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CONSICE SYNTHESIS OF TAN1251C

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Dedicated to Prof. Tohru Fukuyama on celebration of his 70th birthday

Abstract – An efficient total synthesis of TAN1251C was accomplished by employing Ugi four-component condensation reaction and Dieckmann condensation to construct the spiro-fused cyclohexanone and γ-lactam ring structure. Diastereoselective reduction by side-chain-controlled hydrogenation of enamide **37** or Zn reduction of oxime **48** enabled construction of the amino group with the desired stereochemistry.

INTRODUCTION

In 1991, researchers at the Takeda Pharmaceutical Company reported the isolation of the TAN1251 series of compounds (A–D) (Figure 1) from a culture of *Penicillium thomii* RA-89.[1] These compounds possess a unique tricyclic skeleton with 1,4-diazabicyclo[3.2.1]octane and spiro-fused cyclohexanone moieties, and are muscarinic antagonists with potential value as antispasmodic or antiulcer agents.[1] On the other hand, the immunosuppressant FR901483(**2**), isolated from the fermentation broth of *Cladobotryum* sp. No 11231 by a Fujisawa group in 1996,[2] is also biosynthetically related to this series. The biosynthesis of these natural products could proceed from modified tyrosine dimer **3** via oxidative addition to construct the spiro ring, together with two types of cyclization (Scheme 1). Intramolecular aldol reaction of **6** would provide the 5-azatricyclo[6.3.1.$0^{1,5}$]dodecane core leading to FR901483(**2**). On the other hand, dienamine formation from the secondary amine to the aldehyde of **5** would provide the 1,4-diazabicyclo[3.2.1]octane core leading to **1a-d**. Considering the unique structures and potent biological activities of these

compounds, they have attracted considerable interest, and several total syntheses have been reported.[3,4] During the course of our synthetic studies on natural products with a nitrogen atom on tetrasubstituted carbon,[5] we accomplished a total synthesis of FR901483 (**2**)[6] using an Ugi four-component condensation (4CC) reaction.[7] Inspired by this success, we expected that an efficient and flexible synthesis of **1c** could be accomplished by means of similar methodology.

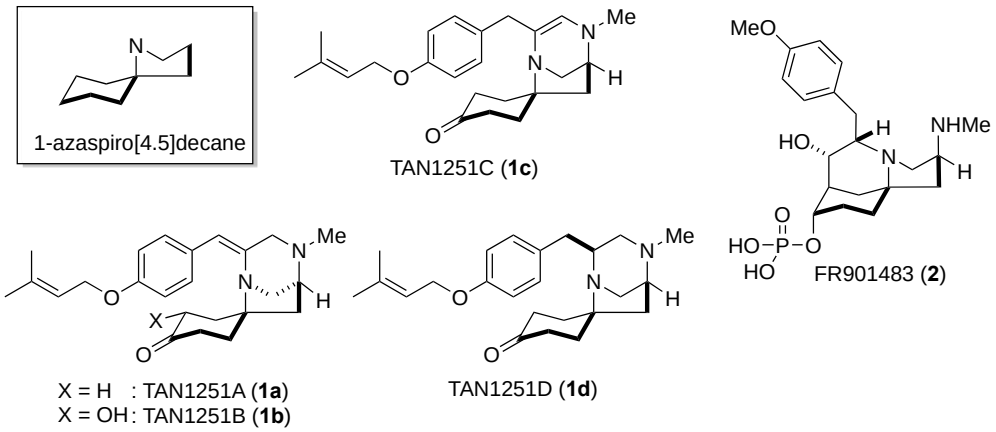
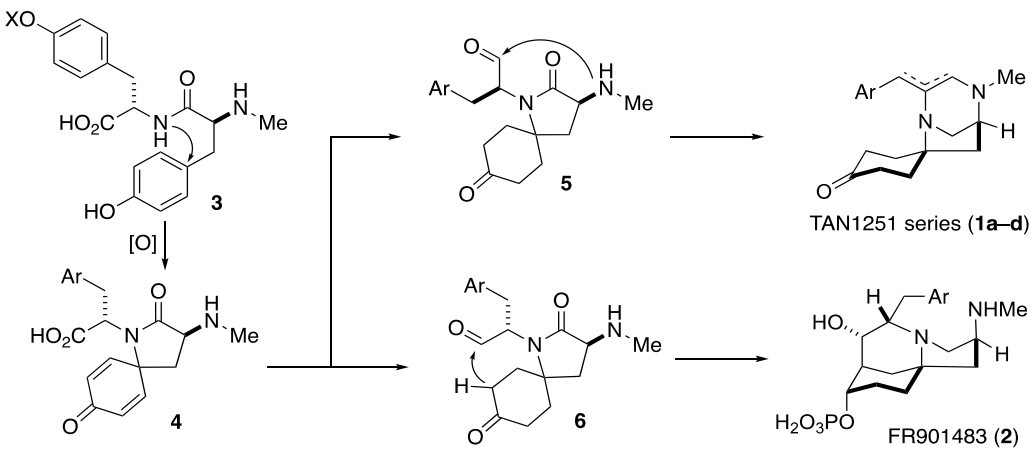


Figure 1

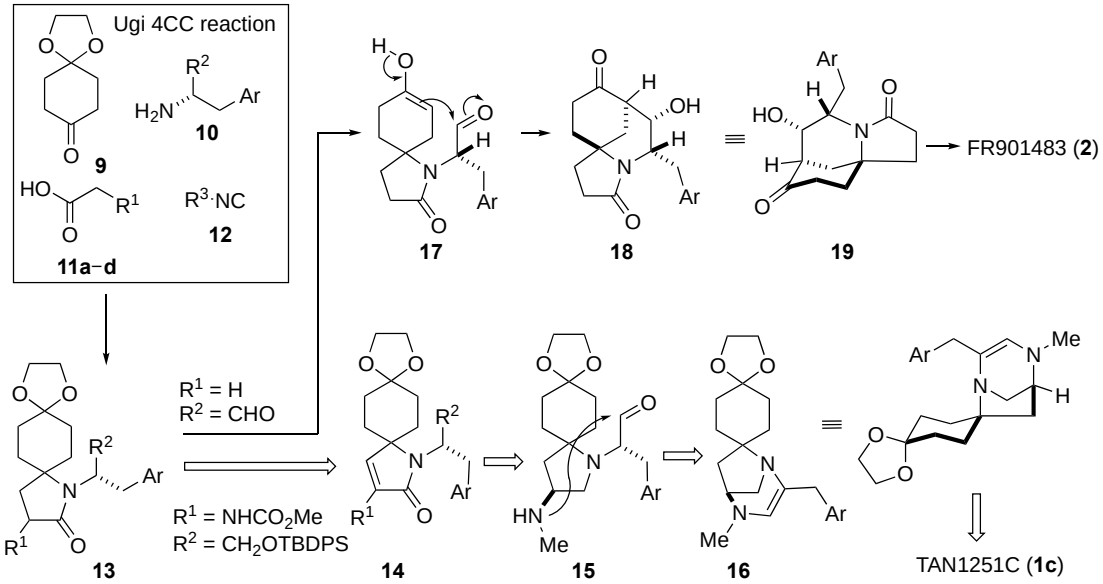


Scheme 1

RESULTS AND DISCUSSION

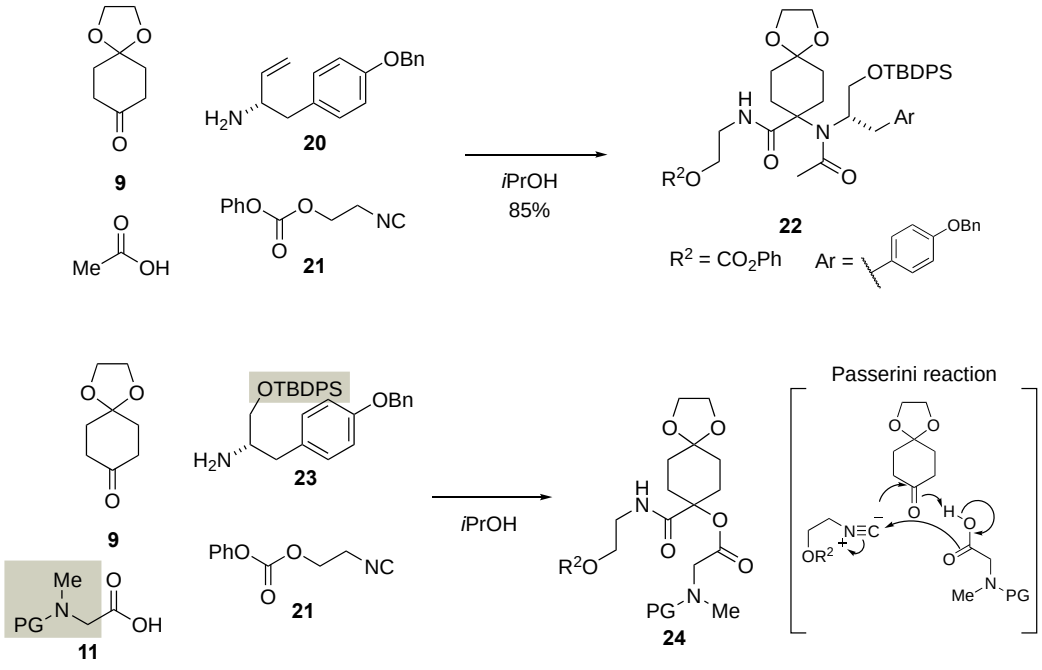
The heart of our synthetic strategy for **1c** is illustrated in Scheme 2. The tricyclic skeleton of **1c** would be constructed by intramolecular dienamine formation of *N*-methylamino aldehyde **15** based on the biosynthetic hypothesis in Scheme 1. Although the combination of Ugi 4CC reaction[6] and Dieckmann condensation allowed for facile construction of the spirolactam in the total synthesis of **2**, the late-stage incorporation of the monomethylamine unit onto the spirolactam ring required a tedious five-step sequence. We envisioned that the Ugi 4CC reaction with glycine derivatives **11b-d** (R^1 = $NHCO_2R$) instead of acetic acid (**11a**, R^1 = H) would enable easy incorporation of the amine group into the Ugi

adduct, enabling introduction of all of the atoms required for the ring system of **1c** in a single step. Furthermore, the use of our odorless isonitrile **12**[8] would be favorable in the Dieckmann condensation.



