s).

6-Hydroxytetrahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-3,8(2*H*,5*H*)-dione (5).

To a stirred solution of foregoing crude product of **14** (25.6 mmol as theoretical amount) in benzene (50 mL) at rt was added a catalytic amount of CSA (297 mg, 1.28 mmol). The reaction mixture was heated to 90 °C for 5 min. After the reaction mixture was cooled to rt, the mixture was filtered to give a white solid, which was washed with Et_2O and dried in vacuo, to yield pure **5** (4.30 g, 20.6 mmol, 80% for 2 steps) as a white solid: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.82-2.25 (6H, m), 2.42-2.71 (4H, m), 2.90-2.96 (2H, m), 4.00 (1H, m), 4.42 (1H, dd, *J* = 7.3, 13.7 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.0, 31.7, 35.4, 37.4, 38.9, 43.8, 51.7, 57.2, 66.9, 173.6, 210.7; IR (KBr) 3189, 2915, 1705, 1665, 1641, 1450, 1419, 1218, 1087 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{16}NO_3$ 210.1125 [$(M+H)^+$], found 210.1124.

6,8-Dihydroxyoctahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (15).

To a stirred mixture of $NaBH(OAc)_3$ (72.0 g, 340 mmol), MeCN (380 mL) and AcOH (77 mL) was added **5** (17.6 g, 84.1 mmol) at 0 °C. After stirring at 0 °C for 2 h, the mixture was warmed to rt where it was stirred for an additional 2 h. The reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (CH_2Cl_2:MeOH=95:5-90:10) to afford crude product of **15**, which was used in the next reaction without further purification.

6,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (17).

To a stirred solution of foregoing crude product of **15** (84.1 mmol as theoretical amount) in CH_2Cl_2 (250 mL) at rt was added Et_3N (94 mL, 674 mmol) followed by TBSOTf (57.5 mL, 250 mmol). After stirring at rt for 2 h, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine then dried over $MgSO_4$. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=0:1-1:1) to afford crude product of **17**, which was used in the next reaction without further purification.

8-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxyoctahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (18).

To a stirred solution of foregoing crude product of **17** (84.1 mmol as theoretical amount) in THF (450 mL) at rt was added TBAF (1 M in THF) (134 mL, 134 mmol) slowly. After complete addition (2 h), saturated aqueous ammonium chloride was added and the mixture was extracted with AcOEt. The combined organic layer was washed with brine then dried over Na_2SO_4. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=0:1-9:1) to afford **18** (26.6 g, 81.7 mmol, 97% for 3 steps) as a white solid: ^{1}H-NMR ($CDCl_3$ d 7.26, 400 MHz) δ 0.05 (6H, s), 0.88 (9H, s), 1.67-2.00 (6H, m), 2.22-2.36 (3H, m), 2.44-2.52 (1H, m), 2.96 (1H, br), 3.04 (1H, t, *J* = 11.9 Hz), 4.02 (1H, br), 4.18 (1H, dd, *J* = 8.2, 13.7 Hz), 4.28 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.9, 18.0, 25.8, 30.1, 30.5, 32.9, 33.0, 34.1, 43.0, 45.0, 58.6, 64.4, 66.7, 173.8; IR (KBr) 3209, 2953, 2928, 1678, 1452, 1252 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{31}NO_3Si$ 325.2073 (M^+), found 325.2065.

8-{[*tert*-Butyl(dimethyl)silyl]oxy}tetrahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-3,6(2*H*,5*H*)-dione (19).

To a solution of oxalyl chloride (0.398 mL, 4.56 mmol) in CH_2Cl_2 (6 mL) at –78 °C was added DMSO (0.485 mL, 6.83 mmol). After the resulting mixture was stirred for 1 h, **18** (0.741 g, 2.28 mmol) in CH_2Cl_2 (4 mL) was added and the mixture was stirred for 30 min before Et_3N (1.27 mL, 9.11 mmol) was added. The mixture was allowed to warm to rt. After stirring at rt for 30 min, saturated aqueous ammonium chloride was added and the mixture was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=1:2-1:1) to afford the pure **19** (620 mg, 1.92 mmol, 84%) as a white solid: ^{1}H-NMR ($CDCl_3$ δ 7.26, 400 MHz) d 0.07 (6H, s), 0.89 (9H, s), 1.48-1.57 (1H, m), 1.70-2.05 (6H, m), 2.34-2.40 (1H, m), 2.48-2.52 (1H, m), 2.57-2.66 (1H, m), 2.72 (1H, s), 3.99 (1H, d, *J* = 22.0 Hz), 4.00 (1H, d, *J* = 3.7 Hz), 4.20 (1H, d, *J* = 22.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ –5.1, 18.0, 25.6, 29.2, 30.1, 31.1, 32.1, 34.2, 52.0, 52.4, 58.6, 67.2, 174.0, 205.7; IR (film) 2933, 2894, 2857, 1711, 1688, 1411, 1255 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{30}NO_3Si$ 324.1995 [$(M+H)^+$], found 324.1981.

