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Laboratory note

Synthesis of cytotoxic 1-polyhydroxyalkyl-β-carboline derivatives

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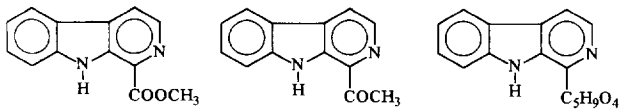
Summary — *dl*-1-(1-Oxo-3,4-*threo*-3,4,5-trihydroxy-1-pentyl)-β-carboline **16a** was synthesized from 1-formyl-β-carboline in 13 steps. The prepared compound is one of the diastereomers of an alkaloid **3** produced by the inter-generic somatic hybrid cell culture of *Rauwolfia serpentina* Benth and *Rhazya stricta* Decaisne (family: Apocynaceae). The N9-benzyl and N9-methyl derivatives **16b,c** were also prepared. The final compounds and some of the intermediates showed cytotoxic activity against human promyelocytic leukemia cells HL 60 and/or human diploid embryonic lung fibroblast cells.

β-carboline alkaloids / polyhydroxyalkyl derivatives / Wittig reaction / stereoselective synthesis / N9-benzyl- and N9-methyl-derivatives / cytotoxic activity

Introduction

Numerous alkaloids of the β-carboline-type with various substituents at the alpha position display growth inhibitory activity, such as: Eudistomins (antibiotic, antiviral agents) [1, 2]; Lavendamycine (antitumor, antibiotic agent) [3, 4]; Oxopropalines (cytocidal agents) [5, 6]; Manzamine C (antitumor agent) [7]; and others [8]. We recently isolated a new β-carboline alkaloid **3** together with other known indole alkaloids **1a**, **2** (fig 1) from a plant cell suspension culture which is produced from the hybrid cells of *Rauwolfia serpentina* with *Rhazya stricta* [9]. The new alkaloid, with the molecular formula $C_{16}H_{16}N_2O_{14}$, was elucidated to be a 1-polyhydroxyalkyl-β-carboline derivative **3** from PMR and other spectral analysis. However, the stereochemistry of alkaloid **3** is not yet explored. We initially planned the synthesis of compound **3** possessing the 3,4-dihydroxy in the *erythro* form.

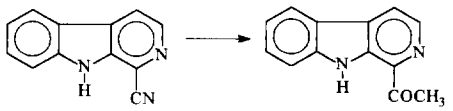


1a **2** **3**

Fig 1.

Chemistry

Here we would like to report a synthetic procedure by which alkaloids **1a**, **2** as well as **16a**, one of the diastereomers of alkaloid **3**, could be prepared. Alkaloid **1a** was prepared by condensation of tryptamine with glycoxylic acid [10] followed by esterification [1, 2] and successive dehydrogenation [11]. Synthesis of alkaloid **2** was provided by the Grignard reaction of methylmagnesium bromide, which reacted with 1-cyano-β-carboline **4** [1, 2] in THF (fig 2) followed by mild acid hydrolysis of the intermediate, giving 1-acetyl-β-carboline **2**.



4 **2**

Fig 2.

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Compound **1a** was chosen as a building block for this synthetic task. The N9-methyl or -benzyl derivatives **1b,c** were respectively obtained by *N*-alkylation of **1a** with methyl iodide or benzyl chloride in the presence of NaH [12]. The reduction of the ester group of **1a–c** into 1-formyl-β-carboline derivatives **5a–c**, was conducted using diisobutylaluminum hydride [13, 14]. Stepwise build-up of the carbon unit side chain was provided by the Grignard reaction of **5a–c** with allylmagnesium bromide to afford the alcohols **6a–c**. Protection of the resultant alcohol as the *tert*-butyldimethylsilyl (TBS) ether [15] quantitatively afforded **7a–c**. A *tert*-butoxycarbonyl (BOC) group [16] was introduced at N9 of **7a** to avoid the cyclization between the aldehyde group, which would be formed in the subsequent reaction, and the N9 function. Oxidation of **7b–d** with osmium tetroxide [17] gave the dihydroxy derivatives **8b–d**. Oxidative cleavage of the vicinal diol in **8b–d** followed by immediate Wittig alkenation in CH_2Cl_2 stereoselectively afforded the corresponding *E*-alkene **10b–d**. In PMR spectra of **10b–d** the proton of C-3' of the substituted pentene side chain was observed down-field around δ 7.21 (J = 15.5; *trans* coupling) and that of C-4 observed around δ 6.08 (J = 15.5). The geometry of the alkene (for example **10d**) was further confirmed by nuclear overhauser effect (NOE) experiments. Thus, irradiation of the proton of C-4 led to enhancement (3.10%) of that of C-2, and (0.77%) of that of C-1, which revealed an *E* configuration. Treatment of **10d** with HCOOH to remove the (BOC) group provided **10a** in 85% yield. Oxidation of **10a–c** with OsO_4 afforded the diol esters **11a–c**. The diol esters **11a–c** were protected as the corresponding acetonides **12a–c**, then reduced to the primary alcohols **13a–c**. The reduction was done with $LiBH_4$ [18, 19] in diethyl ether due to its greater selectivity than $LiAlH_4$ or DIBAL-H and gave higher yields. Deprotection of the *O*-silyl ether with tetra(*n*-butyl)ammonium fluoride [20] afforded **14a–c**. Oxidation of **14a–c** of the ketones using activated MnO_2, then heating with HCl and methanol gave the final compounds **16a–c**. Obviously, for compounds **11a–c**, **12a–c**, **13a–c** and **14a–c**, when obtained as mixtures of diastereoisomers, both isomers are described. Otherwise, a major isomer could be obtained from the reaction mixture.