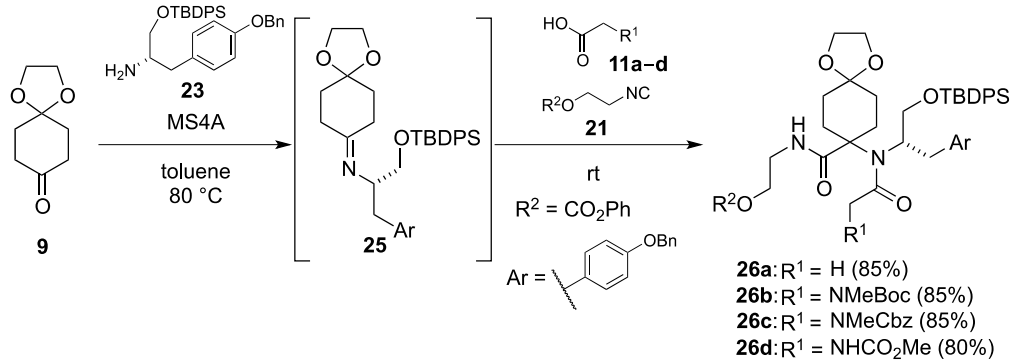
Scheme 2

The Ugi 4CC reaction of ketone **9**, amine **23**, carboxylic acids **11** and isonitrile **21** was investigated, as shown in Scheme 3. In our previous investigation, the Ugi 4CC reaction with a less bulky (2-aryl-1-vinyl)ethylamine component **22**[6a] proceeded smoothly upon simple mixing of the four components in isopropanol. In the case of the bulker amine component **23**, the undesired Passerini reaction occurred predominantly.



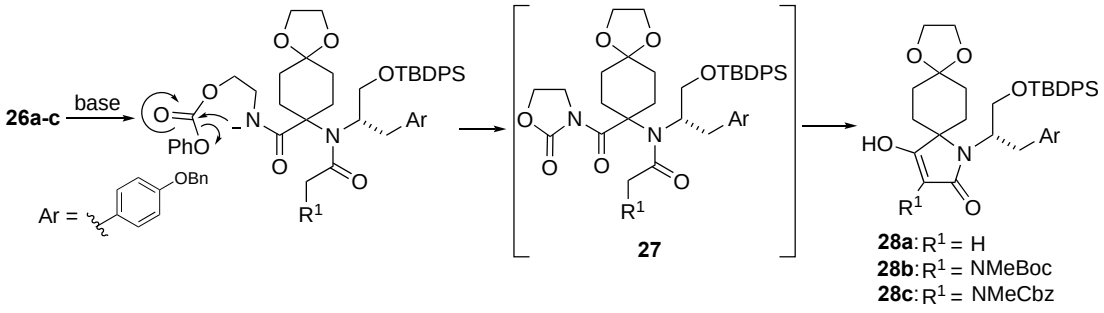
Scheme 3

Since the reactivity of the bulky amine was not sufficient for imine formation, the reaction was examined under anhydrous conditions (Scheme 4). After treatment of ketone **9** with amine **23** in the presence of 4 Å molecular sieves (MS 4A) to form the imine intermediate, subsequent addition of carboxylic acids **11** and isonitrile **21** furnished the desired Ugi products **26a-d** in high yields.

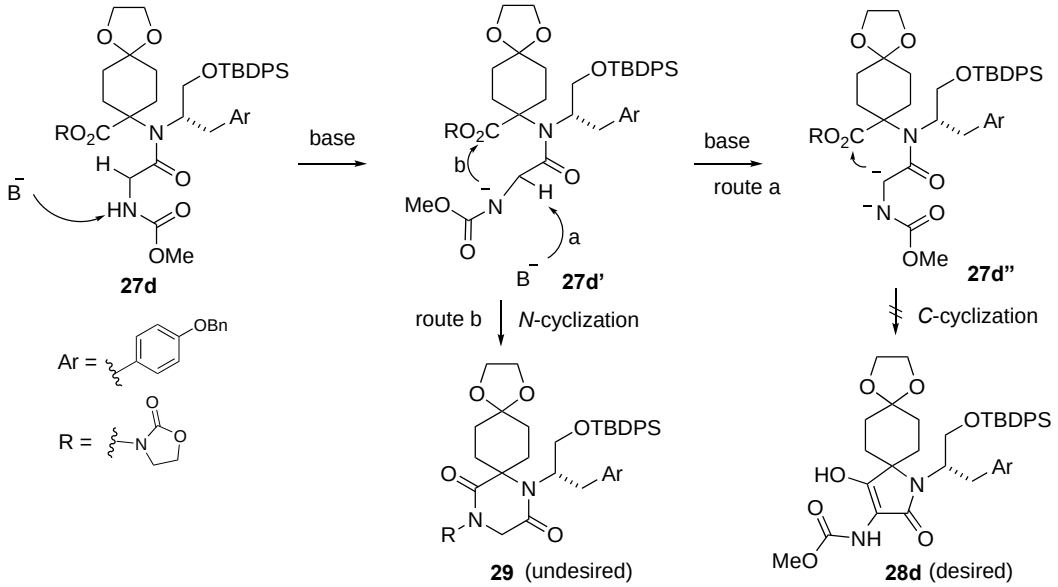


Scheme 4

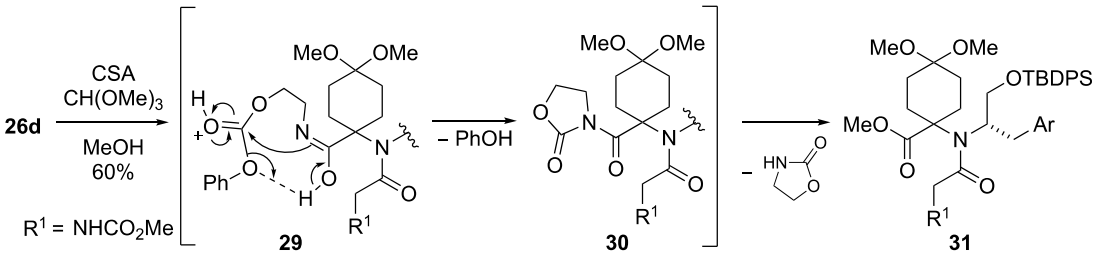
In anticipation of the direct formation of the *N*-methyl group from the *N*-carbamate, the synthetic investigation proceeded from **26d**. The Ugi adducts **26a-c** derived from our isonitrile **21** were easily converted to an oxazolidinone ring compound under basic conditions (Scheme 5); however, **26d** was converted into the undesired diketopiperazine **29** (Scheme 6, route b). In order to construct the spirolactam ring, construction of the oxazolidinone ring and formation of the dianion are required (route a). In this case, the second deprotonation was not fast enough for *C*-cyclization, because the base was utilized for the formation of the oxazolidinone ring. Additionally, nucleophilic attack at the neopentyl imide carbonyl group proved difficult. Thus, methanolysis of the secondary amide bond through the imide intermediate **30** and concomitant conversion to the dimethyl acetal were carried out under acidic conditions to provide the corresponding methyl ester **31** in 60% yield (Scheme 7).



Scheme 5



Scheme 6

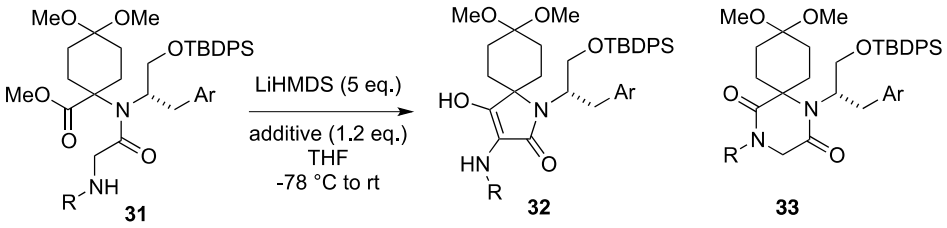


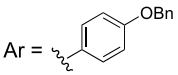
Scheme 7

Next, construction of the spirolactam ring was performed by means of Dieckmann condensation reaction (Table 1). When KHMDS or *sec*-BuLi was used as a base for the cyclization reaction of **31**, only the by-product **33** was observed. Upon treatment of methyl ester **31** with five equivalents of LiHMDS, the desired *C*-cyclization proceeded predominantly to give β-keto lactam **32**. Although several additives were examined, generation of the by-product could not be suppressed. Fortunately, the desired β-keto lactam **32** could be obtained in a large amount, since the separation of **32** and **33** was straightforward.

Selective reduction of the ketone in **32** (keto-form) followed by mesylation and β-elimination afforded the desired α,β-unsaturated lactam **34** (Scheme 8). Subsequently, dimethyl acetal **34** was converted to the more stable ethylene ketal **36** after hydrolysis according to Noyori's protocol.[9] Removal of the TBDPS group of **36** by treatment with TBAF gave the primary alcohol **37**.

