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Synthesis of a Tetracyclic Substructure of Manzamine A *via* the Diels-Alder Reaction of Dihydropyridinones

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Abstract: *Synthesis of the tetracyclic core (**19**) of manzamine A (**1**) was achieved via Diels-Alder reaction of the dihydropyridinones (**5**, **6**). Conversion of the two D-A products (**7**, **8**) to the key tricyclic ketone (**10**) was conducted through a conventional pathway (Scheme III) as well as a new pathway developed (Scheme IV). For effective construction of the required azocine ring systems, model studies were carried out to find intramolecular amide formation by pentafluorophenyl ester and DPPA methods, which were successfully applied to the real substrate to furnish the titled core structure (**19**).*

INTRODUCTION

The alkaloids manzamines are a unique family of oncolytic β-carboline-linked azacycles, which have been isolated from several Okinawan marine sponges by Higa since 1986[1]. Further progress was added recently by the isolation of the new and closely related members[2], as well as an ingenious proposal for their biosynthetic path[3]. The first isolated congener manzamine A (**1**) has been the subject of intensive synthetic investigations[4] owing to its unique molecular structure and significant biological properties including antitumor and antibacterial activities. Following the first successful entry into the tetracyclic skeleton by Hart[5], we and others have also investigated another synthetic route to this ABCD tetracyclic core[6]. Based on our original key strategy[7], we have developed a new and an efficient route to the tetracyclic core[8], which is featured by an efficient Diels-Alder (D-A) reaction of the suitably protected dihydropyridinones under usual thermal conditions. Detailed herein is the full scope of these researches, as well as some efforts to optimize each step towards the more advanced intermediates.

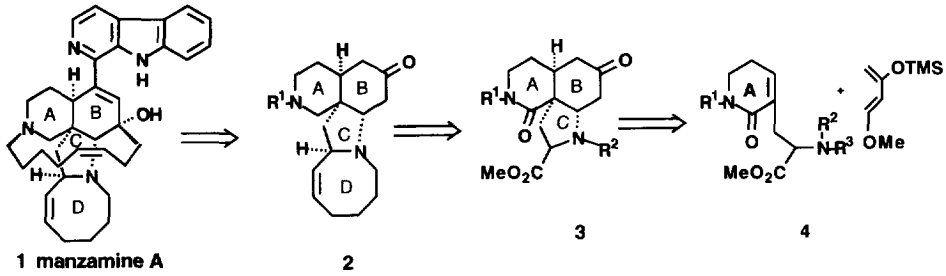
RESULTS AND DISCUSSION

Diels-Alder Reaction with the N-Trifluoroacetyl Dienophiles

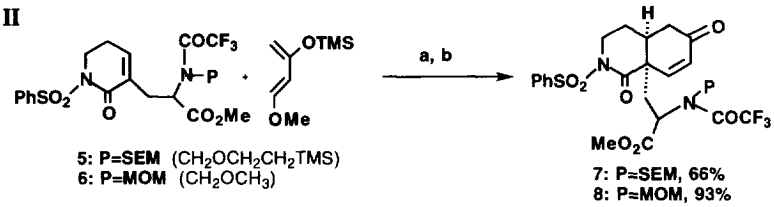
Based on our retrosynthetic analysis shown in Scheme I, we had already described a route to the key tricyclic intermediate (**3**) utilizing a super high-pressure D-A reaction of the dihydropyridinone (**4**)[7], in where the protecting groups employed are R^1=TolSO$_2$, R^2=Me and R^3=*t*-butoxycarbonyl(BOC). Further search was then required to find a more suitable dienophile dihydropyridinone, with which D-A reaction can be carried out under more convenient conditions, and subsequent transformations can easily be attained by the choice of suitable nitrogen protecting groups (R^2 and R^3).

After several attempts, we have successfully found the new COCF$_3$ attached dienophiles (**5**, **6**)[9], which

Scheme I



Scheme II



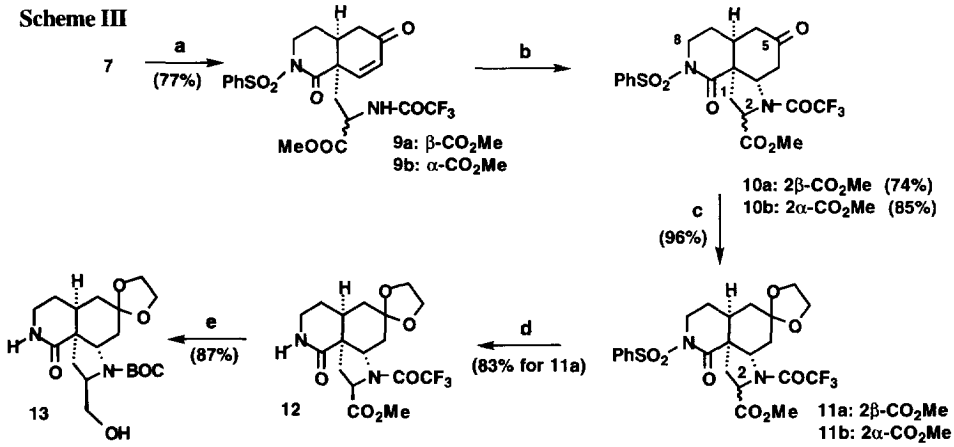
(a) *p*-cymene, reflux, 5 h; (b) CSA, CH_2Cl_2

were the most suitable ones in view of their easiness in preparation and reactivity in D-A reaction. Thus, the D-A reactions of **5** and **6** with Danishefsky diene were conducted at normal pressure under reflux in *p*-cymene for *ca.* 5h to furnish the enones **7** and **8** in 66 and 93 % yields, respectively after an acid treatment (Scheme II).

*Conversion to the Key Tricyclic Intermediate (**11**, **12**, **13**)*

Next task was an efficient conversion of the D-A product (**7**) to a suitably protected tricyclic intermediate.

Scheme III



(a) CF_3COOH, CH_2Cl_2 rt; (b) DABCO, DME, rt; (C) ethylene glycol, PPTS, benzene, reflux;
(d) Na, anthracene, DME, -60 °C; (e) i) $LiBH_4$, $B(OMe)_3$, THF, rt ii) NaOH, $(BOC)_2O$, rt

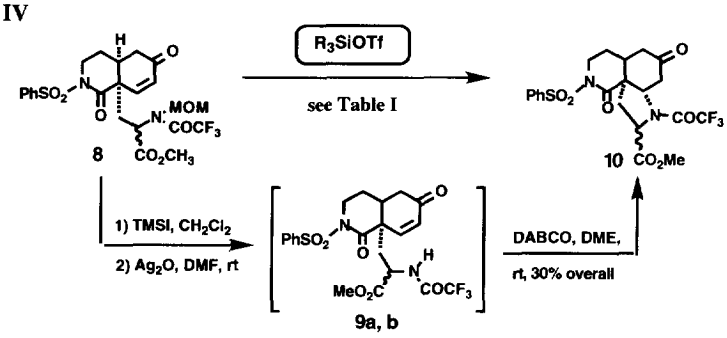
Towards this end, the crude *N*-trimethylsilylethoxymethyl(SEM) adduct (**7**) was directly deprotected by trifluoroacetic acid (TFA) to furnish the *NH*-enone (**9**), which was converted to the tricyclic system (**10**) by a brief treatment with 1, 4-diazabicyclo- [2. 2. 2]octane (DABCO) at room temperature in 85% yield (Scheme III).