Results and discussion

The synthetic compound **16a** exhibited UV, MS and ^{13}C-NMR in accord with those of the natural compound but ^{1}H-NMR showed differences in the configuration regarding the 3,4-dihydroxy groups. Wittig reaction resulted in trans compounds **10b–d** and the method of addition selectively gives the *threo* form of the final compounds **16a–c**. Thus, the synthetic compound was *dl*-1-[1-oxo-3,4-*threo*-3,4,5-trihydroxy-1-pentyl]-β-carboline and is the diastereomer of the natural compound (alkaloid **3**) which now appeared to be the *erythro* isomer.

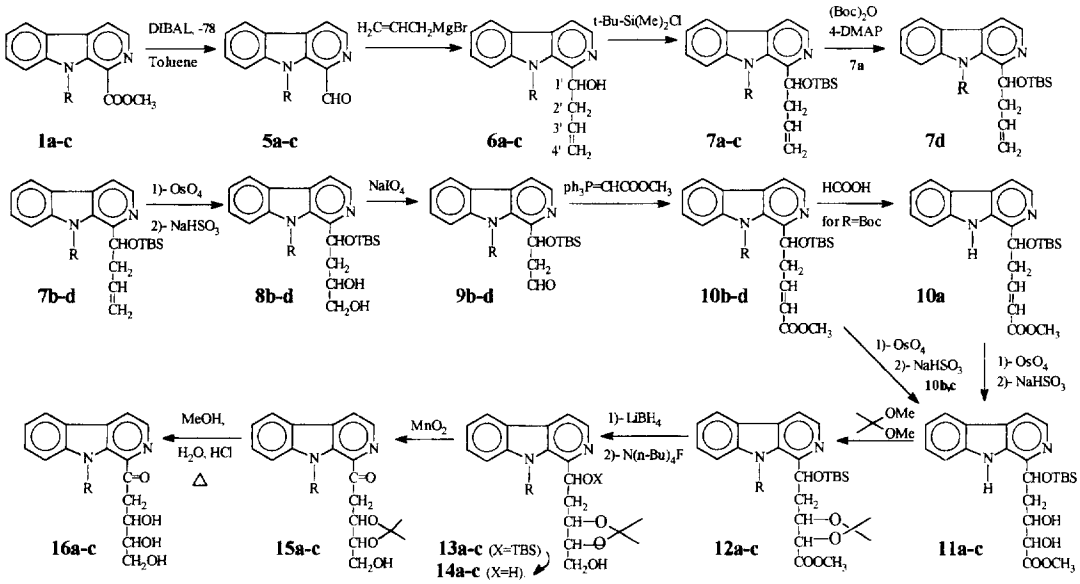
Standard cell-culture techniques were adopted by the Research Institute of TOSOH Co Ltd, Japan, to determine the 50% effective concentrations of the tested compounds (μM/mL) that arrest viral (EC_{50}) and cellular (EE_{50}) growth. Several cell lines were used. Azidothymidine (AZT) was used as a reference with the following activity concentrations: EC_{50} = 0.0004 μM/mL and CC_{50} = 131 μM/mL. Compounds **5a–c**, **8b–d**, **11b,c** and **16a–c** did not show antiviral activities against influenza virus, respiratory syncytial virus, human immunodeficiency virus, herpes simplex virus type 1 and 2, and human cytomegalovirus. However, some compounds showed cytotoxic activity against human promyelocytic leukemia cells HL60 (CC_{50} (50% cytotoxic concentration based on the inhibition of cell growth), **5a**; 1.8 μM, **5b**; 0.36 μM, **5c**; 1.7 μM, **8b**; 5.5 μM, **8c**; 4.4 μM, **11b**; 2.0 μM, **16a**; 8.6 μM) and against human diploid embryonic lung fibroblast (HEL) cells (CC_{50}, **5a**; 4.0 μM, **5b**; 0.9 μM, **5c**; 0.8 μM, **8c**; 2.0 μM, **8d**; 4.0 μM, **11b**; 4.0 μM, **16b**; 8.8 μM, **16c**; 10.2 μM).

Experimental protocols

Melting points (mp) were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were measured with a Hitachi-260 spectrophotometer, and UV spectra were measured in methanol with a Hitachi-U3400 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM A-500 (500 and 125.65 MHz) respectively with a JEOL JNM A-500 using tetramethylsilane as internal standard, chemical shifts are recorded in δ values. Mass spectra were taken with a Hitachi RMU-6E and RMU-7M or a JEOL JMS-AM20 (LR-EI) and GEOL JMS-HX-110A spectrometer. Thin-layer chromatography was performed on Merck precoated Silica gel 60 F_{254} plates. Column chromatography was carried out on Merck Silica gel 60 (230–400 mesh for flash chromatography) pre-packed columns [silica gel, Kusano CPS-HS-221-05 (for medium-pressure column chromatography)], and Merck Al_2O_3 90 (activity II–III). The ester **1a** was prepared according to reported methods [1, 2, 10, 11, 21].