8-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)tetrahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-3,6(2*H*,5*H*)-dione (20).

To a solution of **19** (17.3 g, 53.5 mmol) in THF (540 mL) at –78 °C were added TMEDA (40.3 mL, 267 mmol) and KHMDS (0.5 M in toluene), (110.2 mL, 55.1 mmol). After stirring at –78 °C for 30 min, *p*-methoxybenzylbromide (30.0 mL, 160 mmol) in THF (200 mL) was added slowly. After complete addition (10 h), the reaction mixture was allowed to warm to rt and then, saturated aqueous ammonium

chloride was added. The mixture was extracted with AcOEt. The combined organic layer was washed with brine then dried over Na_2SO_4. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=1:9-2:8) to afford **20** (15.2 g, 34.2 mmol, 64%) as a colorless oil: ^{1}H-NMR ($CDCl_3$ δ 7.26, 400 MHz) d 0.03 (6H, s), 0.84 (9H, s), 1.23-1.34 (2H, m), 1.46-1.59 (3H, m), 1.71-1.89 (2H, m), 2.26 (1H, s), 2.38-2.44 (1H, m), 2.57-2.67 (1H, m), 3.10 (1H, dd, *J* = 2.7, 13.7 Hz), 3.77 (3H, s), 3.80 (2H, m), 3.92 (1H, m), 4.54 (1H, d, *J* = 2.7 Hz), 6.78 (2H, d, *J* = 9.2 Hz), 6.88 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ –5.1, 17.9, 25.6, 27.0, 28.9, 30.9, 31.5, 34.1, 35.3, 51.8, 55.2, 59.4, 64.2, 68.0, 113.8, 128.7, 130.8, 158.7, 174.5, 210.0; IR (film) 2935, 2857, 1713, 1689, 1513, 1396, 1252, 1029 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{38}NO_4Si$ 444.2570 [$(M+H)^+$], found 444.2565.

8-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (23).

The solution of SmI_2 in THF was freshly prepared by addition of diiodomethane (6.08 mL, 75.7 mmol) to a suspension of Sm (13.6 g, 90.6 mmol) in THF (725 mL) and stirring at rt for 9 h. To the above solution of SmI_2 in THF, a degassed mixture of MeOH (6.12 mL, 151 mmol), HMPA (65.8 mL, 378 mmol) and THF (70 mL) was added. To the mixture, **20** (6.63 g, 15.1 mmol) in degassed THF (100 mL) was added dropwise at –78 °C and the reaction was left to stir overnight. Saturated aqueous sodium hydrogen bicarbonate was added at rt and the mixture was extracted with AcOEt. The combined organic layer was washed with brine then dried over $MgSO_4$. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=1:9-6:4) to afford **23** containing inseparable HMPA, which was used in the next reaction without further purification.

6,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (24).

To a stirred solution of the foregoing crude **23** (34.9 mmol as theoretical amount) in CH_2Cl_2 (174 mL) at rt was added 2,6-lutidine (12.2 mL, 105 mmol) followed by TBSOTf (14.9 mL, 69.6 mmol). After stirring at rt for 2.5 h, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=5:95-3:7) to afford **24** (16.6 g, 29.7 mmol, 85% for 2 steps) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$ δ 7.26, 400 MHz) δ -0.01-0.02 (12H, m), 0.86 (9H, s), 0.92 (9H, s), 1.55-1.95 (6H, m), 2.03 (1H, s), 2.25-2.43 (2H, m), 3,07-3.13 (1H, m), 3.63 (1H, m), 3.77 (1H, s), 3.78 (3H, s), 3.82-3.87 (1H, m), 4.04-4.09 (1H, m), 6.81 (2H, d, *J* = 9.2 Hz), 7.21 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ –5.0, –4.9, –4.7, –4.1, 18.0, 18.3, 25.7, 25.9, 27.2, 29.5, 31.1, 32.1, 33.7, 34.0, 45.3, 55.2, 58.5,

60.6, 67.5, 69.3, 113.5, 130.2, 132.6, 157.7, 176.1; IR (film) 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.