Subsequent ketalization of **10** afforded the stable ketal (**11**) as a *ca.* 1:1 diastereomeric mixture, which could easily be separated by recrystallization from CH_2Cl_2 / Et_2O, although the diastereomers corresponding to **9** and **10** could be separated by column chromatography. For a large scale preparation, these deprotection-cyclization-ketalization steps were conveniently conducted without purification, to furnish the desirable isomer (**11a**) in 30% yield from the *N*-SEM dienophile (**5**).

Next stage was a selective deprotection of the two *N*-protecting groups (i.e., $PhSO_2$ and $COCF_3$). After many abortive trials with typical reducing agents, we finally found the best-suited conditions for the conversion of **11** to **12** in up to 83 % yield by the use of Na / anthracene[10] in 1,2-dimethoxyethane(DME) at -60 °C. Then the reductive removal of $COCF_3$ group by $LiBH_4$ / $B(OMe)_3$ followed by protection of the newly generated NH group by BOC group gave the alcohol (**13**) in 87 % yield from **12**.

Another efficient preparation of the tricyclic intermediate (**10**) was realized by the reaction of *N*-MOM adduct (**8**) with trialkylsilyl triflate (R_3SiOTf) at room temperature (Scheme IV).

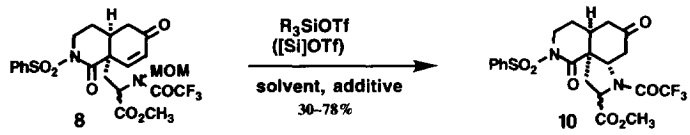
Scheme IV



Among the triflates examined, *t*-butyldimethylsilyl triflate (TBDMSOTf) gave a better yield than a simple trimethylsilyl triflate (TMSOTf) especially in the presence of DABCO. Further optimization increased the yield up to 67% by addition of SiO_2 powder in the reaction mixture in toluene. The highest yield was attained finally, by the use of triethylsilyl triflate (TESOTf) in the presence of both SiO_2 powder and Na_2SO_4, where the reaction was completed within 12 h which became the most convenient and economical method to obtain **10** (Table I).

On the other hand, the reaction of the *N*-MOM derivative (**8**) with trimethylsilyl iodide (TMSI) or trimethylsilyl bromide (TMSBr) followed by treatment with silver oxide gave only the deprotected products (**9a, b**), which finally afforded the cyclized product (**10**) by DABCO in 30% yield from **8**.

Table I

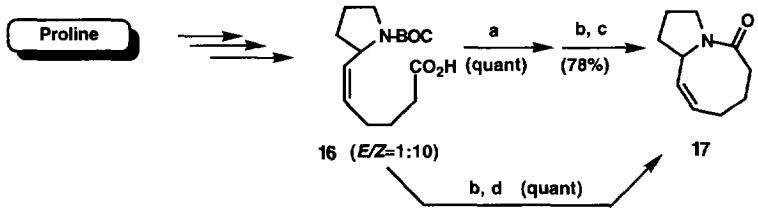


run.	solvent	[Si]OTf	reaction time (h)	additive	Yield (%)
1	CH_2Cl_2	[Si]=TMS	24	none	41
2	CH_3CN	[Si]=TMS	24	none	44
3	CH_2Cl_2	[Si]=TBDMS	48	none	30
4	CH_2Cl_2	[Si]=TBDMS	48	DABCO	50
5	toluene	[Si]=TBDMS	72	DABCO	60
6	toluene	[Si]=TBDMS	42	SiO_2	67
7	toluene	[Si]=TES	12	SiO_2-Na_2SO_4	78

Azocine Ring Construction

The key precursor (**13**) in hand, we next turned our attention to the crucial azocine ring formation[11]. Careful model study was required because almost no general method has been established for the effective azocine ring formation from the corresponding amino-acid precursor[11]. After several trials, effective methods were found for the conversion of the model system (**16**) into the corresponding bicyclic azocinone ring system (**17**)[12]. The pentafluorophenyl (PFP) ester obtained from **16** was treated with TFA in methylene chloride, followed by a reaction with excess 4-dimethylaminopyridine (DMAP) in dioxane under heating gave the desired bicyclic azocine (**17**) in 78% yield. Alternatively, the removal of the BOC group of **16** with TFA, followed by a diphenyl phosphorazidate (DPPA) treatment gave **17** in excellent yield[13]. (Scheme V)

Scheme V



(a) C_6F_5OH, DCC, rt (b) CF_3COOH, CH_2Cl_2, rt (c) DMAP, dioxane, 80~90 °C (d) DPPA, DMF, 5 °C~rt

With these two methods available for the formation of simple bicyclic azocine(**17**), we next examined the effectiveness of these methods in our real substrate. For this purpose, the alcohol (**13**) was oxidized to the

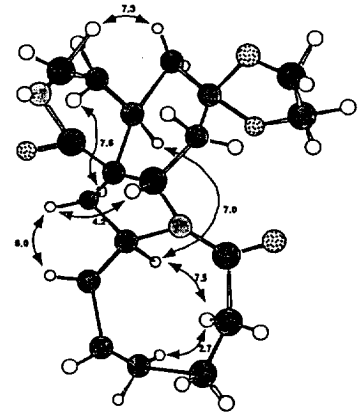
aldehyde (**14**) in 67 % yield, which was then subjected to a Wittig reaction with the ylide generated from 4-carboxybutyltriphenylphosphonium bromide to furnish the cyclization precursor (**15**).

In view of the easiness in isolation of the intermediate, we applied the PFP ester method to our substrate (**15**). Treatment of the crude acid (**15**) with pentafluorophenol by the aid of dicyclohexylcarbodiimide (DCC) afforded the easily separable PFP ester (**18**), which was a *E* / *Z* (2 / 5) mixture based on its NMR analysis. The crucial cyclization was then carried out by heating **18** in dioxane to give the desired tetracycle (**19**) in 58 % from the PFP-ester (**18**).

The structure of **19** was definitely confirmed by a X-ray crystallographic analysis[8] and careful NOE experiments (Fig.1) as well as conventional IR, NMR (^{1}H and ^{13}C) and MS spectroscopy.