1-Acetyl-β-carboline **2**

A solution of methylmagnesium bromide (2.1 equiv, 0.94 mmol/1 mL) was added over 10 min to a solution of 1-cyano-β-carboline **1** (1.0 equiv) in dry THF, cooled in an ice–water bath. The reaction mixture was stirred at room temperature for 2 h then treated with a saturated NH_4Cl solution, diluted with water, acidified, shaken briefly, basified with aqueous ammonia, and extracted with $CHCl_3$. Workup and purification by column chromatography (SiO_2, $CHCl_3$) gave **2** as pale yellow needles in 73% yield. All physical data (mp, EA) and spectral data (MS, UV, PMR) were identical with those of the natural compound and reported data [22, 23].



a; (R= H), **b**; (R= CH_3), **c**; (R= $CH_2C_6H_5$); **d**; (R= Boc, $COOC(CH_3)_3$), DIBAL= diisobutylaluminum hydride. TBS= t-butyldimethylsilyl.

Fig 3.

*Preparation of the esters **1b,c***

General procedure: the ester **1a** (1.0 g, 4 mmol) was dissolved in hexamethylphosphoramide and cooled in an ice bath. NaH (60% dispersion in mineral oil, 1.1 equiv) was added portion-wise over a period of 10 min with stirring which was continued for 5 h. Methyl iodide or benzyl chloride (1 equiv) was added after cooling to 0 °C. Stirring was then continued overnight (0 °C to room temperature). The reaction mixture was diluted with water and extracted with ether. The organic layer was washed, dried ($MgSO_4$) and purified by flash column using *n*-hexane, then hexane:EtOAc (polarity increased gradually) to afford the products with the following data.

*1-Methoxycarbonyl-9-methyl-β-carboline **1b***
Obtained as an oil (yield 91%). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.53 (H-3, d, *J* = 4.9); 8.12 (H-4, d, *J* = 4.9); 8.15 (H-5, dd, *J* = 7.6, 0.9); 7.34 (H-6, ddd, *J* = 7.6, 7.1, 0.6); 7.66 (H-7, ddd, *J* = 8.5, 7.1, 0.9); 7.51 (H-8, dd, *J* = 8.5, 0.6); 3.98 (3H, s, $COOCH_3$); 4.12 (3H, s, N–CH_3).

*9-Benzyl-1-methoxycarbonyl-β-carboline **1c***
Obtained as an oil (yield 88.6%). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.53 (H-3, d, *J* = 4.9); 8.17 (H-4, d, *J* = 4.9); 8.20 (H-5, dd, *J* = 7.8, 0.9); 7.35 (H-6, ddd, *J* = 7.8, 7.6, 0.9); 7.61 (H-7, ddd, *J* = 8.3, 7.6, 0.9); 7.49 (H-8, dd, *J* = 8.3, 0.9); 3.80 (3H, s, $COOCH_3$); 7.26–7.18 (3H, m, H-3", 4", 5" of C_6H_5); 6.92 (2H, ddd, H-2", 6" of C_6H_5); 5.83 (2H, s, CH_2 of benzyl group). MS; *m/z* (%): 316 (M^+, 53), 284 (10), 256 (51), 255 (100), 128 (36), 91 (88).

*Preparation of the aldehydes **5a–c***

General procedure: the appropriate ester **1a–c** (1.0 equiv) in dry toluene was cooled to –78 °C. DIBAL-H [14] in toluene (3.4 equiv in the case of **1a**, and 1.7 equiv in the case of **1b,c**) was added dropwise with stirring. The rate of addition was adjusted so as to keep the temperature below –65 °C. In the case of **1b,c** further interactions should be done at –78 °C, while in the case of **1a**, the temperature should be increased to –20 °C. The reaction was then quenched by methanol and slowly poured into ice-cold 1 N HCl. The solution was made alkaline with NaOH and extracted with EtOAc. The extract was washed (brine), dried ($MgSO_4$) and purified by open column (SiO_2, *n*-hexane:EtOAc; 3:1) to give the products as yellow to pale yellow needles from *n*-hexane and ethyl acetate.

5a: mp = 204–205 °C (lit 202 [9]), yield = 75%. Anal calc for $C_{12}H_8N_2O$: C, 73.45; H, 4.10; N, 14.27. Found: C, 73.36; H, 3.90; N, 14.35. MS; *m/z*: 196 (M^+, 17), 168 (16), 69 (37), 60 (59), 55 (100). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 10.34 (s, 1H, CHO); 10.08 (br, NH); 8.64 (d, H-3, *J* = 4.9); 8.16 (d, H-4, *J* = 4.9); 8.17 (dd, H-5, *J* = 8.5, 0.6); 7.37–7.34 (ddd, H-6, *J* = 8.5, 7.5, 1.2); 7.64–7.61 (ddd, H-7, *J* = 8.2, 7.5, 0.6); 7.59 (dd, H-8, *J* = 8.2, 1.2).