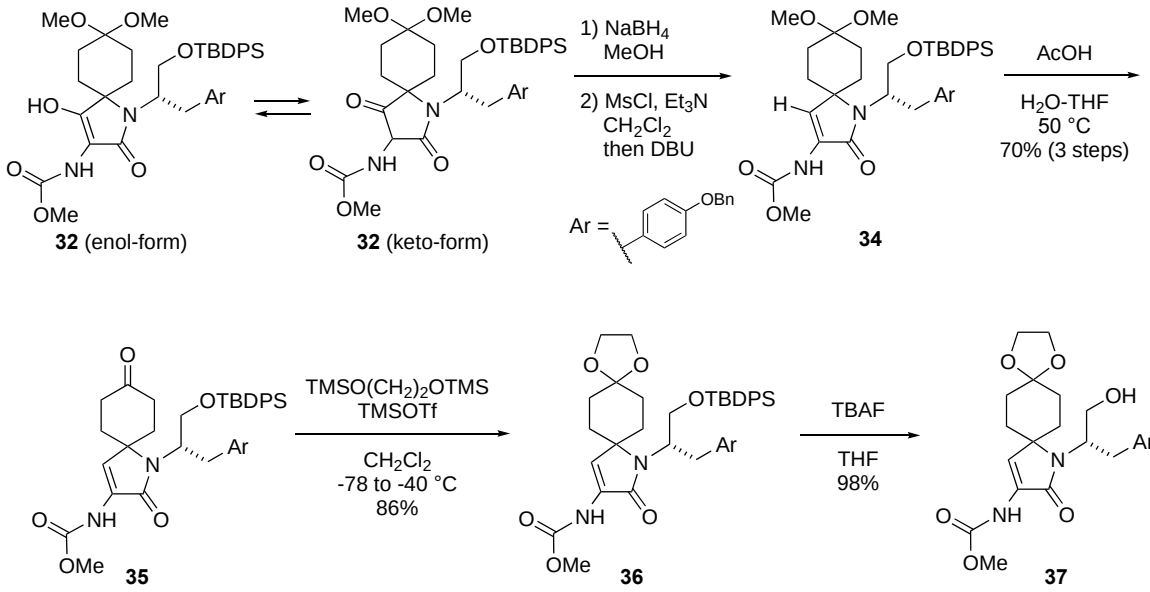
Table 1. Construction of the spirolactam ring



Ar =  R = CO_2Me

entry	Additive	yield (%) 32	yield (%) 33	selectivity[a] (32 : 33)
1	-	60	20	3:1
2	$ZnCl_2$	46	46	1:1
3	$MgBr_2 \cdot OEt_2$	32	16	2:1
4	TMSCl	53	14	3:1
5	TMS·imidazole	44	22	2:1

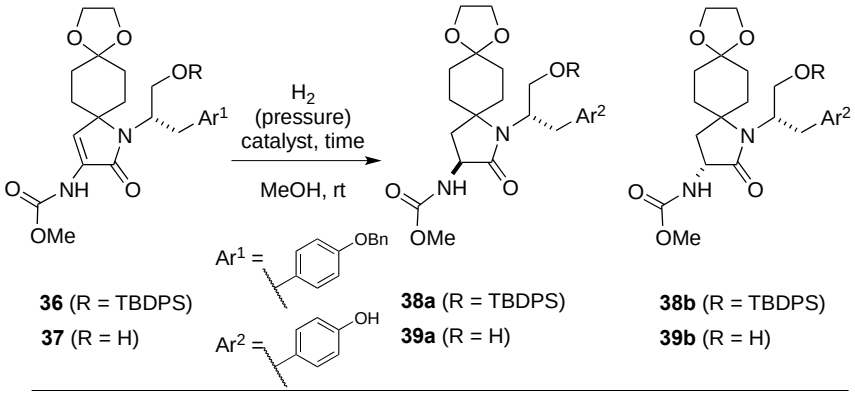
[a]The ratio was determined by ^{1}H-NMR analysis of the crude product.



Scheme 8

Next, we investigated the stereoselective reduction of the double bonds of **36** and **37**. While reduction of the TBDPS ether **36** required a high-pressure condition (Table 2, entry 1), reduction of the primary alcohol **37** proceeded under atmospheric pressure (entries 2–5). Since the selectivity was not satisfactory, several catalysts were tested (entries 3–5). Among them, the best result was obtained with PtO_2 (entry 4). Although hydrogenation of **37** with Pt/C gave a 1:1 mixture of the diastereomers, the treatment of **37** with PtO_2 provided the desired lactam **39a** selectively as a 4 : 1 mixture.

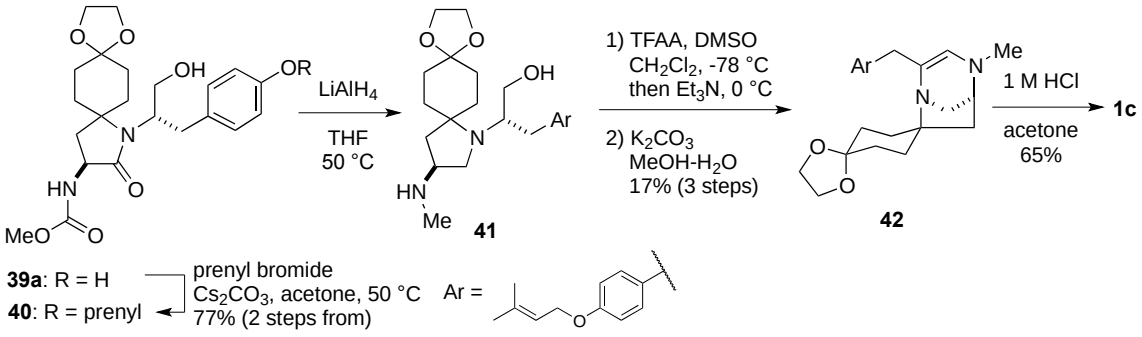
Table 2. Diastereoselective reduction of enamides **36** and **37**



entry	enamide	pressure	catalyst	time (h)	yield (%)	selectivity[a] (**a** : **b**)
1	**36**	500 psi	Pd/C	4.5	89	1:1
2	**37**	1 atm	Pd/C	8	83	1:1
3	**37**	1 atm	$Pd(OH)_2$	24	67	1:1
4	**37**	1 atm	PtO_2	96	80	4:1
5	**37**	1 atm	Pt/C	24	66	1:1

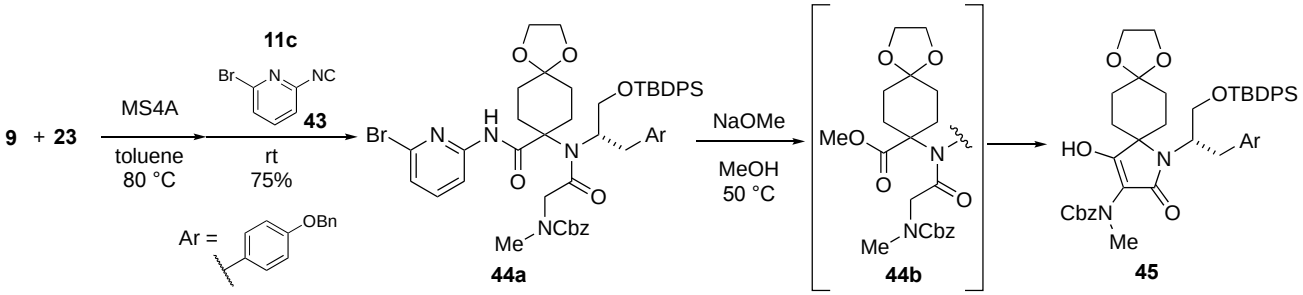
[a]The selectivity was determined by ^{1}H-NMR analysis.

After the prenylation of the phenolic hydroxy group of **39**, reduction of carbamate and amide with $LiAlH_4$ afforded the desired *N*-methylamine **41** as an inseparable diastereomeric mixture (Scheme 9). Upon treatment of **41** with trifluoroacetic anhydride, dimethyl sulfoxide and triethylamine, trifluoroacetamide formation and oxidation of the primary alcohol occurred to give the aldehyde intermediate smoothly. After the hydrolysis of trifluoroacetamide, the construction of 1,4-diazabicyclo[3.2.1]octane proceeded to afford protected TAN1251C **42**. Finally, treatment of **42** with 1 M HCl in acetone completed the total synthesis of TAN1251C in 14 steps. However, isolation of the desired diastereomer **39a** from the mixture of diastereomers was difficult. Thus, although the number of reaction steps had been successfully reduced, we tried to develop a modified synthesis. Considering the excellent results in our synthesis of FR901483 (**2**),[6] we thought that Zn reduction of the oxime would be suitable for incorporation of the amino functionality, utilizing the ene carbamate unit within **36** and **37**.



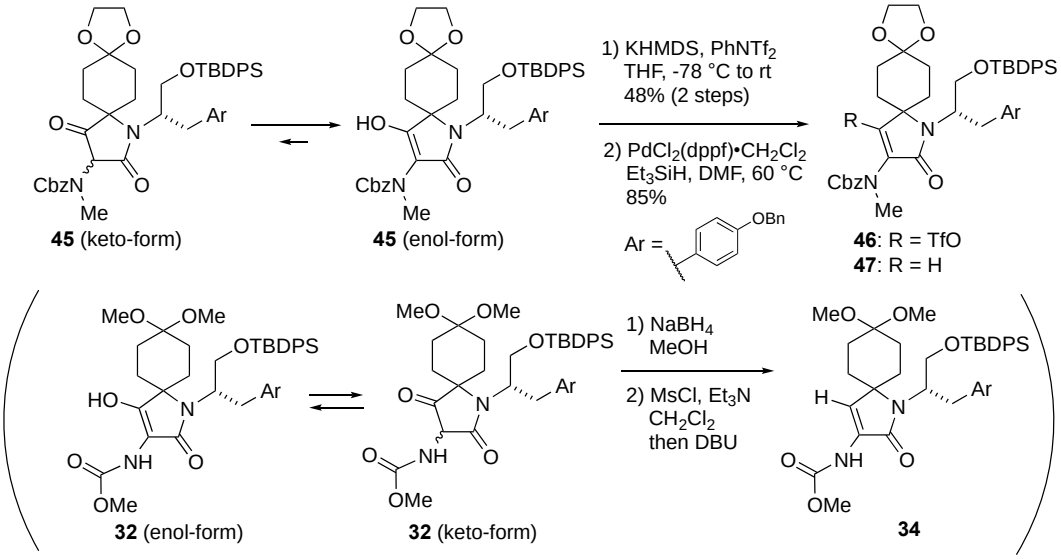
Scheme 9

As shown in Scheme 10, the Ugi 4CC reaction was carried out using the combination of ketone **9**, amine **23**, acid **11c** and isonitrile **43**[101] to provide **44a** (isonitriles can be used in the Ugi reaction[10]). As expected, methanolysis of the bromopyridine amide of **44a** proceeded smoothly to afford **45** through subsequent Dieckmann condensation via the corresponding methyl ester **44b**.