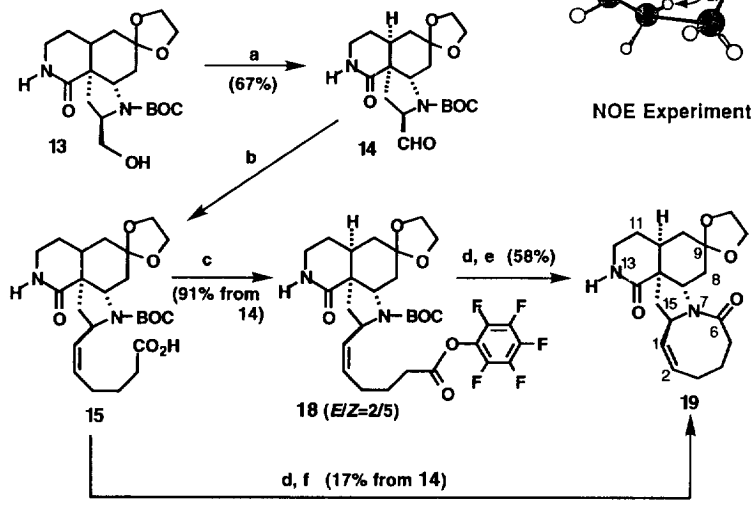
In summation, we have detailed here an efficient synthesis of the manzamine A tetracyclic core based on a D-A reaction of the useful dihydropyridinones (**5**, **6**). The 14-steps preparation of **19** in 6 % overall yield from 3-phenylthiopiperidone is suitable for further elaboration of the 13-membered azacycle as well as β–carboline conjunction, which are now in progress in our laboratory.

Figure I



NOE Experiment

Scheme VI



(a) PCC, CH_2Cl_2, Al_2O_3, rt (b) $Ph_3P{=}CH(CH_2)_3COOK$, toluene, rt (c) C_6F_5OH, DCC, rt; (d) CF_3COOH, CH_2Cl_2, rt (e) DMAP, dioxane, 80~90 °C; (f) DPPA, DMF, 5° C~rt

EXPERIMENTAL

General. Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus and are uncorrected. Infrared (ir) spectra (υ in cm^{-1}) were recorded with a Hitachi 260-10 spectrophotometer. Unless otherwise noted, ir spectra referred to KBr disks. Mass spectra (MS) were recorded on a Hitachi M-60, RMU-7, JEOL HX-110, or JMS-AM 20 mass spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H-and ^{13}C-NMR) spectra were recorded on JNM-GSX-500, and JNM-GSX-500A apparatus (500MHz for ^{1}H-NMR, 125MHz for ^{13}C-NMR). Nmr spectra were measured in $CDCl_3$, unless otherwise noted, and chemical shifts were recorded in δ values (ppm) relative to Me_4Si internal standard. Microanalyses were performed on a Perkin Elmer 240 C, H, N analyzer. All reactions were carried out under argon atmosphere and column chromatography was performed with Merck SiO_2 60 unless otherwise specified.

2-Benzenesulfonyl-8a-{2-[*N*-trifluoroacetyl-*N*-(2-trimethylsilylethoxymethyl)amino]-methoxycarbonylethyl}-1, 6-dioxo-*cis*-1, 2, 3, 4, 4a, 5, 6, 8a-octahydroisoquinoline (7).

A) Small scale preparation. In a well-dried argon flushed 50 mL round-bottomed flask equipped with a short cooler was placed the dienophile (**5**[9], 425 mg, 0.75 mmol), Danishefsky diene (1.5 mL) and *p*-cymene (15 mL, distilled and dried over molecular sieves-4A). The whole was heated in an oil bath at 190~200 °C for 5 h in an atmosphere of Ar. The resulting orange mixture was cooled to rt and evaporated under reduced pressure to remove solvent and excess diene. The residue obtained was taken into CH_2Cl_2 (10 mL) and treated with CSA (60 mg) at rt. After stirring for 1 h, the mixture was quenched by the addition of saturated aq. $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of the dried solvents gave a crude oil (608 mg), which was purified by repeated SiO_2 column (i SiO_2: 25 g, *n*-hexane / AcOEt=1 / 3, ii then SiO_2: 7 g, $CHCl_3$ / AcOEt=50 / 1) to afford the enone (**7**, 314 mg, 66 %) as a colorless amorphous solid: IR cm^{-1}: 2950, 1750, 1690, 1360, 1170. FABMS (NaCl) *m/z*: 655 (MNa^+, 3), 144 (100) . HRFABMS Calcd for $C_{27}H_{35}F_3N_2NaO_8SSi$: 655.1733. Found: 655.1749. ^{1}H-NMR δ (a mixture of diastereoisomers) 0.025 (9H, s), 0.91 (2H, m), 1.91 (1H, m), 2.07 (1H, m), 2.18-2.41 (2H, m), 2.58 (1H, m), 2.69-3.05 (2H, m), 3.54 (2H, m), 3.61 (1.5H, s), 3.64 (1.5H, s), 3.87 (1H, m), 4.08 (1H, m), 4.34 (1H, dd, *J*=6.0, 4.4 Hz), 4.44 (1H, t, *J*=5.7 Hz), 4.74 (2H, m), 5.95 (1/2H, d, *J*=10.3 Hz), 6.00 (1/2H, d, *J*=10.3 Hz), 6.58 (1H, d, *J*=10.3 Hz), 7.54 (2H, m), 7.64 (1H, m), 8.02 (2H, m).

B) Large scale preparation. A mixture of **5** (14.28 g, 25.3 mmol) and Danishefsky diene (45 mL) in *p*-cymene (100 mL) was heated under gentle reflux at 200 °C for 5.5 h under argon. Resulting orange mixture was worked up as above and the residue was treated with CSA (250 mg) in CH_2Cl_2 (200 mL) at rt for 1 h. After usual work-up, crude enone (**7**, 20 g) obtained was directly subjected to the deprotection step as described below.

2-Benzenesulfonyl-8a-{2-[*N*-trifluoroacetyl-*N*-(2-methoxymethyl)amino]methoxycarbonylethyl}-1, 6-dioxo-*cis*-1, 2, 3, 4, 4a, 5, 6, 8a-octahydroisoquinoline (8).