5b: mp = 125–126 °C, yield = 71%. Anal calc for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.11; H, 4.63; N, 13.35. MS; *m/z*: 210 (M^+, 31), 211 (M + 1, 5), 182 (22), 181 (100). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 10.33 (s, 1H, CHO); 8.65 (d, H-3, *J* = 4.9); 8.18 (d, H-4, *J* = 4.9); 8.17–8.15 (dd, H-5, *J* =

7.6, 0.6); 7.39–7.35 (ddd, 1H, H-6, J = 7.7, 7.6, 0.9); 7.70–7.66 (ddd, 1H, H-7, J = 8.3, 7.7, 0.6); 7.54 (dd, H-8, J = 8.3, 0.9); 4.25 (s, 3H, N-CH_3).

5c: mp = 106–107 °C, yield = 72%. Anal calc for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.92; N, 9.78. Found: C, 79.22; H, 4.88; N, 9.68. MS; *m/z*: 286 (M^+, 16), 258 (29), 257 (100), 91 (47). ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 10.21 (s, 1H, CHO); 8.68 (d, H-3, J = 4.9); 8.23 (d, H-4, J = 4.9); 8.21–8.19 (dd, H-5, J = 7.6, 1.2); 7.39–7.36 (ddd, H-6, J = 7.9, 7.6, 0.9); 7.63–7.59 (ddd, H-7, J = 8.2, 7.9, 1.2); 7.50 (dd, H-8, J = 8.2, 0.9); 7.21–7.16 (m, 3H, H-3", 4", 5"); 6.95–9.93 (dd, 2H, H-2", 6", J = 6.1, 2.8); 6.19 (s, 2H of CH_2-C_6H_5).

*Preparation of the alcohols **6a–c** by Grignard reaction*

General procedure: a solution of allylmagnesium bromide (5.3 mmol) [prepared from Mg turning (0.282 g, 11.78 g atom)], anhydrous ether (0.7 mL), a few crystals of iodine, and allyl bromide (0.64 g, 5.3 mmol) mixed with anhydrous ether (4.8 mL) [24] was added over a period of 10 min to a solution of the appropriate **5a–c** (1.78 mmol) in dry THF cooled to –20 °C under argon. The reaction mixture was then stirred for 4 h (–20 °C ~ room temperature), then a saturated NH_4Cl solution was added. The organic layer was separated and the aqueous layer was saturated with NaCl and extracted with EtOAc. The combined organic solution was washed and dried. Workup and purification by column chromatography (SiO_2, *n*-hexane:EtOAc, 1:1) afforded compounds **6a–c** with the following data.

6a: white crystals from $CHCl_3$ and a few drops of *n*-hexane; mp = 166–167 °C; yield = 76%. Anal calc for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.43; H, 5.72; N, 11.81. MS, *m/z*: 238 (M^+, 2), 197 (100), 168 (62), 140 (57). UV (max, MeOH, nm): 213, 235, 241, 250, 288, 339, 350. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 9.27 (br, 1H, NH); 8.31 (d, H-3, J = 5.2); 7.84 (d, H-4, J = 5.2); 8.11 (dd, H-5, J = 8.0, 0.6); 7.29–7.26 (ddd, H-6, J = 8.0, 7.4, 1.2); 7.57–7.53 (ddd, H-7, J = 8.3, 7.4, 0.6); 7.51 (dd, H-8, J = 8.3, 1.2); 5.94–5.85 (m, H-3'); 5.27–5.24 (dd, H-1', J = 8.6, 4.2); 5.21–5.15 (m, 2H at C-4'); 3.78 (br s, –OH); 2.88–2.83 (m, 1H at C-2'); 2.70–2.64 (m, 1H at C-2').

6b: pale yellow crystals from $CHCl_3$ and a few drops of *n*-hexane; mp = 99–100 °C, yield = 72%. Anal calc for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.13; H, 6.30; N, 11.05. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.39 (d, H-3, J = 5.2); 7.92 (d, H-4, J = 5.2); 8.15–8.13 (dd, H-5, J = 7.9, 0.6); 7.33–7.29 (ddd, H-6, J = 7.9, 7.5, 0.6); 7.64–7.61 (ddd, H-7, J = 8.2, 7.5, 0.6); 7.49 (dd, H-8, J = 8.2, 0.9); 6.03–5.95 (pair of pentet, H-3', J = 17.1, 14.1, 3.7); 5.59–5.58 (dd, H-1', J = 4.8, 1.2); 5.36 (br, –OH); 5.18–5.11 (m, 2H at C-4'); 4.08 (s, 3H, N-CH_3); 2.77–2.72 (m, 1H at C-2'); 2.53–2.47 (m, 1H at C-2').