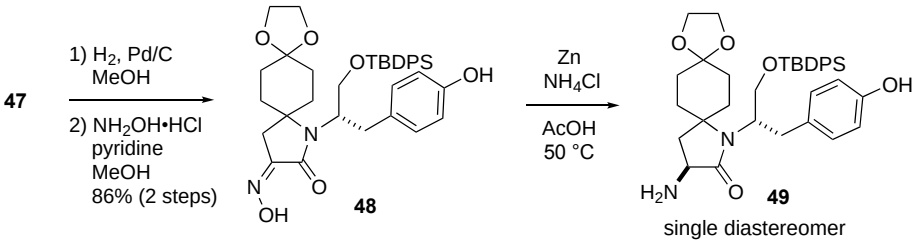
Scheme 10

However, reduction of the enol moiety of **45** was difficult, in contrast to **32**. Thus, we decided to convert **45** to the corresponding enol triflate **46** (Scheme 11). Upon treatment of **45** with excess KHMDS and sequential addition of triflic imidate, the desired enol triflate **46** was obtained. Next, reductive removal of the triflate group was achieved by treatment with Et_3SiH in the presence of $PdCl_2$(dppf) to afford **47** in good yield.



Scheme 11

After removal of the Cbz group of **47**, treatment with excess hydroxylamine gave the desired oxime **48** (Scheme 12). Reduction of **48** with Zn in acetic acid in the presence of NH_4Cl proceeded smoothly to give **49** as a single diastereomer.



Scheme 12

In order to clarify the stereoselectivity observed in this reaction, we calculated the most stable conformers of **50** and **48** by the use of a previously reported shell script.[11] Briefly, 300 energy-minimized 3-dimensional structures of the compounds were generated from the 2-dimensional chemical structures by Open Babel and Balloon.[12,13] The single-point energy of each conformer was calculated with the PM7 Hamiltonian by MOPAC2012.[14] Several low-energy conformers were geometrically optimized at the B3LYP/6-31G* level of theory in the gas phase by Gaussian 09.[15] After detailed conformational analysis, the most stable forms of **50** and **48** were simulated as shown in Figure 2. Since deprotection of benzyl ether proceeded before hydrogenolysis of the enamide group of **37**, optimization was carried out with **50**. Presumably due to the sp^2-nature of the amide carbonyl group or steric hindrance of the spiro-skeleton, the side chain of the lactam ring of **50** and **48** was fixed in the same conformation in both the presence and absence of the bulky TBDPS group. As shown in Figure 3, the aromatic ring was oriented at the β-face and the hydroxy group, as well as the TBDPS ether, was fixed at the α-side of the lactam ring. This orientation should play a key role in the selective reduction. Our hypothesis to explain the induction of the stereochemistry is illustrated in Figure 3. Hydrogenation of **50** would proceed through coordination of Pt catalyst with the primary alcohol, such as **51**. On the other hand, Zn-reduction of **48** proceeded through the chelating intermediate **52** generated after reduction of the oxime double bond. Since the Zn atom of **52** would be located at the less hindered β-side of the spiro-lactam, sequential protonation occurred from the α-side to provide **52** with the desired stereochemistry. The interesting induction of this stereochemistry might arise from the constrained conformation of the side chain of the rigid spiro-skeleton.

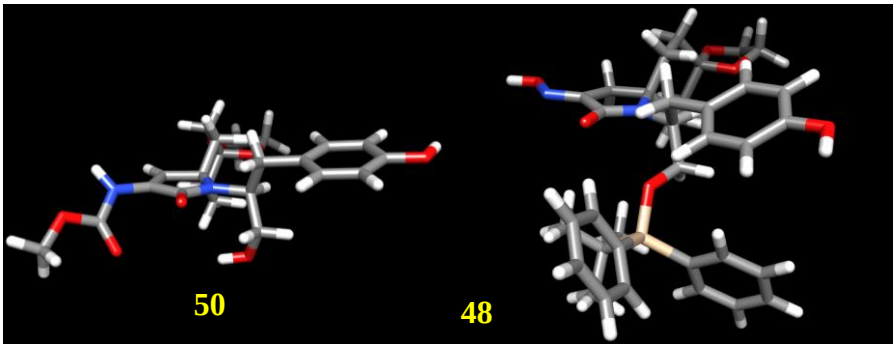


Figure 2

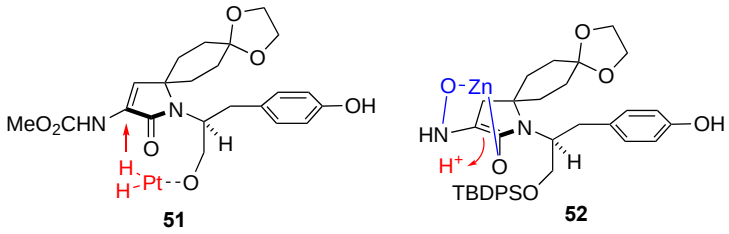
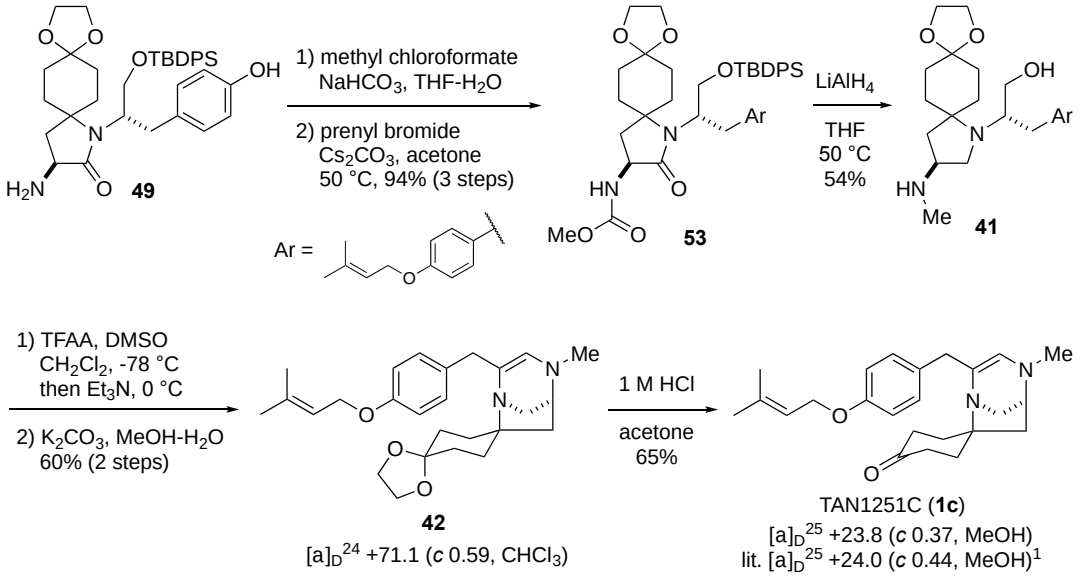


Figure 3

Finally, dienamine formation was performed according to Snider's method,[4a] as shown in Scheme 13. After incorporation of a methoxycarbonyl group and prenyl ether into **49**, treatment with $LiAlH_4$ allowed simultaneous reduction of the lactam and methyl carbamate, and concomitant deprotection of the TBDPS ether provided **41**. Swern oxidation of **41** with excess trifluoroacetic anhydride provided the desired aldehyde without *N*-oxidation. After the construction of the 1,4-diazabicyclo[3.2.1]octane, removal of the ketal group by treatment with 1 M HCl afforded TAN1251C (**1c**).[16] The spectroscopic data for synthetic **1c** were in good agreement with those of the natural product.



Scheme 13

In conclusion, we have accomplished a stereoselective total synthesis of TAN1251C (**1c**) from ketone **9** in 13 steps with 5.2% overall yield. Our synthesis features Ugi 4CC reaction and diastereoselective incorporation of the amine functionality by Zn-mediated reduction of oxime. Considering the applicability of the Ugi 4CC reaction for obtaining various amine and carboxylic acid derivatives, this protocol should provide ready access to a variety of spiro-compounds. Further investigations are underway in our laboratory.

EXPERIMENTAL

Optical rotations were measured on a JASCO P-1030 polarimeter in 10 cm cells at 25 °C.

Nuclear magnetic resonance [^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)] spectra were determined on JEOL ECA-500 and JEOL α-500 instrument. Chemical shifts for ^{1}H NMR were reported in parts per million downfields from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the centerline of a triplet at 77.0 ppm for deuteriochloroform.

High-resolution mass spectra (HRMS) were obtained on a BRUKER DALTONICS micrOTOF (ESI).

Infrared (IR) spectra were recorded on a SHIMADZU IRPrestige-21.

Optical rotations were measured on a JASCO P-1030 Polarimeter at rt using the sodium D line.