In a 200 mL round-bottomed flask (well-dried and argon flushed) equipped with a short cooler was placed the dienophile (**6**[9], 11.3 g, 23.6 mmol), Danishefsky diene (37 mL) and *p*-cymene (70 mL, distilled and dried over MS-4A). The whole was heated in an oil bath at 200~210 °C for 5.5 h in atmosphere of Ar. The resulting orange mixture was cooled to rt and evaporated under reduced pressure to remove solvent and excess diene. The residue obtained was taken into CH_2Cl_2 (200 mL) and treated with CSA (200 mg) at rt. After stirring for 3 h, the mixture was quenched by the addition of saturated aq. $NaHCO_3$ (200 mL) and diluted with CH_2Cl_2. After extraction with CH_2Cl_2 (200 mL x 3), the organic extracts were washed with brine (200 mL) and dried over $MgSO_4$. Evaporation of the dried solvents gave a crude oil (15.0 g), which was purified by repeated SiO_2 column to afford the enone (**8**, 12.0 g, 93 %) as a yellow amorphous solid: IR cm^{-1}: 2950, 1740, 1700, 1360, 1450. FABMS *m/z*: 547 (MH^+, 64.5) , 515 (100) . HRFABMS Calcd for $C_{23}H_{26}F_3N_2O_8S$: 547.1362. Found: 547.1361. ^{1}H-NMR δ (a mixture of diastereoisomers): 1.90 (1H, m), 2.05 (1H, m), 2.15-2.40 (2H, m), 2.55 (1H, m), 2.65-3.05 (2H, m), 3.55 (2H, m), 3.37 (1.5H, s), 3.36 (1.5H, s), 3.68 (1H, m), 4.05 (1H, m), 4.35 (1H, dd, *J*=6.0, 4.4 Hz), 4.45 (1H, t, *J*=5.7 Hz), 4.75 (2H, m), 5.96 (1/2H, d, *J*=10.3 Hz), 6.00 (1/2H, d, *J*=10.3 Hz), 6.58 (1H, d, *J*=10.3 Hz), 7.54 (2H, m), 7.64 (1H, m), 8.02 (2H, m).

Conversion of the D-A Product (7) to the Tricyclic Ketal (11)

A) 2-Benzenesulfonyl-8a-[2-(*N*-trifluoroacetylamino)-2-methoxycarbonylethyl]-1, 6-dioxo-*cis*-1, 2, 3, 4, 4a, 5, 6, 8a-octahydroisoquinoline (9).

i) Small scale preparation. To a cooled (10 °C) and stirred solution of the enone (**7**, 2.17 g, 3.43 mmol) in CH_2Cl_2 (80 mL) was added slowly TFA (7.9 mL, 103 mmol) and the resulting mixture was kept stirring at rt for 3 h. The mixture was quenched by the addition of brine (50 mL) and extracted with CH_2Cl_2 (ca 200 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and brine. After drying over $MgSO_4$, the solvent was evaporated to give a residue (1.87 g), which was purified by SiO_2 column (SiO_2: 70 g, AcOEt / *n*-hexane= 1 / 4). After first less polar fraction gave the recovered **7** (200 mg, 9 %), the second fraction afforded the desired 2β-COOMe isomer (**9a**, 742 mg, 43 %), and from the third fraction, was obtained the more polar 2α-COOMe isomer (**9b**, 584 mg, 34 %) as a colorless amorphous solid. **9a**: IR (KBr) cm^{-1}: 3350, 1710, 1680, 1350, 1170. FABMS *m/z*: 503 (MH^+, 32). HRFABMS Calcd for $C_{21}H_{22}F_3N_2O_7S$: 503.1099. Found: 503.1111. ^{1}H-NMR δ: 2.01-2.04 (2H, m), 2.15 (1H, dd, *J*=14.7, 6.9 Hz), 2.43 (1H, dd, *J*=18.5, 3.9 Hz), 2.65 (1H, dd, *J*=14.7, 8.1 Hz), 2.80-2.86 (2H, m), 3.58 (3H, s), 3.75 (1H, m), 4.30 (1H, m), 4.54 (1H, m), 5.97 (1H, dd, *J*=10.3, 0.7 Hz), 6.32 (1H, dd, *J*=10.3, 1.8 Hz), 7.37 (1H, d, *J*=7.3 Hz), 7.54 (2H, m), 7.64 (1H, m), 8.01 (2H, dd, *J*=8.4, 1.3 Hz). NOE was observed between OMe and aromatic H. **9b**: IR (neat) cm^{-1}: 3300, 1710, 1670, 1350, 1165. FABMS *m/z*: 503 (MH^+, 32). HRFABMS Calcd for $C_{21}H_{22}F_3N_2O_7S$: 503.1100. Found: 503.1082. ^{1}H-NMR δ: 1.93-1.99 (2H, m), 2.29 (1H, dd, *J*=15.2, 3.9 Hz), 2.43 (1H, dd, *J*=16.7, 1.6 Hz), 2.69-2.75 (3H, m), 3.65 (1H, m), 3.74 (3H, s), 4.21 (1H, m), 4.73 (1H, m), 5.97 (1H, dd, *J*=10.3, 0.8 Hz), 6.38 (1H, dd, *J*=10.3, 2.0 Hz), 7.20 (1H, d, *J*=8.4 Hz), 7.55 (2H, m), 7.66 (1H, m), 7.98 (2H, m).

ii) Large scale preparation. To a cooled (10 °C) solution of **7** (20.0 g, obtained as above) in CH_2Cl_2 was added TFA (70 mL) slowly and the resulting mixture was kept stirring at rt for 3 h. The mixture was worked up as above and the residue thus obtained (15.2 g) was purified by SiO_2 column (350 g, AcOEt / *n*-hexane = 1 / 1.5) to afford **9** (9.89 g, 78 % from **5**).

B) *rac*-Methyl (2R*, 3aS*, 6aS*, 10aS*)-9-benzenesulfonyl-3-trifluoroacetyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline-2-carboxylate (10a) and *rac*-Methyl (2S*, 3aS*, 6aS*, 10aS*)-9-benzenesulfonyl-3-trifluoroacetyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline-2-carboxylate (10b).

i) Small scale preparation. the β-COOMe-*NH*-enone (**9a**, 102 mg, 0.2 mmol) and DABCO (22 mg, 0.2 mmol) in DME (3 mL) was stirred at rt for overnight. The mixture was then poured into a 5 % AcOH under ice-cooling and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the dried solvent gave a residue, which was purified by SiO_2 column (SiO_2: 1.5 g, $CHCl_3$ / AcOEt = 1 / 1.5) to afford the desired tricyclic ketone (**10a**, 75 mg, 74 %) as colorless crystals, mp 103-104.5 °C (CH_2Cl_2-petroleum ether). IR cm^{-1}: 2950, 1745, 1720, 1665, 1355, 1170. FABMS *m/z*: 503 (MH^+, 57). HRFABMS Calcd for $C_{21}H_{22}F_3N_2O_7S$: 503.1100. Found: 503.1115. ^{1}H-NMR δ: 1.85-2.01 (2H, m), 2.25-2.44 (5H, m), 3.03 (1H, dd, *J*=13.7, 1.3 Hz), 3.24 (1H, dd, *J*=16.5, 5.3 Hz), 3.70 (3H, s), 3.77 (1H, m), 4.23 (1H, m), 4.81-4.85 (2H, m), 7.55 (2H, m), 7.76 (1H, m), 7.97 (2H, m).