6c: oil, yield = 75%. HR-FAB mass: calc: 328.1577, found: 328.1579, for $C_{22}H_{20}N_2O$. MS *m/z*: 328 (M^+, 53), 287 (100), 257 (31), 237 (41). ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.43 (d, H-3, J = 4.9); 7.98 (d, H-4, J = 4.9); 8.20–8.18 (dd, H-5, J = 8.0, 0.6); 7.34–7.31 (ddd, H-6, J = 8.0, 7.5, 0.9); 7.57–7.54 (ddd, H-7, J = 8.4, 7.5, 0.6); 7.39 (dd, H-8, J = 8.4, 0.9); 7.26–7.20 (m, 3H, H-3",-4",-5"); 6.93–6.91 (dd, 2H, H-2", 6", J = 8.2, 2.1); 5.92–5.85 (m, H-3'); 5.82 (d, 1H of CH_2 in (N–CH_2–C_6H_5), J = 18.0); 5.65 (d, 1H of CH_2 in (N–CH_2–C_6H_5), J = 18.0); 5.24–5.23 (dd, H at C-1', J = 8.2, 2.7); 5.07–4.98 (m, 3H: 2H at C-4' and –OH); 2.59–2.54 (m, 1H at C-2'); 2.44–2.37 (m, 1H at C-2').

*Silylated secondary alcohols **7a–c***

General procedure: to a solution of the appropriate **6a–c** (1.72 mmol) in dry pyridine was added $AgNO_3$ (0.496 g, 2.92 mmol) with stirring for 5 min at room temperature [15]. *t*-Butyldimethyl-silylchloride (0.44 g, 2.92 mmol) was added and stirring was continued for 30 min. CH_2Cl_2 was added and the reaction mixture was filtered into 10% $NaHCO_3$ solution. Workup and purification by chromatography (SiO_2, *n*-hexane: EtOAc, 3:1) to give the products as colorless to pale yellow oils with the following data.

7a: yield = 95%, ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 9.11 (br, NH); 8.33 (d, H-3, J = 5.2); 7.85 (d, H-4, J = 5.2); 8.14–8.12 (dd, H-5, J = 7.5, 1.0); 7.29–7.26 (ddd, H-6, J = 7.9, 7.5, 0.9); 7.57–7.54 (ddd, H-7, J = 8.2, 7.9, 1.0); 7.51–7.49 (dd, H-8, J = 8.2, 0.9); 5.88–5.80 (m, 1H at C-3'); 5.25–5.22 (dd, 1H at C-1', J = 7.6, 4.8); 5.09–5.02 (m, 2H at C-4'); 2.76–2.63 (m, 2H at C-2'); 0.92 (s, 9H, $3CH_3$ of Si-$C(CH_3)_3$); 0.14 (s, 3H, Si-CH_3); –0.11 (s, 3H, Si-CH_3).

7b: yield = 76%. MS; *m/z*: 366 (M^+, 12), 309 (61), 286 (87), 236 (15), 181 (10), 134 (13), 73 (100). HR-FAB mass: calc: 366.2129, found: 366.2143, for $C_{22}H_{30}N_2OSi$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.37 (d, H-3, J = 4.9); 7.92 (d, H-4, J = 4.9); 8.15–8.13 (dd, H-5, J = 8.8, 1.2); 7.32–7.29 (ddd, H-6, J = 8.8, 7.6, 1.0); 7.64–7.60 (ddd, H-7, J = 8.3, 7.6, 1.2); 7.49 (dd, H-8, J = 8.3, 1.0); 5.95–5.87 (m, 1H at C-3'); 5.45–5.42 (dd, H at C-1', J = 8.8, 5.9); 5.13–5.09 (m, H at C-4'); 5.07–5.04 (m, H at C-4'); 4.32 (s, 3H, N–CH_3); 2.96–2.90 (m, H at C-2'); 2.83–2.77 (m, H at C-2'); 0.81 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.06 (s, 3H, Si–CH_3); –0.16 (s, 3H, Si–CH_3).

7c: yield = 80%. MS; *m/z*: 442 (M^+, 1.5), 443 (M + 1, 14), 386 (77), 385 (100), 344 (36). HR-FAB mass: calc: 442.2442, found: 442.2430, for: $C_{28}H_{34}N_2OSi$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz, measured at 60 °C): 8.44 (d, H-3, J = 5.0); 7.96 (d, H-4, J = 5.0); 8.18–8.16 (dd, H-5, J = 8.3, 1.2); 7.31–7.28 (m, 2H: H-6 and H-8); 7.51–7.48 (ddd, H-7, J = 8.3, 7.8, 1.2); 7.26–7.18 (m, 3H, H-3", 4", 5"); 6.92–6.91 (dd, 2H, H-2", 6", J = 6.8, 2.1); 6.46–6.43 (br d, 1H of CH_2–C_6H_5); 5.86 (d, 1H of –CH_2–C_6H_5, J = 17.9); 5.77–5.69 (m, H at C-3'); 5.35–5.32 (dd, H at C-1', J = 8.1, 6.2); 4.91–4.89 (dd, 1H at C-4', J = 10.3, 1.9); 4.83–4.79 (dd, 1H at C-4', J = 17.1, 1.7); 2.68–2.61 (m, 2H at C-2'); 0.82 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.16 (s, 3H, Si–CH_3); –0.20 (s, 3H, Si–CH_3).

*Preparation of N-BOC derivative **7d***

To a solution of **7a** (0.57 g, 1.62 mmol) in dry CH_2Cl_2 was added 4-dimethylamino pyridine (DMAP) (20 mg, 0.1 equiv) and di-*t*-butyl dicarbonate [$(BOC)_2O$, 0.53 g, 0.1 equiv] [15] with stirring at room temperature under argon. After one hour the mixture was evaporated and purified by column chromatography (SiO_2, *n*-hexane, then *n*-hexane and EtOAc, 6:1) to afford 0.71 g of **4d** as a viscous colorless oil in 97% yield.