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 (29).

To a solution of diisopropylamine (1.20 mL, 8.56 mmol) in THF (10 mL) was added *n*-BuLi (1.59 M in hexane)(4.38 mL, 6.96 mmol) at –78 °C, the resulting solution was stirred at 0 °C for 20 min before it was cooled to –78 °C. To the solution was added a solution of **24** (321 mg, 0.573 mmol) in THF (1.5 mL) by dropwise. After stirring for 1 h at –78 °C, crashed dry-ice blocks were added until remaining 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 (7 times) and CH_2CH_2 (6 times). The combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure then resulting residue was washed with hexane and filtered over a pad of Celite. The filtrate was concentrated under reduced pressure to give crude product of **29**, which was used in the next reaction without further purification: MS (FAB) *m*/*z* 604 (M^++1), 582, 482, 450.

6,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-2,3-dione 2-oxime (31).

To a stirred solution of **29** in 5:1 Et_2O/H_2O (2.4 mL) at 0 °C was added $NaNO_2$ (400 mg, 5.8 mmol) followed by conc.HCl (0.25 mL, 3.00 mmol) cautiously in four portions for 3 h. After stirring at rt for 2.5 h, saturated aqueous ammonium chloride was added and stirred for an additional 1 h. The mixture was extracted with AcOEt and CH_2CH_2 (4 times). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure then resulting residue was purified by PTLC (AcOEt:hexane=3:2 x2) to afford **31** (12.6 mg, 21.4 μmol, 57% for 2 steps) as a pale orange solid: ^{1}H-NMR ($CDCl_3$ δ 7.26, 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); ^{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 (film) 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-Amino-6,8-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(4-methoxybenzyl)octahydro-3*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-3-one (28).

To a stirred solution of oxime **31** (526 mg, 0.893 mmol) in AcOH (20 mL) at rt was added activated zinc dust (2.30 g, 35.2 mmol) and NH_4Cl (ca.1.00 g, 18.7 mmol). 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, was added saturated aqueous sodium hydrogen bicarbonate and the mixture was extracted with CH_2CH_2. The combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=1:1–MeOH:CH_2Cl_2=1:9) to afford **28** (406 mg, 0.706 mmol, 79%) as a pale orange solid: ^{1}H-NMR ($CDCl_3$ δ 7.26, 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; IR (film) 2952, 2930, 2857, 1697, 1513, 1250, 1078, 1050 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{55}N_2O_4Si_2$ 575.3700 [$(M+H)^+$], found 575.3728.

Benzyl 8-{[*tert*-butyl(dimethyl)silyl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]methylcarbamate (32).

To a stirred solution of **28** (13.4 mg, 23.3 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added the mixture (0.2 mL) of HCO_2H (1.3 mL, 34 mmol) and Ac_2O (0.80 mL, 8.5 mmol) dropwise. After stirring at 0 °C for 10 min, the reaction mixture was warmed to rt and was added small amount of toluene. The solvent was removed under reduced pressure to give crude product of the above formamide, this unstable product was used in the next reaction without purification: ^{1}H-NMR ($CDCl_3$ δ 7.26, 400 MHz) δ –0.01-0.06 (12H, m), 0.85 (9H, s), 0.92 (9H, s), 1.57-2.10 (10H, m), 2.61 (1H, dd, *J* = 8.2, 12.8 Hz), 3.09 (1H, dd, *J* = 10.1, 17.4 Hz), 3.53 (1H, d, *J* = 2.7 Hz), 3.70 (1H, br), 3.79 (3H, s), 3.90-3.96 (2H, m), 4.36 (1H, q, *J* = 6.4 Hz), 6.39 (1H, br), 6.84 (2H, d, *J* = 8.2 Hz), 7.18 (2H, d, *J* = 9.2 Hz), 8.19 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ –4.9, –4.9, –4.8, –4.0, 18.0, 18.1, 25.7, 25.8, 25.9, 30.1, 32.2, 33.6, 41.4, 45.2, 50.8, 55.2, 58.6, 59.4, 67.1, 69.5, 113.8, 129.6, 131.9, 157.9, 161.7, 172.2; IR (film) 3286, 2952, 2931, 2857, 1677, 1541, 1250, 1078, 1051 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{55}N_2O_5Si_2$ 603.3644 [$(M+H)^+$], found 603.3618.