The α-COOMe-*NH*-enone (**9b**, 201 mg, 0.4 mmol) and DABCO (44 mg,0.4 mmol) in DME (5 mL) was stirred at rt for overnight. The mixture was then poured into a 5 % AcOH under ice-cooling and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the dried solvent gave a residue, which was purified by SiO_2 column (SiO_2: 2.0 g, $CHCl_3$ / AcOEt = 1 / 1.5) to afford the the desired tricyclic ketone (**10b**, 170 mg, 85 %) as colorless crystals, mp 209-210 °C (CH_2Cl_2-Et_2O). IR cm^{-1}: 2950, 1760, 1720, 1680, 1350, 1170. FABMS *m/z*: 503 (MH^+ 73). HRFABMS *m/z*: Calcd for $C_{21}H_{22}F_3N_2O_7S$: 503.1100. Found: 503.1103. ^{1}H-NMR δ 1.66-1.79 (1H, m), 2.15 (3H, m), 2.42-2.54 (2H, m), 2.63-3.04 (3H, m), 3.76 (3H, m), 3.80 (2/3H, m), 3.90 (1/3H, m), 4.07 (1/3H, m), 4.18 (2/3H, m), 4.48 (2/3H, dd, *J*=11.1, 6.5 Hz), 4.68 (1H, m), 4.81 (1/3H, t, *J*=8.1 Hz), 7.54 (2H, m), 7.67 (1H, m), 7.97 (2H, m).

ii) Large scale preparation. A mixture of the *NH*-enone (**9**, 1.26 g, 2.5 mmol, diastereomeric mixture) and DABCO (280 mg, 2.5 mmol) in DME (20 mL) was stirred at rt for overnight. The mixture was then poured into a 5 % AcOH (30 mL) under ice-cooling and

extracted with AcOEt (~150 mL). The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the dried solvent gave a residue (1.25 g), which was purified by SiO_2 column (SiO_2: 300 g, $CHCl_3$ / AcOEt = 1 / 1.5) to afford the the desired tricyclic ketone (**10**, 1.07 g, 85 %, diastereomeric mixture) as a white amorphous solid, along with the recovered **9** (195 mg, 15 %).

C) *rac*-Methyl (2R*, 3aS*, 6aS*, 10aS*)-9-benzenesulfonyl-3-trifluoroacetyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline-2-carboxylate 5-ethylene ketal (11a) and *rac*-Methyl (2S*, 3aS*, 6aS*, 10aS*)-9-Benzenesulfonyl-3-trifluoroacetyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline-2-carboxylate 5-Ethylene Ketal (11b).

A mixture of the tricyclic ketone (**10**, 5.00 g, 1.0 mmol), ethylene glycol (5 mL), and PPTS (500 mg) in dry benzene (150 mL) was heated under reflux for 1.5 h by the aid of a Dean-Stark apparatus. Benzene distilled off into a separator was removed at every 30 min to ensure the reaction. The mixture was then cooled to rt and solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (100 mL) and saturated aq. $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the dried solvent gave a residue (6.0 g), which was recrystallized from CH_2Cl_2-Et_2O to afford the desired ketal with 2β-COOMe configuration (**11a**, 1.64 g) as colorless crystals. Further recrystallization of this mother liquor furnished **11a** (1.09 g, totaling **11a**. 2.73 g, 50 %). Concentration of mother liquor then gave the nearly pure isomeric ketal with 2α-COOMe configuration (**11b**, 2.53 g, 46 %). **11a**: mp. 227-230 °C ($CHCl_3$-AcOEt decomp.). IR cm^{-1}: 1730, 1670. FABMS *m/z*: 547 (MH^+, 86). HRFABMS Calcd for $C_{23}H_{26}F_3N_2O_8S$: 547.1362. Found: 547.1351. ^{1}H-NMR δ 1.37 (1H, dd, *J*=15.2, 4.4 Hz), 1.52 (1H, d, *J*= 13.4 Hz), 1.65 (1H, ddd, *J*=13.4, 3.9, 2.2 Hz), 1.90 (1H, m), 2.15-2.59 (3H, m), 2.57 (1H, dd, *J*=13.2, 8.3 Hz), 2.81 (1H, ddd, *J*=15.2, 4.2, 2.2 Hz), 3.72 (3H, s), 3.73-3.39 (5H, m), 4.20 (1H, m), 4.70 (2H, m), 7.55 (2H, m), 7.66 (1H, m), 7.99 (2H, m). Anal. Calcd for $C_{23}H_{25}F_3N_2O_8S$: C, 50.55. H, 4.61. N, 5.13. Found: C, 50.32. H, 4.53. N, 4.98. **11b**: mp. 164-168 °C (MeOH). IR cm^{-1}: 2950, 1740, 1680, 1350, 1170. FABMS *m/z*: 547 (MH^+, 100). HRFABMS Calcd for $C_{23}H_{26}F_3N_2O_8S$: 547.1362. Found: 547.1364. ^{1}H-NMR δ: 1.59-1.74 (4/3H, m), 1.85-1.91 (5/3H, m), 1.59-2.34 (5H, m), 2.58 (2/3H, dd, *J*=13.3, 9.3 Hz), 2.77 (1/3H, dd, *J*= 13.3, 9.3 Hz), 3.73 (3H, s), 3.78-4.08 (6H, m), 4.19 (2/3H, dd, *J*=11.6, 5.6 Hz), 4.44 (1/3H, dd, *J*=11.6, 5.6 Hz), 4.77 (2/3H, t, *J*=9.3 Hz), 4.80 (1H, t, *J*=10.0 Hz), 7.50 (2H, m), 7.62 (1H, m), 7.95 (2H, m).

Conversion of the D-A Adduct (8) to the Tricyclic Intermediate (10)

By TMSOTf

i) In CH_2Cl_2; To a solution of the *N*-MOM enone (**8**, 100 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added TMSOTf (0.2 mL, 0.81 mmol) slowly and the mixture was kept stirring at rt for 24 h. The mixture was then quenched by the addition of saturated aq. $NaHCO_3$ (5 mL) and extracted with AcOEt (20mL x 2). Combined organic layer was washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a crude residue, which was purified by SiO_2 column (*n*-hexane / AcOEt =1 / 2) to afford the cyclized material (**10**, 37.1 mg, 41.1%).

ii) In CH_3CN; To a solution of the *N*-MOM enone (**8**, 100mg, 0.18 mmol) in CH_3CN (2 mL) was added TMSOTf (0.2 mL, 0.81 mmol) slowly and the mixture was kept stirring at rt for 24 h. The mixture was then quenched by the addition of saturated aq. $NaHCO_3$ (5 mL) and extracted with AcOEt (20 mL x 2). Combined organic layer was washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a crude residue, which was purified by SiO_2 column (*n*-hexane / AcOEt = 1 / 2) to afford the cyclized material (**10**, 40.0 mg, 44.3%).