^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.67 (H-3, d, J = 4.9); 7.75 (H-4, d, J = 4.9); 8.03 (2H, m, H-5 and H-8); 7.39 (H-6, ddd, J = 8.2, 7.6, 1.3); 7.57 (H-7, ddd, J = 8.6, 8.2, 1.2); 6.12–6.04 (1H, pair of pentet, H at C-3', J = 17.1, 13.5, 7.2, 4.3, 2.7); 5.34 (H, dd, H at C-1', J = 9.2, 3.1); 5.24 (1H, dd x 2, H at C-4', J = 17.1, 5.2 , 2.1); 5.11 (1H, dd x 2, H at C-4', J = 10.1, 3.4, 2.4); 3.00–2.94 (1H, m, H at C-2'); 2.92–2.87 (1H, m, H at C-2'); 1.74 (9H, s, –$OC(CH_3)_3$); 0.69 (9H, s, –Si–$C(CH_3)_3$); –0.18 (3H, s, –Si–CH_3); –0.28 (3H, s, –Si–CH_3).

Preparation of the diols ***8b–d***

General procedure: OsO_4 [17] (1.1 equiv) was added to a stirred solution of the appropriate **7b–d** (1 equiv) in dry pyridine–THF (1:1) and the mixture was stirred at room temperature for 3 h under argon. A solution of $NaHSO_3$ (4 times the amount of OsO_4) in water was added and the mixture was stirred for a further 2 h. The reaction mixture was basified with 10% aqueous Na_2CO_3 extracted with $CHCl_3$ which was washed (brine), dried ($MgSO_4$), evaporated and the residue was purified by column chromatography (SiO_2, MeOH:$CHCl_3$, 10:90) to afford the products as sandy white crystals (from EtOAc) with the following data.

8b: mp = 152–153 °C, yield = 88%. UV (max, MeOH, nm): 217, 237, 262, 289, 345, 359. HR-FAB mass: calc: 400.2183, found: 400.2153, for $C_{22}H_{32}N_2O_3Si$. Anal calc: C, 65.96; H, 8.05; N, 6.99. Found: C, 65.27; H, 7.95; N, 6.79. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.36 (d, H-3, *J* = 5.2); 7.91 (d, H-4, *J* = 5.2); 8.12–8.10 (dd, H-5, *J* = 7.9, 1.0); 7.30–7.27 (ddd, H-6, *J* = 7.9, 7.6, 0.9); 7.62–7.59 (ddd, H-7, *J* = 8.5, 7.6, 1.0); 7.47 (dd, H-8, *J* = 8.5, 0.9); 5.82–5.79 (t, H at C-1', *J* = 6.7, 3.2); 4.25 (s, 3H, N–CH_3); 4.06–4.02 (m, H at C-3'); 3.71–3.68 (dd, H at C-4', *J* = 11.0, 3.9); 3.55–3.52 (dd, H at C-4', *J* = 11.0, 7.0); 2.30–2.27 (m, 2H at C-2'); 0.82 (s, 9H, $3CH_3$, [Si–$C(CH_3)_3$]); –0.15 (s, 3H, Si–CH_3); –0.20 (s, 3H, Si–CH_3).

8c: mp = 117–118 °C, yield = 93%. HR-FAB mass: calc: 476.2496, found: 476.2484, for $C_{28}H_{36}N_2O_3Si$. Anal calc: C, 70.55; H, 7.61; N, 5.87. Found: C, 69.44; H, 7.71; N, 5.40. H-NMR (δ, $CDCl_3$, *J* = Hz, 60 °C): 8.38 (d, H-3, *J* = 5.0); 7.98 (d, H-4, *J* = 5.0); 8.17–8.15 (dd, H-5, *J* = 7.3, 0.6); 7.32–7.29 (ddd, H-6, *J* = 7.9, 7.3, 1.0); 7.52–7.51 (ddd, H-7, *J* = 8.3, 7.9, 0.6); 7.35 (dd, H-8, *J* = 8.3, 1.0); 7.25–7.18 (m, 3H, H-3", 4", 5"); 6.93–6.91 (dd, 2H, H-2", 6", *J* = 6.7, 1.5); 6.19–6.15 (br s, 1H of CH_2 of (–CH_2–C_6H_5); 5.91–5.87 (d, 1H of CH_2 of –CH_2–C_6H_5, *J* = 18.0); 5.56–5.54 (dd, H at C-1', *J* = 7.6, 1.5); 3.43–3.40 (dd, H at C-4', *J* = 11.1, 3.4); 3.29–3.26 (dd, H at C-4', *J* = 10.8, 4.5); 2.88 (br s, –OH); 2.03–1.98 (m, 2H at C-2'); 0.79 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.21 (s, 3H, Si–CH_3); –0.38 (s, 3H, Si–CH_3).