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 7 x 20 cm plates prepared with a 0.50 mm layer of Merck silica gel 60 F254. Compounds were eluted from the adsorbent with 10% MeOH in $CHCl_3$. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical) 40–50 μm, Silica Gel 60 (spherical) 63–210 μm, Silica Gel 60 N (spherical, neutral) 63–210 μm or Silica Gel 60 (spherical, NH) 40–50 μm. Reagents and solvents were commercial grades and were used as supplied with following exceptions: CH_2Cl_2, Et_2O, *n*-hexane, THF, toluene: dried over molecular sieves 4A: MeOH, EtOH, MeCN: dried over molecular sieves 3A. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Ugi Product 26d. To a solution of amine **23** (16.8 g, 33.9 mmol, 1.01 eq.) in toluene (285 mL) were added 1,4-cyclohexanedione monoethylene ketal (**9**) (5.25 g, 33.6 mmol, 1.00 eq.) and MS 4A (16.8 g). The solution was stirred at 80 °C for 3 h. Then the solution was cooled to room temperature and carboxylic acid **11d** (4.47 g, 33.6 mmol, 1.00 eq.) and isonitrile **21** (6.43 g, 33.6 mmol, 1.00 eq.) were added. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. Then the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1) to afford pure **26d** (28.1 g, 80%) as a white amorphous solid. $[\alpha]_D^{27}$ –2.49 (*c* 1.00, $CHCl_3$); IR (film) 3393, 2955, 1763, 1724, 1678, 1656, 1510, 1240, 1215, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 1.03 (s, 2.5H), 1.07 (s, 6.5H), 1.50–1.62 (m, 4H), 1.89–2.11 (m, 3H), 2.25 (d, *J* = 14.7, 1H), 2.80–2.98 (m, 2H), 3.16–3.37 (m, 2H), 3.58 (s, 1H), 3.61 (s, 2H), 3.76–4.31 (m, 12H), 5.03–5.09 (m, 2H), 5.44 (s, 0.3H), 5.69 (s, 0.2H), 6.10 (s, 0.5H), 6.87–6.97 (m, 1H), 6.94 (d, *J* = 8.5, 1H), 7.06 (d, *J* = 8.5, 1H), 7.14–7.24 (m, 3H), 7.29–7.44 (m, 14H), 7.44–7.54 (d, *J* = 7.37, 0.5H), 7.60–7.63 (m, 3.5H); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.0, 19.1, 19.2, 27.0, 27.1, 31.6, 31.8, 38.2, 38.5, 44.5, 45.0, 52.1, 52.2, 64.0, 64.1, 64.4,

64.5, 65.4 (2C), 66.6, 67.0, 67.1, 70.0, 107.5, 108.0, 115.4, 115.5, 120.9, 121.0, 126.0, 127.4, 127.9, 128.0 (2C), 128.6, 129.4 (2C), 125.9, 129.6 (2C), 130.0 (2C), 130.2, 132.6, 132.9, 135.3, 135.4 (2C), 136.8, 151.1, 153.3, 157.7, 174.5; HRMS-ESI: calcd for $C_{54}H_{63}N_3O_{11}SiNa$ 980.4124 $(M+Na)^+$; found 980.4093.

Methyl Ester 31. To a solution of **26d** (15.0 g, 15.7 mmol, 1.00 eq.) in MeOH (104 mL) and trimethyl orthoformate (104 mL) was added CSA (10.9 g, 47.0 mmol, 3.00 eq.) at room temperature. After stirring for 13 h, the reaction mixture was added Et_3N and concentrated under reduced pressure. Then the residue was diluted with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Then the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 7:3 to 3:7) to afford pure **31** (7.60 g, 60%) as a white amorphous solid. $[\alpha]_D^{22}$ –0.64 (*c* 1.00, $CHCl_3$). IR (film) 2953, 1730, 1648, 1512, 1241, 1218, 1107, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.99 (s, 4.5H), 1.05 (s, 4.5H), 1.17–1.23 (td, *J* = 13.8, 2.86, 0.5H), 1.62–1.80 (m, 2.5H), 1.90–2.06 (m, 3H), 2.17–2.22(m, 1H), 2.51–2.54 (m, 0.5H), 2.83 (dd, *J* =13.8, 8.59, 0.5H), 2.99–3.20 (m, 7H), 3.58–4.17 (m, 11H), 5.04 (s, 1.5H), 5.05 (s, 0.5H), 5.49 (s, 0.4H), 5.60 (s, 0.6H), 6.84–6.90 (m, 2H), 6.97–7.06 (m, 2H), 7.26–7.28 (m, 1H), 7.25–7.48 (m, 11H), 7.58–7.64 (m, 3H); ^1H NMR (Pyridine-d_5, mixture of rotamers) δ 1.07 (s, 4H), 1.14 (s, 5H), 1.51 (td, *J* = 13.17, 4.01, 0.5H), 1.79–2.15 (m, 5H), 2.24–2.41 (m, 2.5H), 2.92–2.95 (m, 0.5H), 3.06–3.17 (m, 6H), 3.28–3.31 (m, 0.5H), 3.52–3.42 (m, 1H), 3.56–3.61 (m, 6H), 4.09–4.12 (m, 0.5H), 4.44–4.21 (m, 3H), 4.61–4.50 (m, 1.5H), 4.96 (brs, 1H), 5.10 (s, 2H), 7.04 (d, *J* = 8.59, 1H), 7.11 (d, *J* = 8.59, 1H), 7.52–7.26 (m, 12H), 7.71 (d, *J* = 6.87, 1H), 7.81–7.83 (m, 1H), 7.85–7.89 (m, 2H), 8.08–8.09 (m, 0.5H), 8.44 (t, *J* = 5.44, 0.5H); ^{13}C NMR ($CDCl_3$, mixture of rotamer) δ 19.0, 19.1, 26.7, 26.8, 27.9, 28.7, 28.8, 29.2, 29.5, 37.5, 38.4, 43.8, 45.1, 47.3 (2C), 47.8, 47.9, 51.9, 52.0, 52.1, 52.2, 63.2, 65.2, 66.2, 70.0, 98.6, 98.9, 115.1, 115.3, 127.4, 127.8, 127.9, 128.6 (2C), 129.7, 129.8, 130.0, 130.9 (2C), 132.7, 135.2, 135.5 (2C), 135.6, 137.0, 156.5, 156.8, 157.6, 169.6, 173.4, 173.6; HRMS-ESI: calcd for $C_{46}H_{58}N_2O_9SiNa$ 833.3803 $(M+Na)^+$; found 833.3791.

Spiro Lactam 32. To a solution of **31** (6.31 g, 7.78 mmol, 1.00 eq.) in THF (77.8 mL) was added LiHMDS (1.00 M in THF) (38.9 mL, 38.9 mmol, 5.00 eq.) at -78 °C under an argon atmosphere, and the reaction mixture was warmed up to room temperature. After stirring for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 4:1 to 7:3) to afford pure **32** (3.39 g, 56%) as a white amorphous solid. $[\alpha]_D^{26}$ –56.6 (*c* 1.00, $CHCl_3$); IR (film) 2951, 1654, 1510, 1439, 1427, 1352, 1273, 1116, 1057 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.48 (d, *J* = 13.6, 1H), 1.07 (s, 9H), 1.14 (dt, *J* = 13.6, 4.53, 1H), 1.30 (d, *J* = 13.6, 1H), 1.60 (d, *J* =

12.5, 1H), 1.77–1.83 (m, 2H), 1.91 (dt, *J* = 13.6, 4.53, 1H), 1.97–2.02 (m, 1H), 3.07 (s, 3H), 3.11 (dd, *J* = 12.5, 4.0, 1H), 3.17 (s, 3H), 3.26–3.37 (m, 2H), 3.76 (s, 3H), 3.87–3.90 (m, 1H), 4.04–4.07 (m, 1H), 5.03–5.07 (m, 2H), 6.73 (br s, 1H), 6.84 (d, *J* = 8.50, 2H), 7.02 (d, *J* = 8.50, 2H), 7.30–7.43 (m, 11H), 7.63–7.64 (m, 4H), 10.5 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.9, 27.7, 27.8, 27.9, 29.6, 34.2, 47.3, 47.8, 53.5, 57.6, 61.3, 64.3, 69.9, 98.7, 100.9, 114.8, 127.3, 127.7, 127.8, 128.5, 129.6, 130.5, 131.9, 133.3, 133.4, 135.5, 137.1, 156.6, 157.2, 157.4, 165.6; HRMS-ESI: calcd for $C_{45}H_{54}N_2O_7SiNa$ 801.3542 $(M+Na)^+$; found 801.3546.