By TESOTf

To a cooled suspension of the *N*-MOM enone (**8**, 1.14 g, 2.08 mmol), SiO_2 (Merck SiO_2 60, 2.20 g), and Na_2SO_4 (2.20 g) in toluene (40 mL) was added TESOTf (1.89 mL, 8.35 mmol, 4.6 eq) slowly and the mixture was kept stirring at rt. for 12 h. The organic layer was carefully decantated and the residue was extracted with AcOEt (40 mL x 3). Combined organic layers were washed with brine

and dried over $MgSO_4$. Concentration of the solvent gave a crude residue (4.50 g), which was purified by SiO_2 column (*n*-hexane / AcOEt = 1 / 2) to afford the cyclized material (**10**, 2.06 g, 78%).

Conversion of 11a to the Ketal-alcohol (13) *via* 12

A) *rac*-Methyl (2R*, 3aS*, 6aS*, 10aS*)-3-trifluoroacetyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline-2-carboxylate 5-Ethylene Ketal (12).

To a cooled (-65 °C) and stirred solution of the ketal (**11a**, 1.00 g, 1.83 mmol) in DME (200 mL) was added dropwise a solution of sodium anthracenide (6 mL, prepared from 1.2 g of anthracene and 140 mg of Na by Johnson's protocol)[10] and the mixture was kept stirring at this temperature for 1 min, to which was added saturated aq. $NaHCO_3$ (100 mL). After warming to rt, the mixture was extracted with AcOEt (~300 mL) and the organic layer was washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gave a residue (1.50 g), which was purified by SiO_2 column (SiO_2: 20 g, $CHCl_3$ then 5% MeOH in AcOEt) to afford the deprotected amide (**12**, 617 mg, 83 %) as colorless crystals, along with the recovered **11a** (113 mg, 11 %), mp. 254.5-255.5 °C ($CHCl_3$-*n*-hexane). IR cm^{-1}: 3400, 2950, 1740, 1660, 1650. FABMS *m/z*: 407 (MH^+, 100). HRFABMS Calcd for $C_{17}H_{22}F_3N_2O_6$: 407.1430. Found: 407.1431. ^{1}H-NMR δ: 1.65 (2H, m), 1.73 (1H, d-like), 1.81 (1H, t, *J*=13.2 Hz), 2.16-2.27 (3H, m), 2.59 (1H, dd, *J*=12.9, 8.0 Hz), 3.07 (1H, dt, *J*=15.4, 3.3 Hz), 3.30 (1H, m), 3.47 (1H, m), 3.76 (3H, s), 3.73-4.13 (4H, m), 4.76 (1H, t, *J*=9.4 Hz), 4.87 (1H, t, *J*=9.4 Hz), 6.04 (1H, br s).

B) *rac*-(2R*, 3aS*, 6aS*, 10aS*)-3-(*t*-butoxycarbonyl)-2-hydroxymethyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline 5-Ethylene Ketal (13).

To a stirred solution of **12** (184 mg, 0.45 mmol) in THF (40 mL) was added $LiBH_4$ (60 mg, 2.7 mmol), and $B(OMe)_3$ (0.04 mL) at rt and the mixture was kept stirring for 6 h. After quenching by the addition of 1 *N* NaOH (5 mL) and stirring for 10 min, $(BOC)_2O$ (654 mg, 3 mmol) was added to the mixture and stirring was continued for overnight. The mixture was concentrated to a syrupy residue, to which was added brine and extracted with CH_2Cl_2 (~100 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a residue (440 mg). Purification by SiO_2 column chromatography (SiO_2: 6 g, AcOEt / MeOH = 20 / 1) furnished the alcohol (**13**, 150 mg, 87 %) as colorless crystals, mp. 184.5-185.5 °C (CH_2Cl_2-AcOEt). IR cm^{-1}: 3400, 2950, 1655. FABMS *m/z*: 383 (MH^+, 63), 327 (56), 283 (100). HRFABMS Calcd for $C_{19}H_{31}N_2O_6$: 383.2182. Found:383.2177. ^{1}H-NMR δ: 1.48 (9H, s), 1.53-1.91 (5H, m), 2.15-2.49 (3H, m), 2.48 (1/2H, d-like, *J*=10.6 Hz), 2.95 (1/2H, br), 3.30-3.45 (2H, m), 3.67-4.11 (7H, m), 5.23 (1H, d-like *J*= 9.7 Hz), 6.36 (1H, brs).

6-(1-*t*-Butoxycarbonyl-2, 3, 4, 5-tetrahydro-2-pyrrolyl)-5-hexenoic Acid (16)

To a stirred solution of *L*-*N*-*t*-butoxycarbonylproline methyl ester (3.00 g, 13.1 mmol) in anhydrous toluene was slowly added diisobutylaluminum hydride (DIBAL), (1 *M* toluene sol., 17.5 mL, 17.5 mmol) at -78 °C. After stirring for 1.5 h, 1 *N* $KHSO_4$ (10 mL) was added to the mixture, and warmed to rt. After adding AcOEt until the mixture became clear, 1 *N* $KHSO_4$ and brine was added and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue (3.0 g), which was purified by column chromatography (SiO_2: 30 g, AcOEt / *n*-hexane = 1 / 3) to furnish the aldehyde (2.60 g, quant) as a colorless oil. ^{1}H-NMR δ : 1.44-1.49 (9H, m) 1.86-2.12 (4H, m), 3.47-3.55 (2H, m), 4.05 (1/2H, m), 4.21 (1/2H, m), 9.41 (1/2H, s), 9.56 (1/2H, s).

To a stirred suspension of 4-carboxybutyltriphenylphosphonium bromide (8.86 g, 20 mmol) in dry toluene (50 mL) was added a toluene (40 mL) solution of $KN(TMS)_2$ (1.055 g, 5.3 mmol) under argon and stirring was continued for 60 min to form an orange ylide solution. To this was slowly added a toluene (5 mL) solution of the aldehyde (2.59 g, 13 mmol) by a cannula. After stirring at rt for 10 min, the mixture was quenched by the addition of brine and extracted with water. The aqueous layer was cooled in an ice bath and 1 *N* $KHSO_4$ was added to adjust to pH=3. The mixture was extracted with AcOEt and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue (5.75 g), which was purified by column chromatography (SiO_2: 100 g, AcOEt

/ *n*-hexane = 2 / 1) to furnish the carboxylic acid (**16**, 2.38 g, 65%) as a pale yellow oil. IR cm^{-1}: 2690, 1730, 1690. FABMS *m/z:* 283 (M^+, 100), 58 (100). HRFABMS Calcd for $C_{15}H_{26}NO_4$ (MH^+): 284.1861. Found: 284.1856. ^{1}H-NMR δ (a mixture of isomers: *Z* / *E* = 10 / 1) 1.43 (9H, s), 1.58-1.91 (5H, m), 2.02-2.20 (3H, m), 2.33 (2/11H, t, J=7.7 Hz), 2.38 (20/11H, t, J=7.0 Hz), 3.34-4.40 (2H, m), 4.23 (1/11H, brs), 4.49 (10/11H, m), 5.28-5.40 (2H, m).