8d: mp = 161–162 °C, yield = 98%. UV (max, MeOH, nm): 225, 249, 275, 283, 315, 323. MS; *m/z*: 486 (M^+, 0.3), 454 (03), 428 (17), 372 (63), 328 (32), 253 (44), 194 (100). HR-FAB mass: calc: 486.2551, found: 486.2541, for $C_{26}H_{38}N_2O_5Si$. Anal calc: C, 64.16; H, 7.87; N, 5.75. Found: C, 63.98; H, 7.82; N, 5.70. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.67 (d, H-3, *J* = 4.8); 8.07 (d, H-4, *J* = 4.8); 8.04–8.02 (dd, H-5, *J* = 7.1, 1.6); 7.43–7.40 (ddd, H-6, *J* = 7.3, 7.1, 1.2); 7.61–7.58 (ddd, H-7, *J* = 7.3, 7.3, 1.6); 7.79 (dd, H-8, *J* = 7.3, 1.2); 5.62 (br s, H at C-1'); 4.13 (m, H at C-3'); 3.74–3.70 (m, H at C-4'); 3.66–3.60 (m, H at C-4'); 2.47–2.42 (m, H at C-2'); 2.37 (m, H at C-2'); 1.74 (s, 9H, $3CH_3$ of O–$C(CH_3)_3$); 0.75 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.21 (s, 3H, Si–CH_3); –0.36 (s, 3H, Si–CH_3).

Preparation of ***9b–d*** *by glycol cleavage oxidation of the vicinal diols*

General procedure: to a solution of the appropriate **8b–d** (1.0 equiv) in methanol was added with stirring at room temperature [25] a solution of $NaIO_4$ (1.1 equiv in water). Stirring was continued for 30 min, and the mixture was then extracted with CH_2Cl_2 which was washed, dried ($MgSO_4$) and evaporated under vacuum at low temperature (bath temperature ~ 25 °C), to afford the crude aldehydes as colorless to pale yellow oil. The products were used for the next step without purification (single spot in TLC using alumina, *n*-hexane:EtOAc; 3:2). MPLC was adopted (MeOH:$CHCl_3$; 1:99), to get a pure sample for NMR analysis. Products have the following data.

9b: yield = 90%. MS, *m/z*: 368 (M^+, 1.5), 353 (02), 312 (38), 311 (100), 267 (08), 237 (14). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 9.92 (s, 1H of CHO); 8.55 (d, H-3, *J* = 4.9); 8.03 (d, H-4, *J* = 4.9); 8.16–8.15 (dd, H-5, *J* = 7.0, 0.9); 7.36–7.33 (ddd, H-6, *J* = 7.6, 7.0, 1.0); 7.68–7.65 (ddd, H-7, *J* = 8.3, 7.6, 0.9); 7.51–7.50 (dd, H-8, *J* = 8.2, 1.0); 6.15–6.12 (t, H at C-1', *J* = 7.2, 3.8); 4.29 (s, 3H, N–CH_3); 3.28 (dd, 2H at C-2', *J* = 7.4, 3.7); 0.80 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.12 (s, 3H, Si–CH_3); –0.26 (s, 3H, Si–CH_3).

9c: yield = 91%. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz, 60 °C): 9.71 (s, 1H of CHO); 8.42 (d, H-3, *J* = 5.2); 7.97 (d, H-4, *J* = 5.2); 8.16 (d, H-5, *J* = 7.9, 0.6); 7.32–7.29 (ddd, H-6, *J* = 7.9, 7.5, 0.9); 7.55–7.51 (ddd, H-7, *J* = 8.2, 7.5, 0.6); 7.37 (dd, H-8, *J* = 8.2, 0.9); 7.27–7.21 (m, 3H, H-3", 4", 5"); 6.96 (d, 2H, H-2"; 6", *J* = 7.0); 6.02 (s, 2H of –CH_2–C_6H_5); 5.88–5.85 (dd, H at C-1', *J* = 7.6, 5.9); 3.02–2.98 (m, 2H at C-2'); 0.79 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.12 (s, 3H, Si–CH_3); –0.39 (s, 3H, Si–CH_3).

9d: yield = 95%. MS, *m/z*: 396 [M^+ – 58 (*t*-Bu), 12], 340 (100), 296 (18), 266 (38). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 10.04 (s, 1H of CHO); 8.67 (d, H-3, *J* = 4.8); 7.79 (d, H-4, *J* = 4.8); 8.03 (dd, H-5, *J* = 7.6, 0.6); 7.43–7.40 (ddd, H-6, *J* = 7.6, 7.4, 1.1); 7.61–7.58 (ddd, H-7, *J* = 8.5, 7.4, 0.6); 8.07 (d, H-8, *J* = 8.5, 1.1); 5.93–5.91 (dd, H at C-1', *J* = 8.2, 3.4); 3.43–3.37 (m, H at C-2'); 3.21–3.17 (dd, H at C-2', *J* = 10.0, 3.4, 2.5); 1.74 (s, 9H, $3CH_3$ of [O–$C(CH_3)_3$]; 0.69 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.20 (s, 3H, Si-CH_3); –0.34 (s, 3H, Si–CH_3).

Preparation of ***10b–d***

General procedure: the appropriate aldehyde **9b–d** (1.0 equiv) was dissolved in dry CH_2Cl_2 and cooled to 0 °C (no cooling in the case of **10b**). Methyl(triphenylphosphoranylidene)acetate (3 equiv) [26, 27] was added and the mixture was stirred for 15–18 h under argon (–20 °C to room temperature). The solvent was then evaporated under vacuum and the residue was extracted with *n*-hexane (petroleum ether was used in the case of **10d**), evaporated and purified by MPLC (*n*-hexane and EtOAc, 1:1) to afford the esters **10b–d** as pale yellow oils with the following data.