To a stirred solution of foregoing crude product of the above formamide (23.0 μmol as theoretical amount) in THF (2.0 mL) at 0 °C was added LAH (28.0 mg, 0.740 mmol). After stirring at 50 °C overnight, water (28 μL), 15% aqueous sodium hydroxide (28 μL), water (84 μL) and sufficient amount of Et_2O was added at rt successively. After stirring for 30 min, the mixture was filtered over a pad of Celite and the filtrate was concentrated under reduced pressure to give the crude methylamine, this polar product was used in the next reaction without purification.

To a stirred solution of the foregoing crude methylamine (23.0 μmol as theoretical amount) in 3:1 CH_2Cl_2/H_2O (2.4 mL) at rt was added Na_2CO_3 (25.0 mg, 236 μmol) followed by CbzCl (15.0 μL, 105 μmol). After stirring at rt for 1 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 then resulting residue was purified by PTLC (AcOEt:hexane=1:1 x2) to afford **32** (11.5 mg, 19.3 μmol, 84% for 3 steps) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$ δ 7.26, 400 MHz) δ –0.03-0.02 (6H, m), 0.85 (9H, s), 1.43-2.02 (8H, m), 2.71-2.75 (1H, m), 2.82 (3H, s), 3.23 (1H, br), 3.45 (2H, br), 3.71 (1H, s), 3.79 (3H, s), 4.82 (1H, br), 5.11 (2H, d, 2.7 Hz), 6.83 (2H, d, *J* = 9.2 Hz), 7.20 (2H, d, *J* = 9.2 Hz), 7.31-7.36 (5H, m); ^{13}C-NMR (CD_3CN δ 118.2, 100 MHz) δ –4.6, –4.5, 18.6, 23.3, 26.3, 29.3, 31.5, 31.8, 36.3, 44.4, 46.9, 51.3, 52.7, 55.7, 58.6, 59.6, 67.4, 68.6, 114.4, 128.5, 128.7, 129.4, 131.1, 132.7, 138.4, 156.8, 158.8; IR (film) 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 6,8-dihydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]methylcarbamate (33).

To a stirred solution of **32** (179 mg, 0.301 mmol) in MeCN (9 mL) at 0 °C was added 48% aqueous HF (2.0 mL). After stirring at 0 °C for 5 h, the reaction mixture was diluted with CH_2Cl_2 and was added saturated aqueous sodium hydrogen bicarbonate. The mixture was extracted with CH_2Cl_2 (3 times) and $CHCl_3$ (3 times), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=3:1–MeOH:CH_2Cl_2=1:9) to afford **33** (127 mg, 0.264 μmol, 88%) as a white foam: ^{1}H-NMR (CD_3CN δ 1.93, 400 MHz) δ 1.35-2.25 (9H, m), 2.55-2.59 (8H, m), 3.30 (1H, br), 3.49 (2H, br), 3.68 (1H, br), 3.73 (3H, s), 4.69 (1H, br), 5.04 (2H, s), 6.82 (2H, d, *J* = 8.2 Hz), 7.22 (2H, d, *J* = 9.2 Hz), 7.35 (5H, s); ^{13}C-NMR (CD_3CN δ 118.2, 100 MHz) δ 2.93, 29.7, 35.7, 44.5, 50.2, 51.9, 55.0, 58.3, 66.9, 67.1, 113.7, 127.6, 127.9, 128.3, 130.0, 130.2, 136.4, 156.3, 157.9; IR (film) 3406, 2935, 1684, 1512, 1454, 1334, 1248 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{37}N_2O_5$ 481.2697 [$(M+H)^+$], found 481.2694.

Benzyl 8-{[bis(benzyloxy)phosphoryl]oxy}-6-hydroxy-5-(4-methoxybenzyl)octahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-2-yl]methylcarbamate (34)

To a stirred solution of **33** (125 mg, 0.260 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 1-*H*-tetrazole (182 mg, 2.60 mmol). After stirring for 20 min at 0 °C, dibenzyl(*N,N*-diisopropyl)phosphoramidite (90%) was added portionwise (slowly) until no starting material was detectable by TLC analysis (ca.147 μL, 0.49 mmol). When the reaction was completed, the reaction mixture was cooled to –78 °C. To the solution was added TBHP (5 M in decane)(0.15 mL) and allowed to stir for 30 min at –78 °C before the addition of saturated aqueous Na_2SO_3. The mixture was extracted with CH_2CH_2 and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure then resulting residue was purified by silica gel chromatography (AcOEt:hexane=4:1–MeOH:CH_2Cl_2=2:8) to afford pure **34** (130 mg, 0.175 mmol, 68%) as a pale yellow oil: ^{1}H-NMR (CD_3OD δ 3.31, 400 MHz)