5-Oxo-1, 2, 3, 5, 6, 7, 8, 10a-octahydropyrrolo[1, 2-*a*]azocine (17)

A) via PFP ester. To an ice-cooled and stirred solution of the *N*-BOC acid (**16**, 851.9 mg, 3.01 mmol) and pentafluorophenol (562.3 mg, 3.06 mmol) in anhydrous AcOEt (17 mL) was added an AcOEt (5 mL) solution of DCC (630.4 mg, 3.06 mmol) and the whole was stirred under cooling for 2.5 h. After adding further amount of DCC (59.6 mg, 0.29 mmol), stirring was continued for overnight to warm the mixture slowly to rt. Filtration of the insoluble precipitate followed by the concentration gave a residue, which was purified by SiO_2 column ($CHCl_3$ / *n*-hexane = 3 / 1) to furnish the corresponding PFP ester (1.35g, quantitative, *E* / *Z* = 1 / 10) as a colorless oil. IR cm^{-1}: 2950, 1570, 1690. FABMS *m/z:* 450 (MH^+, 37), 394 (56), 348 (75). HRFABMS Calcd for $C_{21}H_{25}F_5NO_4$: 450.1704. Found: 450.1704. ^{1}H-NMR δ (a mixture of isomer *E* / *Z* =1 / 10): 1.44 (9H, s) 1.60 (4H, m), 1.81-1.92 (4H, m), 2.08-2.65 (2H, m), 2.70 (2H, m), 3.20 (2/11H, m), 3.39 (20/11H, m), 4.25 (1/11H, m), 4.47 (10/11H, m), 5.37-5.44 (2H, m).

To a stirred solution of the PFP ester (157.4 mg, 0.35 mmol, prepared above) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL) and stirring was continued under ice cooling for 30 min. After removing the solvents under reduced pressure, the residue (TFA salt) obtained was taken into anhydrous dioxane (15 mL) and added slowly through a dropping funnel to a heated (90 °C) solution of DMAP (110 mg, 0.9 mmol) in anhydrous dioxane (160 mL) over a period of 1.5 h. After the completion of addition, heating was continued for 2 h. Being cooled to rt, the solvent was removed to give a residue, which was purified by SiO_2 column (SiO_2: 3.5 g, AcOEt) to furnish the bicyclic azocine (**17**, 41.2 mg, 78 % based on the *Z* isomer) as a colorless oil. $[\alpha]_D^{22}$ -64.8 (*c* 0.94, $CHCl_3$). IR cm^{-1}: 2950, 1620. FABMS *m/z:* 165 (MH^+, 60), 136 (100). HRFABMS Calcd for $C_{10}H_{16}NO$ (MH^+): 166.1232. Found: 166.1239. ^{1}H-NMR δ: 1.67-1.99 (6H, m), 2.15-2.33 (3H, m), 2.66 (1H, td, *J*=12.2, 6.1 Hz), 3.47 (1H, m), 3.64 (1H, m), 4.45 (1H, brs), 5.44 (1H, ddd, *J*=11.9, 3.4, 1.8 Hz), 5.67 (1H, m). ^{13}C-NMR δ: 22.85, 23.23, 25.82, 33.21, 33.73, 46.31, 59.69, 127.51, 132.78, 172.98.

B) by DPPA. To a stirred solution of *N*-BOC acid (**16**, 300 mg, 1.06 mmol, *E* / *Z*=1 / 10 mixture) in CH_2Cl_2 (3 mL) was added TFA (1 mL) and stirring was continued for 30 min. After removing the solvents under reduced pressure, the residue obtained (TFA salt) was taken into DMF (530 mL, to form a 2 m*M* solution) and cooled in an ice-bath. To this solution was added DPPA (538 mg, 2.12 mmol) and Et_3N (428 mg, 4.24 mmol) and the mixture was kept at 5 °C for 3 days. To ensure completion of the reaction, the mixture was then stirred at rt for 1 day. After evaporation of the solvents, the crude residue (1.30 g) was chromatographed on SiO_2 (13 g, AcOEt) to give the desired bicyclic azocine (**17**, 159 mg, quantitaive based on the *Z* isomer) as a colorless oil.

***rac*-(2R*, 3aS*, 6aS*, 10aS*)-3-(*t*-butoxycarbonyl)-2-formyl-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydro-pyrrolo[2, 3-*i*]isoquinoline 5-Ethylene Ketal (14).**

To a well stirred suspension of pyridinium chlorochromate (PCC, 1.35 g, 6.24 mmol), NaOAc (1.02 g, 12.48 mmol) and neutral Al_2O_3 (140 mg, Wohlem, oven-dried) in dry CH_2Cl_2 (20 mL) was added a CH_2Cl_2 (10 mL) solution of the alcohol (**13**, 400 mg, 1.04 mmol) and the mixture was kept stirring at rt for 0.5 h. After adding a proper portion of Celite, the mixture was diluted with ether (40 mL) and filtered through a pad of Celite to remove the insoluble solid. Most of the solvents were removed under reduced pressure to leave an oil, which was purified by column chromatography (SiO_2:12 g, AcOEt / MeOH = 40 / 1) to afford the aldehyde (**14**, 265 mg, 67 %) as a colorless solid, mp. 214-218 °C ($CHCl_3$-Et_2O). IR cm^{-1}: 3400, 2950, 1720, 1690, 1650. FABMS *m/z*: 381 (MH^+, 19), 325 (100), 281 (M-BOC, 94). HRFABMS Calcd for $C_{19}H_{29}N_2O_6$: 381.2026. Found: 381.2024. ^{1}H-NMR δ: 1.43 (17H, m), 2.45 (1/2H, dd, *J*=13.1, 4.2 Hz), 2.52 (1/2H, q, *J*=7.1 Hz), 3.28-3.44 (1/2H, m), 3.85-3.99 (4H, m), 4.12 (1/2H, dd, *J*=8.2, 2.6 Hz), 4.22 (1/2H, dd, *J*=8.3, 3.3 Hz), 4.32 (1/2H, dd, *J*=10.1, 4.4 Hz), 4.52 (1/2H, dd, *J*=7.1, 4.6 Hz, C2-H, or C3a-H), 6.02 (1/2H, brs), 6.09 (1/2H, brs), 9.47 (1/2H, s), 9.59 (1/2H, s).