Ketone 35. To a solution of **32** (3.25 g, 4.18 mmol) in MeOH (20.9 mL) was added $NaBH_4$ (474 mg, 12.6 mmol, 3.00 eq.) at 0 °C and stirred for 1 h at the same temperature. Then the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was used in the next reaction without further purification. To the solution of crude material (4.18 mmol) in CH_2Cl_2 (20.9 mL) were added Et_3N (1.64 mL, 11.7 mmol, 2.8 eq.) and methanesulfonyl chloride (776 μL, 10.0 mmol, 2.4 eq.) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 3.5 h. Then the reaction mixture was added DBU (3.12 mL, 20.9 mmol, 5.0 eq.). After stirring for 4.5 h, the reaction mixture was diluted with EtOAc, acidified with 1 M HCl and the aqueous layer was extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product **34**, which was used in the next reaction without further purification. The solution of crude material including **34** (4.18 mmol) was dissolved in AcOH (7.00 mL), THF (7.00 mL) and water (7.00 mL) and stirred at 50 °C for 20.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then, the resulting residue was diluted with $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (*n*-hexane:EtOAc = 4:1 to 2:1) to afford pure **35** (2.11 g, 70%, 3 steps) as a white amorphous solid. $[\alpha]_D^{27}$ –68.1 (*c* 1.00, $CHCl_3$); IR (film) 1736, 1719, 1678, 1545, 1510, 1425, 1337, 1223, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.29–0.33 (m, 1H), 1.07 (s, 9H), 1.17–1.25 (m, 2H), 1.43 (td, *J* = 13.6, 4.53, 1H), 2.06 (dt, *J* = 15.3, 2.27, 1H), 2.14 (dt, *J* = 15.3, 2.27, 1H), 2.25 (td, *J* = 14.7, 6.24, 1H), 2.34 (td, *J* = 14.7, 6.24, 1H), 3.12–3.19 (m, 2H), 3.45–3.50 (dd, *J* = 14.7, 11.9, 1H), 3.74–3.76 (m, 1H), 3.78 (s, 3H), 4.19 (dd, *J* = 10.8, 8.50, 1H), 5.02 (s, 2H), 6.82 (d, *J* = 8.50, 2H), 6.98 (d, *J* = 8.50, 2H), 7.02 (br s, 1H), 7.07 (br s, 1H), 7.30–7.46 (m, 11H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.9, 31.6, 32.9, 33.4, 38.6, 38.7, 52.7, 58.2, 63.7, 63.9, 69.9, 114.9, 118.8, 127.3, 127.8, 127.9, 128.5, 129.9, 130.1, 130.4, 130.8, 131.4, 132.8, 133.3, 135.5, 135.7, 136.9, 153.9, 157.3, 165.0, 208.3; HRMS-ESI: calcd for $C_{43}H_{48}N_2O_6SiNa$ 739.3174 $(M+Na)^+$; found 739.3176.

Ketal 36. To a solution of the ketone **35** (1.30 g, 1.81 mmol, 1.00 eq.) in 13.5 mL of CH_2Cl_2 at -78 °C was added 1,2-bis(trimethylsilyloxy)ethane (490 μL, 1.99 mmol, 1.10 eq.) followed by trimethylsilyl trifluoromethanesulfonate (64.0 μL, 0.36 mmol, 0.20 eq.). The reaction mixture was warmed up to -40 °C and stirred for 15.5 h. The mixture was quenched with a solution of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1 to EtOAc:MeOH = 10:1) to afford pure **36** (1.19 g, 86%) as a white amorphous solid. $[\alpha]_D^{26}$ –50.9 (*c* 1.00, $CHCl_3$); IR (film) 1676, 1545, 1510, 1427, 1222, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14–0.17 (m, 1H), 1.04–1.07 (m, 1H), 1.07(s, 9H), 1.36 (td, *J* = 13.6, 3.97, 1H), 1.47 (d, *J* = 10.8, 1H), 1.54–1.67 (m, 3H), 1.83 (td, *J* = 13.0, 5.10, 1H), 3.15 (dd, *J* = 10.2, 18.1, 1H), 3.40–3.46 (m, 2H), 3.76 (s, 3H), 3.85–3.94 (m, 5H), 4.11 (dd, *J* = 10.2, 6.80, 1H), 5.01 (d, *J* = 12.5, 1H), 5.03 (d, *J* = 12.5, 1H), 6.82 (d, *J* = 8.50, 2H), 6.95 (br s, 1H), 7.02 (d, *J* = 8.50, 2H), 7.04 (br s, 1H), 7.29–7.44 (m, 11H), 7.64–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 165.2, 157.2, 153.9, 137.1, 135.6, 135.5, 133.4, 133.2, 131.6, 130.6, 129.8, 129.7, 129.6, 128.5, 127.8, 127.7 (2C), 127.4, 120.3, 114.8, 107.3, 69.9, 64.9, 64.4, 64.3, 63.8, 57.8, 52.6, 33.5, 32.6 (2C), 31.9, 29.9, 26.9, 19.2; HRMS-ESI: calcd for $C_{45}H_{52}N_2O_7SiNa$ 783.3466 $(M+Na)^+$; found 783.3457.

Alcohol 37. To a solution of the ketal **36** (500 mg, 0.65 mmol, 1.00 eq.) in THF (13 mL) was added TBAF (1.0 M in THF, 0.65 mL, 0.65 mmol, 1.5 eq.) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 4.0 h. Then, the reaction mixture was added TBAF (1.0 M in THF, 0.65 mL, 0.65 mmol, 1.5 eq.) at 0 °C and warmed up to room temperature and stirred for 4.0 h. The reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layers was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1 to 0:1 to EtOAc:MeOH = 10:1) to afford pure **37** (333 mg, 98%) as a white amorphous solid. $[\alpha]_D^{27}$ –27.7 (*c* 1.00, $CHCl_3$); IR (film) 1740, 1665, 1545, 1510, 1439, 1221, 1109 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (d, *J* = 9.64, 1H), 1.31 (dd, *J* = 12.47, 2.27, 1H), 1.67–1.80 (m, 5H), 2.05 (dd, *J* = 21.5, 9.07, 1H), 3.06 (dd, *J* = 13.6, 7.37, 1H), 3.32–3.37 (m, 1H), 3.49 (br s, 1H), 3.76–3.86 (m, 5H), 3.90–3.97 (m, 4H), 4.34 (d, *J* = 7.94, 1H), 5.04 (s, 2H), 6.89 (d, *J* = 7.94, 2H), 7.07 (br s, 1H), 7.12 (br s, 1H), 7.17 (d, *J* = 7.94, 2H), 7.30–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.7, 32.6 (2C), 33.4, 52.7, 57.1, 64.3, 64.5, 64.7, 65.8, 69.9, 107.1, 114.9, 121.2, 127.4, 127.9, 128.5, 129.8, 130.5, 130.7, 137.0, 153.9, 157.5, 166.7; HRMS-ESI: calcd for $C_{29}H_{34}N_2O_7SiNa$ 545.2258 $(M+Na)^+$; found 545.2248.

Prenyl Ether 40. To a solution of **37** (270 mg, 0.51 mmol) in MeOH (6.80 mL) was added PtO_2 (270 mg, 2.4 eq.) at room temperature. The resulting mixture was stirred at room temperature for 37 h under H_2 atmosphere (balloon). Then the reaction mixture was filtered through a pad of Celite® and the filtrate was

concentrated under reduced pressure. The resulting residue was used in the next reaction without further purification. To the solution of crude material including **39a** (0.51 mmol) and Cs_2CO_3 (335 mg, 1.03 mmol, 2.0 eq.) in acetone (5.1 mL) was added 3,3-dimethylallyl bromide (127 μL, 1.03 mmol, 2.0 eq.) at room temperature. Then the reaction mixture was warmed up to 50 °C, and stirred for 4 h. Then the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 3:7 to 0:1) to afford the inseparable mixture (194 mg, 77% for 2 steps) **40** and its diastereomer (4:1 determined by ^{1}H NMR) as a white amorphous solid. $[\alpha]_D^{26}$ –43.5 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2885, 1724, 1672, 1510, 1443, 1238, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, mixture of diastereomers) δ 0.84 (br s, 1H), 1.74 (s, 3H), 1.79 (s, 3H), 1.49–1.98 (m, 7H), 2.78–2.90 (m, 1H), 3.00–3.04 (m, 1H), 3.13–3.38 (m, 2H), 3.71 (s, 3H), 3.71–3.87 (m, 2H), 3.86–3.95 (m, 6H), 4.13–4.31 (m, 1H), 4.48 (d, *J* = 6.80, 2H), 5.24 (br s, 0.8H), 5.35 (br s, 0.2H), 5.48 (t, *J* = 6.80, 1H), 6.84 (d, *J* = 7.94, 2H), 7.14 (d, *J* = 7.94, 2H); ^{13}C NMR ($CDCl_3$) δ 18.1, 25.8, 30.6, 31.1, 32.1, 33.5, 34.0, 37.0, 51.1, 52.4, 57.4, 61.9, 64.0, 64.2, 64.4, 64.7, 106.9, 114.6 (2C), 119.6, 130.3, 130.5 (2C), 138.0, 157.0, 157.5, 173.7; HRMS-ESI: calcd for $C_{27}H_{38}N_2O_7Na$ 525.2571 $(M+Na)^+$; found 525.2571.

The Ketal of TAN1251C 42 (via hydrogenation with PtO_2). To a solution of **40** (96.2 mg, 0.19 mmol) in THF (3.80 mL) was added $LiAlH_4$ (0.14 mg, 3.8 mmol) at 0 °C under an argon atmosphere. After stirring 50 °C for 8 h, sufficient amount of Et_2O, H_2O (0.14 mL), 15% aqueous NaOH (0.14 mL) and H_2O (0.14 mL) was added at 0 °C successively. After stirring at room temperature for 30 min, the mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was used in the next reaction without further purification. To a stirred solution of DMSO (0.20 mL, 2.85 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C was added TFAA (0.17 mL, 1.23 mmol) and the resulting mixture was stirred at this temperature under an argon atmosphere for 30 min. A crude material including **41** (0.19 mmol) in CH_2Cl_2 (2.75 mL) was added to the mixture and stirred for 90 min. Et_3N (0.32 mL, 2.28 mmol) was added and the mixture was allow to warm to 0 °C, stirred for 1 h and was taken up in CH_2Cl_2, which was washed with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude material. To the crude material (0.19 mmol) in 3:2 MeOH / H_2O (12.6 mL) was added K_2CO_3 (210 mg, 1.52 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 4 h. The solvent was concentrated under reduced pressure and the residue was taken up in CH_2Cl_2, which was washed with H_2O and brine and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and purified by preparative TLC (CH_2Cl_2:EtOAc = 1:1) to afford pure **42** (14.3 mg, 17% for 3 steps) as yellow oil. $[\alpha]_D^{24}$ +56.5 (*c* 0.70, $CHCl_3$); IR (film) 3368, 2941, 2880, 1672, 1641, 1611, 1582, 1508, 1466, 1445, 1371, 1296, 1234, 1173, 1157, 1107, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44–1.53 (m, 1H), 1.59–1.81 (m, 6H), 1.73 (s, 3H), 1.79 (s,

3H), 1.85–1.91 (m, 1H), 2.01–2.13 (m, 2H), 2.45 (s, 3H), 2.72 (dd, *J* = 11.5, 1.7 Hz, 1H), 3.15 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.21 (s, 2H), 3.30 (dd, *J* = 5.7, 2.3 Hz, 1H), 3.92–3.99 (m, 4H), 4.47 (d, *J* = 6.3 Hz, 2H), 5.09 (d, *J* = 1.2 Hz, 1H), 5.46–5.52 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.3, 26.0, 31.8, 32.6, 33.6, 35.0, 40.6, 41.6, 42.6, 51.7, 59.2, 64.4, 64.8, 72.1, 108.6, 114.4, 120.0, 127.3, 129.3, 130.2, 132.2, 138.1, 157.2; HRMS-ESI: calcd for $C_{26}H_{37}N_2O_3$ 425.2799 $(M+H)^+$, found 425.2805.