δ 1.25-1.55 (2H, m), 1.69 (2H, br), 1.75-2.18 (4H, m), 2.26 (1H, br), 2.72 (3H, s), 2.75-2.97 (3H, m), 3.28 (1H, br), 3.40 (1H, br), 3.66 (1H, br), 3.76 (3H, s), 4.32 (1H, br), 4.71 (1H, br), 4.96-5.05 (4H, m), 5.08 (2H, s), 6.84 (2H, d, *J* = 9.2 Hz), 7.21 (2H, d, *J* = 8.2 Hz), 7.34 (10H, s), 7.34 (5H, s); ^{13}C-NMR (CD_3OD δ 49.0, 100 MHz) 23.0, 29.2, 29.9, 31.1, 36.2, 44.0, 44.7, 51.8, 53.4, 55.7, 59.5, 67.8, 68.3, 70.8, 77.0, 114.8, 128.8, 129.1, 129.2 129.5, 129.7, 129.7, 131.2, 132.2, 137.2, 138.1, 157.9, 159.6; IR (film) 3408, 2935, 1695, 1512, 1454, 1248, 1009 cm^{-1}; HRMS (FAB) calcd for $C_{42}H_{50}N_2O_8P$ 741.3299 [$(M+H)^+$], found 741.3298.

FR901483 (1)

To a solution of **34** (54.2 mg, 73.1 μmol) in MeOH (5 mL) was added aqueous 1 N HCl (0.1 mL). The solvent was removed under reduced pressure giving HCl salt. Pd/C (10%, dry)(150 mg, 141 μmol) and MeOH (15 mL) were added, and the mixture was stirred at rt under 1 atom of hydrogen gas atmosphere for 5 h and filtered over a pad of Celite, which was washed with MeOH. The combined filtrate was concentrated under reduced pressure and then rinsed with MeCN to give FR901483 (**1**) (19.7 mg, 46.2 μmol, 63%) as a white solid: ^{1}H-NMR (CD_3OD δ 3.31, 400 MHz) δ 1.91 (1H, d, *J* = 13.7 Hz), 2.02-2.40 (6H, m), 2.45 (1H, br), 2.66 (1H, dd, *J* = 9.2, 13.7 Hz), 2.78 (3H, s), 3.11 (1H, dd, *J* = 3.2, 12.4 Hz), 3.64 (1H, br), 3.78 (3H, s), 3.85-3.97 (2H, m), 4.22-4.35 (2H, m), 4.49 (1H, dd, *J* = 9.6, 13.3 Hz), 6.90 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 9.2 Hz); ^{13}C-NMR (CD_3OD δ 49.0, 100 MHz) δ 22.4, 27.7, 28.2, 32.4, 34.0, 41.7, 42.8, 51.9, 55.0, 55.7, 62.0, 63.9, 68.8, 71.0, 115.3, 128.6, 131.7, 160.5; IR (film) 3336, 2933, 1612, 1514, 1458, 1248, 1180, 1009 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{32}N_2O_6P$ 427.1992 [$(M+H)^+$], found 427.1996.

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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 synthesis of this family compounds, see: H. Takayama, *J. Synth. Org. Chem. Jpn.*, 2002, **60**, 350.
3. For the 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. Weireb, *J. Org. Chem.*, 2006, **71**, 2046. (h) S. Kanden and H.-U. Lessig, *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, 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.

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) We are in the process of publishing the formal total synthesis of (-)-FR901483 using Ugi reaction, which was investigated independently of 3m.
5. For a review on enantioselective desymmetrization, see: M. C. Willis, *J. Chem. Soc., Perkin Trans. 1,* 1999, **13**, 1765.
6. D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
7. For a similar reaction, see ref 4d.
8. A synthetic protocol based on a $NaBH(OAc)_3$ reduction and selective deprotection of the TBS ether has already been reported in ref 4d. However, transformation of **5** to **18** has been developed independently in our laboratory, see ref 3a.
9. A similar enhancement of the mono-alkylation reaction by the addition of alkyl amine derivatives has been reported, see: M. Goto, K. Akimoto, K. Aoki, M. Shindo, and K. Koga, *Tetrahedron Lett.*, 1999, **40**, 8129.
10. 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.
11. The 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.
12. W. Oppolzer, O. Tamura, and J. Deerberg, *Helv. Chim. Acta,* 1992, **75**, 1965.
13. For a review of the phosphoramidite method, see: R. P. Iyer, *Tetrahedron,* 1992, **48**, 2223.
14. For a similar regioselective phosphorylation, see ref 4a.