***rac*-(2R*, 3aS*, 6aS*, 10aS*)-3-(*t*-Butoxycarbonyl)-2-(*Z*)-(5-carboxy-1-pentenyl)-5, 10-dioxo-1, 2, 3, 3a, 4, 5, 6, 6a, 7, 8, 9, 10-dodecahydropyrrolo[2, 3-*i*]isoquinoline 5-Ethylene Ketal (15).**

To a stirred suspension of 4-carboxybutyltriphenylphosphonium bromide (1.18 g, 2.66 mmol) in dry toluene (25 mL) was added a toluene (15 mL) solution of $KN(TMS)_2$ (1055 mg, 5.3 mmol) and the stirring was continued for 40 min to form an orange ylide solution. To this mixture was added a THF (15 mL) solution of the aldehyde (**14**, 290 mg, 0.76 mmol) by a syringe. After stirring at rt for 20 min, the mixture was quenched by the addition of water and 1 N NaOH to adjust to pH=~10. This basic aqueous layer was separated carefully, to which was added AcOEt (50 mL) and cooled in an ice-bath. After the careful addition of 1 N $KHSO_4$ solution to adjust to pH=~4, the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$-Na_2SO_4. Evaporation of the solvent gave the crude acid (**15**, 684 mg), which was directly used in the next reaction.

***rac*-(7aS*, 10aS*, 14aS*, 15aR*)-3, 4, 5, 6, 8, 9, 10, 10a, 11, 12, 13, 14, 15, 15a-Tetradecahydro-7a*H*-azocino[1, 2-*a*]pyrido[3, 4-*d*]indole-6, 9, 14-trione 9-Ethylene Ketal (19).**

A) via PFP ester (18). To an ice-cooled and stirred solution of the above crude acid (**15**, 330 mg, out of 684 mg obtained above) and pentafluorophenol (363 mg, 1.97 mmol) in AcOEt (6 mL) and CH_2Cl_2 (6 mL) was added DCC (409 mg, 1.99 mmol) and stirring was continued for 5 h under cooling. The mixture was kept stirring for overnight and gradually warmed to rt. After the filtration of the insoluble precipitate, the filtrate was concentrated to give a residue (1.0 g), which was purified by column chromatography (SiO_2: 15 g, $CHCl_3$ / AcOEt = 4 / 1) to give the PFP ester (**18**, 210 mg, 91 % from the aldehyde **14**) as a colorless amorphous solid. IR (neat) cm^{-1}: 3300, 2950, 1785, 1680, 1650. FABMS *m/z*: 631 (MH^+, 11), 531 (M-BOC, 100). HRFABMS Calcd for $C_{30}H_{36}N_2O_7F_5$: 631.2442. Found:631.2441. ^{1}H-NMR (C_6D_6) δ (a mixture of isomers: *Z* / *E* = 5 / 2): 0.95 (1H, m), 1.45-2.95 (23H, m), 2.37 (1H, m), 2.64 (1H, m), 3.50-3.72 (4H, m), 3.91 (1H, dd, *J*=13.4, 7.2 Hz), 4.25 (2/7H, q, *J*=8.6 Hz), 4.53 (5/7H, q, *J*=8.6 Hz), 4.94-5.19 (2H, m), 5.22 (2/7H, dd, *J*= 18.4, 8.8 Hz), 5.29 (5/7H, t, *J*=8.6 Hz), 6.34 (1H, brs).

To a stirred solution of the PFP ester (**18**, 144 mg, 0.23 mmol, mixture of *E* and *Z* isomers) in CH_2Cl_2 (6 mL) was added TFA (1 mL) under ice cooling and the mixture was stirred for 20 min. After removing the solvents under reduced pressure, the residue (TFA salt) obtained was taken into anhydrous dioxane (15 mL) and added slowly through a dropping funnel to a heated (80 °C) solution of DMAP (84 mg, 0.69 mmol) in anhydrous dioxane(100 mL) over a period of 0.5 h with stirring. After the completion of addition, heating was continued for 1 h at this temp. The mixture was cooled to rt and additional DMAP (49 mg, 0.4 mmol) was delivered and stirred at rt for overnight. Evaporation of the solvent gave a residue, which was purified by column chromatography (SiO_2: 3 g, AcOEt / acetone = 1 / 2) to furnish the crude **19** (71 mg). Recrystallization of this material from CH_2Cl_2-AcOEt gave a pure **19** (33 mg, 58 % from Z-ester) as a colorless needles. mp > 300 °C. IR cm^{-1} : 3300, 2950, 1670, 1620. FABMS *m/z*: 347 (MH^+, 100). HRFABMS Calcd for $C_{19}H_{27}N_2O_4$: 347.1971. Found: 347.1966. ^{1}H-NMR δ: 1.58 (1H, m), 1.62 (1H, m), 1.68 (1H, br), 1.73 (1H, dd, *J*=14.8, 4.6 Hz), 1.81 (1H, t, *J*=13.2 Hz), 1.89 (1H, m), 2.02 (1H, m), 2.06 (1H, dd, *J*=12.8, 9.3 Hz), 2.18 (1H, m), 2.25 (2H, m), 2.34 (1H, dd, *J*=12.8, 7.3 Hz), 2.38 (1H, m), 2.64 (1H, td, *J*=12.3, 5.3 Hz), 3.19 (1H, ddd, *J*=14.8, 4.6, 2.2 Hz), 3.29 (1H, dd, *J*=12.3, 5.0 Hz), 3.44 (1H, m), 3.84-4.01 (4H, m), 4.62 (1H, br), 4.78 (1H, t, *J*=4.6 Hz), 5.46 (1H, ddd, *J*=11.9, 3.8, 1.3 Hz), 5.61 (1H, m), 5.90 (1H, brs). ^{13}C-NMR δ 23.7 (C_3), 24.2(C_4), 24.3 (C_{11}), 31.5 (C_8), 32.8 (C_{10a}), 33.8 (C_5), 36.9 (C_{10}), 38.4 (C_{12}), 43.3 (C_{15}), 48.9 (C_{14a}), 58.6 (C_{15a}), 61.4 (C_{7a}), 64. 0 (ketal), 64.9 (ketal), 107.9 (C_9), 126.4 (C_2), 132.6 (C_1), 173.0 (C_{14}), 173.7 (C_6). Anal. Found C 65.81, H 7.43, N 7.99. $C_{19}H_{26}N_2O_4$ requires C 65.88, H 7.56, N 8.09.

B) by DPPA. To a stirred solution of the crude acid (**15**, 250 mg, out of 684 mg obtained above) in CH_2Cl_2 (5 mL) was added TFA (1 mL) and stirring was continued for 30 min. After removing the solvents under reduced pressure, the residue obtained (TFA salt) was taken into DMF (800 mL, to form a 1.56 m*M* solution) and cooled in an ice-bath. To this solution was added DPPA (688 mg, 2.5 mmol) and Et_3N (505 mg, 5 mmol) and the mixture was kept at 5 °C for 2 weeks. After evaporation of the solvents, the crude residue (1.45 g) was chromatographed on SiO_2 (15 g, AcOEt) to give a crude **19** (91 mg) which was recrystallized from CH_2Cl_2-AcOEt to afford the pure **19** (16 mg, 17 % from the aldehyde **14**).

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