Ugi Product 44a. 44a (5.16 g) was prepared in 75% yield as a yellow amorphous according to the same procedure as **26d** by using carboxylic acid **11c** (1.60 g, 8.38 mmol) as the carboxylic acid and isonitrile **43** (1.24 g, 6.78 mmol) as the isonitrile. $[\alpha]_D^{31}$ –56.8 (*c* 2.27, $CHCl_3$); IR (film) 3374, 3069, 3049, 3032, 2955, 2932, 2887, 2859, 1711, 1694, 1659, 1611, 1584, 1564, 1510, 1503, 1485, 1431, 1402, 1383, 1371, 1298, 1240, 1227, 1179, 1157, 1105, 1040, 1028, 1011, 986, 972, 947, 935, 905, 824, 789, 770, 739, 702, 675, 658, 613, 584, 501; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 1.06 (s, 9H), 1.36–1.76 (m, 3H), 1.86–2.19 (m, 2H), 2.21–2.54 (m, 2H), 2.62–3.07 (m, 4.5H), 3.11–3.34 (m, 0.5H), 3.58–4.24 (m, 8.5H), 4.27–4.47 (m, 0.5H), 4.81–5.24 (4H), 6.78–7.01 (m, 3H), 7.02–7.13 (m, 1.6H), 7.14–7.52 (m, 18H), 7.53–7.82 (m, 3.4H), 7.94–8.22 (m, 1H), 8.38–8.69 (m, 1H); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 19.0, 19.2, 27.0, 30.5, 30.8, 31.3, 31.5, 31.8, 35.3, 36.0, 36.4, 37.1, 38.5, 51.8, 52.2, 52.9, 53.3, 60.1, 63.3, 63.9, 64.1, 64.4, 64.5, 65.5, 65.7, 66.1, 66.2, 66.8, 66.9, 67.1, 67.2, 69.9, 70.0, 107.4, 107.6, 107.9, 108.0, 112.5, 112.6, 112.8, 115.5, 115.7 (2C), 122.7, 122.9, 123.3, 127.2, 127.5, 127.8, 128.3, 128.4, 129.8, 132.4, 132.5, 135.1, 135.6 (2C), 136.6, 138.8, 139.0, 139.1, 139.8, 140.0, 140.1, 151.3, 151.6, 151.9, 152.2, 156.1, 156.8, 157.5, 157.6, 170.6, 170.8, 171.5, 171.7, 172.1, 172.3; HRMS (ESI): calcd for $C_{57}H_{63}BrN_4O_8SiNa$ 1063.3486 $(M+Na)^+$, found 1063.3481.

Triflate 46. To a solution of **44a** (307 mg, 0.295 mmol) in MeOH (1.5 mL) was added NaOMe (5.0 M in MeOH, 590 μL, 2.95 mmol) at room temperature. The reaction mixture was heated at 50 °C in a sealed tube and stirred for 2.5 h. Then the reaction mixture was quenched with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 2 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product **45**, which was used in the next reaction without further purification.

To a solution of crude material including **45** and $PhNTf_2$ (211 mg, 0.59 mmol) in THF (3.0 mL) was added dropwise KHMDS (0.5 M in toluene, 2.24 mL, 1.12 mmol) over 1 min at -78 °C under an argon atmosphere, then the reaction mixture was warmed up to room temperature. After stirring for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 19:1 to 7:3) to afford **46** (142 mg, 48% for 2 steps) as a white amorphous

solid. $[\alpha]_D^{31}$ –31.6 (*c* 1.26, $CHCl_3$); IR (film) 2957, 2936, 2886, 2860, 1728, 1697, 1510, 1472, 1425, 1389, 1362, 1306, 1225, 1134, 1113, 1082, 1055, 1028, 910, 824, 804, 781, 745, 702, 606, 590, 505 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.59 (t, *J* = 14.2 Hz, 1H), 1.03 (s, 3H), 1.07 (s, 6H), 1.12–1.32 (m, 2H), 1.37–1.49 (m, 2H), 1.51–1.76 (m, 3H), 1.94–2.15 (m, 1H), 2.98–3.13 (m, 1H), 3.16–3.27 (m, 3H), 3.29–3.53 (m, 2H), 3.83–4.15 (m, 6H), 4.87–4.95 (m, 0.8H), 4.96–5.08 (m, 1.9H), 5.11–5.22 (m, 1.3H), 6.67 (d, *J* = 8.5 Hz, 0.8H), 6.82–6.88 (m, 1.2H), 6.93–7.06 (m, 2H), 7.10–7.16 (m, 1.5H), 7.22–7.46 (m, 14.5H), 7.59–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 19.1, 19.2, 26.6, 26.9, 28.8, 29.2, 30.4, 30.6, 30.8, 33.7, 33.9, 34.3, 34.5, 34.7, 58.6, 58.7, 61.6, 61.8, 63.9, 64.3, 64.4, 68.2, 68.4, 69.9, 70.0, 106.4, 106.6, 114.7, 114.9, 116.8, 119.4, 120.7, 120.8, 127.3, 127.6, 127.7, 127.9, 128.0, 128.3, 128.5, 129.7, 129.8, 130.6, 133.1, 133.2, 135.3, 135.5, 135.7, 137.0, 153.8, 154.0, 157.1, 157.2, 157.4 (2C), 164.0; HRMS (ESI): calcd for $C_{53}H_{59}F_3N_2O_{10}Si$ 999.3528 $(M+H)^+$, found 999.3511.

Unsaturated Lactam 47. To a solution of **46** (5.19 g, 5.19 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (848 mg, 1.04 mmol) in DMF (26 mL) was added Et_3SiH (8.30 mL, 52.9 mmol) at room temperature under an argon atmosphere, and the reaction mixture was warmed up to 60 °C. After stirring for 7.5 h, the reaction mixture was diluted with Et_2O at 0 °C. Then the mixture was filtered through a pad of Celite® and the filtrate was basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 9:1 to 2:1) to afford **47** (3.74 g, 85%) as a white amorphous solid. $[\alpha]_D^{26}$ –50.8 (*c* 0.375, $CHCl_3$); IR (film) 2936, 2886, 2859, 1713, 1686, 1659, 1512, 1450, 1427, 1389, 1323, 1300, 1238, 1150, 1111, 1030, 826, 741, 702, 613, 440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (dd, *J* = 12.5, 2.3 Hz, 1H), 1.07 (s, 9H), 1.01–1.10 (m, 1H), 1.23–1.63 (m, 5H), 1.82 (ddd, *J* = 13.6, 13.6, 4.5 Hz, 1H), 3.13 (dd, *J* = 13.3, 4.5 Hz, 1H), 3.30 (s, 3H), 3.32–3.40 (m, 1H), 3.47 (dd, *J* = 13.3, 10.2 Hz, 1H), 3.83–3.90 (m, 5H), 4.17 (dd, *J* = 9.6, 7.9 Hz, 1H), 4.99 (s, 2H), 5.15 (s, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.98 (br s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.25–7.33 (m, 6H), 7.34–7.44 (m, 10H), 7.63–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.9 (4C), 29.4, 31.7, 32.5 (2C), 33.4, 35.0, 57.9, 63.1, 64.0, 64.3, 64.4, 67.7, 69.9, 107.1, 114.7 (2C), 127.3 (2C), 127.7 (4C), 127.8 (2C), 128.1, 128.5 (4C), 129.6, 129.7, 130.7 (2C), 131.8, 133.3, 133.5, 135.6 (4C), 135.8 (2C), 136.1, 137.1, 155.1, 157.2, 166.1; HRMS (ESI): calcd for $C_{52}H_{58}N_2O_7SiNa$ 873.3906 $(M+Na)^+$, found 873.3906.

Oxime 48. To a solution of **47** (695 mg, 0.82 mmol) in MeOH (16 mL) was added Pd/C (5% wet, 348 mg) and the mixture was stirred under 1 atm of hydrogen for 24 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to afford the crude product. To a solution of crude material in MeOH (8 mL) were added hydroxylamine hydrochloride (85.2 mg, 1.23 mmol) and pyridine (112 μL, 1.39 mmol). After stirring for 10 h, the reaction mixture was

diluted with EtOAc, and the mixture was washed with 1 M HCl and saturated aqueous $NaHCO_3$, then dried over anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 4:1 to 1:4) to afford **48** (438 mg, 86% for 2 steps) as a white amorphous. $[\alpha]_D^{25}$ –74.3 (*c* 0.710, $CHCl_3$); IR (film) 3304, 3292, 2957, 2934, 1692, 1647, 1516, 1441, 1429, 1265, 1254, 1132, 1113, 826, 737, 704, 503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (d, *J* = 11.9 Hz, 1H), 1.07 (s, 9H), 1.02–1.23 (m, 2H), 1.25–1.70 (m, 4H), 1.80 (ddd, *J* = 13.3, 12.8, 4.0 Hz, 1H), 2.45 (d, *J* = 19.3 Hz, 1H), 2.66 (d, *J* = 19.3 Hz, 1H), 3.09 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.35–3.44 (m, 1H), 3.50 (dd, *J* = 12.2, 10.8 Hz, 1H), 3.86–4.08 (m, 5H), 4.17 (dd, *J* = 17.0, 7.4 Hz, 1H), 5.10 (br s, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.35–7.49 (m, 6H), 7.62–7.76(m, 4H), 8.56 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.9, 31.4, 31.5, 31.8, 32.2, 33.3, 33.7, 59.0, 61.2, 63.9, 64.2, 64.3, 106.9, 115.4, 127.7, 129.7 (2C), 130.5, 130.8, 133.2, 133.4, 135.6, 151.4, 154.5, 164.0; HRMS (ESI): calcd for $C_{36}H_{44}N_2O_6SiNa$ 651.2861 $(M+Na)^+$; found 651.2862.

Prenyl Ether 53. To a solution of **48** (1.29 g) in acetic acid (21 mL) at room temperature was added activated zinc dust (5.40 g, 82.5 mmol) and NH_4Cl (2.20 g, 41.3 mmol), and the reaction mixture was stirred at 50 °C for 7 h. Then the mixture was filtered over a pad of Celite® and the filtrate was concentrated under reduced pressure to afford the crude product **49** as an acetic acid salt, which was used in the next reaction without further purification. To a solution of crude material including **49** in 1:1 THF / H_2O (41 mL) at 0 °C was added $NaHCO_3$ (3.5 g, 41.3 mmol) and methyl chloroformate (0.79 mL, 10.3 mmol), and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was taken up in EtOAc, which was washed with brine and dried over anhydrous $MgSO_4$. The solvent was concentrated under reduced pressure to afford the crude product. To a solution of crude material in acetone (21 mL) at room temperature was added Cs_2CO_3 (1.34 g, 4.12 mmol) and prenyl bromide (0.48 mL, 4.12 mmol), and the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 4:1 to 1:1) to afford **53** (1.43 g, 94% for 3 steps) as a white amorphous solid. $[\alpha]_D^{25}$ –40.1 (*c* 0.275, $CHCl_3$); IR (film) 3302, 3051, 2936, 2889, 1728, 1686, 1674, 1612, 1512, 1443, 1373, 1238, 1196, 1169, 1111, 1011, 941, 891, 826, 741, 706, 667, 613 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.11 (d, *J* = 9.1 Hz, 0.8H), 0.36 (d, *J* = 9.1 Hz, 0.2H), 1.06 (s, 7.5H), 1.08 (s, 1.5H), 1.16–1.34 (m, 4H), 1.36–1.52 (m, 3H), 1.54–1.61 (m, 1H), 1.73 (s, 3H), 1.69–1.76 (m, 1H), 1.79 (s, 3H), 2.66–2.86 (m, 1H), 2.96 (ddd, *J* = 11.9, 4.0 Hz, 6.2 Hz, 0.9H), 3.10 (dd, *J* = 13.6, 5.1 Hz, 0.1H), 3.21–3.35 (m, 1.9H), 3.47 (dd, *J* = 13.0, 10.8 Hz, 0.1H), 3.67 (s, 0.4H), 3.69 (s, 2.6H), 3.81–3.96 (m, 4H), 3.99 (dd, *J* = 10.2, 6.2 Hz, 1H), 4.05 (dd, *J* = 10.2, 6.2 Hz, 1H), 4.04–4.14 (m, 1H), 4.42–4.51 (m, 2H), 5.16 (br s, 0.2H), 5.28 (br s, 0.8H), 5.42–5.51 (m, 1H), 6.78 (d, *J* = 8.5 Hz, 1.8H), 6.80 (d, *J* = 8.5 Hz, 0.2H), 6.97 (d, *J* = 8.5 Hz, 1.8H), 7.03 (d, *J* = 8.5 Hz, 0.2H), 7.34–7.45 (m,

6H), 7.61–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 18.2, 19.1, 19.2, 25.8, 26.9, 31.1, 31.2, 32.0, 33.3, 34.2, 35.0, 37.2, 51.1, 52.3, 57.9, 58.2, 63.1, 64.2, 64.3, 64.8, 107.0 (2C), 114.5, 114.6, 119.7, 127.7, 129.6 (2C), 130.5, 131.0, 133.3 (2C), 135.6, 137.9, 157.1, 157.4, 171.9; HRMS (ESI): calcd for $C_{43}H_{56}N_2O_7SiNa$ 763.3749 $(M+Na)^+$, found 763.3722.

Amine 41. To a solution of **53** (103 mg, 0.14 mmol) in THF (3 mL) was added $LiAlH_4$ (106 mg, 2.80 mmol) at 0 °C under an argon atmosphere. After stirring 50 °C for 15 h, sufficient amount of Et_2O, H_2O (106 μL), 4 M NaOH (106 μL) and H_2O (318 μL) was added at 0 °C successively. After stirring at room temperature for 1 h, the mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1 to 0:1, then EtOAc:MeOH = 19:1) to afford pure **41** (33.6 mg, 54%) as a pale yellow oil. $[\alpha]_D^{24}$ +1.4 (*c* 0.515, $CHCl_3$); IR (film) 3348, 2932, 1612, 1510, 1438, 1371, 1236, 1142, 1105, 1034, 943, 887 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22–1.29 (m, 1H), 1.57 (dd, *J* = 12.9, 7.5 Hz, 1H), 1.61–1.71 (m, 2H), 1.75 (s, 3H), 1.80 (s, 3H), 1.71–1.82 (m, 3H), 1.85–1.95 (m, 2H), 2.22 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.46 (s, 3H), 2.41–2.49 (m, 1H), 2.68 (t, *J* = 8.0 Hz, 1H), 2.94 (dd, *J* = 13.5, 2.9 Hz, 1H), 3.09–3.24 (m, 4H), 3.27–3.33 (m, 1H), 3.90–4.01 (m, 4H), 4.49 (d, *J* = 6.9 Hz, 2H), 5.46–5.52 (m, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 31.5, 32.2, 33.0, 35.0, 35.3, 36.3, 41.8, 49.1, 56.0, 57.3, 60.5, 62.3, 64.2, 64.3, 64.7, 108.0, 114.6 (2C), 119.7, 129.7 (2C), 130.8, 138.1, 157.3; HRMS (ESI): calcd for $C_{26}H_{41}N_2O_4$ 445.3061 $(M+H)^+$, found 445.3058.

The Ketal of TAN1251C 42 (via Zn reduction). To a stirred solution of DMSO (0.18 mL, 2.50 mmol) in CH_2Cl_2 (2 mL) at -78 °C was added TFAA (0.16 mL, 1.10 mmol) and the resulting mixture was stirred at this temperature under an argon atmosphere for 50 min. A solution of **41** (75.0 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added to the mixture and stirred for 40 min. Et_3N (0.28 mL, 2.00 mmol) was added and the mixture was allow to warm to 0 °C, stirred for 40 min and was taken up in $CHCl_3$, which was washed with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude product. To a solution of the crude product in MeOH / H_2O (5:2, 12.6 mL) was added K_2CO_3 (0.38 g, 2.70 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 2 h. The solvent was concentrated under reduced pressure and the residue was taken up in $CHCl_3$, which was washed with H_2O and brine and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and purified by preparative TLC (CH_2Cl_2:EtOAc = 1:1) to afford pure **42** (43 mg, 60% for 2 steps) as a yellow oil. $[\alpha]_D^{24}$ +71.1 (*c* 0.590, $CHCl_3$).

TAN1251C (1c). To a solution of **42** (20 mg, 47 μmol) in acetone (5.0 mL) was added aqueous 1 M HCl (1.5 mL), and the reaction mixture was stirred at room temperature for 22 h. Then the reaction mixture was neutralized with saturated aqueous Na_2CO_3. The acetone was concentrated under reduced pressure and the residue was taken up in $CHCl_3$ which was washed with saturated aqueous Na_2CO_3 and brine and

dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and purified by preparative TLC (CH_2Cl_2:EtOAc = 1:1) to afford TAN1251C (**1c**) (12 mg, 65%) as a yellow oil. $[\alpha]_D^{25}$ +23.8 (*c* 0.37, MeOH); IR (film) 3408, 2926, 2853, 1713, 1672, 1641, 1611, 1505, 1445, 1427, 1371, 1335, 1298, 1234, 1172, 1124, 1107, 1055, 1007, 860, 839, 810, 789 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (s, 3H), 1.80 (s, 3H), 1.82–1.91 (m, 3H), 1.97 (ddd, *J* = 13.8, 10.6, 4.6 Hz, 1H), 2.17–2.43 (m, 4H), 2.44–2.50 (m, 1H), 2.51 (s, 3H), 2.56–2.62 (m, 1H), 2.79 (dd, *J* = 11.7, 1.7 Hz, 1H), 3.18–3.24 (m, 3H), 3.38–3.42 (m, 1H), 4.48 (d, *J* = 6.9 Hz, 1H), 5.24 (d, *J* = 1.2 Hz, 1H), 5.48–5.53 (m, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 34.6, 37.2, 37.8, 39.5, 40.3, 41.4, 42.8, 52.1, 59.0, 64.7, 71.4, 114.3 (2C), 119.8, 127.8, 128.2, 129.8 (2C), 131.9, 138.0, 157.1, 211.7; HRMS (ESI): calcd for $C_{24}H_{33}N_2O_2$ 381.2537 $(M+H)^+$, found 381.2547.

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