10b: yield = 85%. MS, *m/z*: 424 (M^+, 52), 367 (99), 325 (13), 294 (11), 268 (100), 233 (18), 181 (07). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.37 (d, H-3, *J* = 4.9); 7.94 (d, H-4, *J* = 4.9); 8.14–8.13 (dd, H-5, *J* = 7.4, 1.3); 7.33–7.30 (ddd, H-6, *J* = 7.9, 7.4, 0.9); 7.65–7.62 (ddd, H-7, *J* = 8.5, 7.9, 1.3); 7.50 (d, H-8, *J* = 8.5, 0.9); 7.14–8.08 (m, H at C-3'); 5.97–5.94 (dd, H at C-4', *J* = 15.6, 1.3); 5.55–5.53 (dd, H at C-1', *J* = 9.1, 5.1); 4.30 (s, 3H, N–CH_3); 3.73 (s, 3H, $COOCH_3$): 3.14–3.07 (m, H at C-2'); 2.98–2.93 (m, H at C-2'); 0.80 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.15 (s, 3H, Si–CH_3); –0.17 (s, 3H, Si–CH_3).

10c: yield = 89%. Low FAB MS, *m/z*: 500 (M^+, 40)*, 444 (20), 401 (10), 344 (66), 293 (12), 253 (47), 219 (14), 91 (100). HR-FAB mass: calc: 500.2496, found: 500.2494, for $C_{30}H_{36}N_2O_3Si$. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz, 60 °C): 8.42 (d, H-3, *J* = 4.9); 7.97 (d, H-4, *J* = 4.9); 8.17–8.15 (dd, H-5, *J* = 8.5, 1.2); 7.32–7.28 (m, 2H, H-6 and -8); 7.52–7.49 (ddd, H-7, *J* = 8.5, 7.9, 1.2); 7.26–7.19 (m, 3H, H-3", 4", 5"); 6.90–6.89 (d, 2H, H-2"; 6", *J* = 7.0, 3.2); 6.86–6.80 (m, ddd, 1H at C-3',

J = 15.5, 7.3); 6.33 (br s, H of CH_2 of CH_2–C_6H_5); 5.87–5.83 (d, H of CH_2 of CH_2–C_6H_5, J = 18.0); 5.57 (d, H at C-4', J = 15.9); 5.39–5.36 (dd, H at C-1', J = 8.8, 5.6); 3.67 (s, 3H, $COOCH_3$); 2.82–2.76 (m, H at C-2'); 2.72–2.68 (m, H at C-2'); 0.89 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.15 (s, 3H, Si–CH_3); –0.26 (s, 3H, Si–CH_3).

10d: yield = 92%. UV (max, MeOH, nm): 203, 221, 255, 285, 303, 344. Low FAB MS, *m/z*: 510 (M^+, 0.2), 410 (46), 397 (36), 353 (100), 311 (56), 254 (93), 219 (28). HR-FAB mass: calc: 510.2550, found: 510.2547, for $C_{28}H_{38}N_2O_5Si$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.68 (d, H-3, J = 4.9); 7.78 (d, H-4, J = 4.9); 8.05–8.02 (m, 2H, H-5 and -8); 7.42–7.39 (ddd, H-6, J = 8.2, 7.3, 0.9); 7.60–7.57 (ddd, H-7, J = 8.6, 7.3, 1.2); 7.21–7.27 (m, H at C-3'); 6.08–6.04 (dd, H at C-4', J = 15.6, 2.4, 1.2); 5.41–5.39 (dd, H at C-1', J = 9.3, 2.9); 3.75 (s, 3H, $COOCH_3$); 3.21–3.41 (m, H at C-2'); 3.10–3.05 (m, H at C-2'); 1.74 (s, 9H, $3CH_3$ of O-$C(CH_3)_3$); 0.68 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.20 (s, 3H, Si–CH_3); –0.33 (s, 3H, Si–CH_3).

*Preparation of **10a** by deprotection of **10d***

Ylide **10d** (0.4 g, 0.79 mmol) was dissolved in HCOOH (20 mL), dimethyl sulfide (7.8 mL, 137 equiv) was added and stirred at room temperature for 30 h [15] under argon. The reaction mixture was then concentrated under vacuum and carefully neutralized with a saturated solution of $NaHCO_3$. Extraction with CH_2Cl_2 and drying (Na_2SO_4) afforded the crude **10a** (0.272 g, 85%) which was purified (by MPLC using MeOH/$CHCl_3$, 3:97) as a yellow oil. MS, *m/z* (%): 410 (M^+, 67), 354 (23), 353 (87), 311 (84), 280 (16), 254 (100), 219 (29), 73 (83). HR-FAB mass: calc: 410.2026, found: 410.2037; for $C_{23}H_{30}N_2O_3Si$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 9.06 (1H, broad, NH); 8.33 (d, H-3, J = 5.1); 7.87 (d, H-4, J = 5.1); 8.13 (dd, H-5, J = 7.8, 1.0); 7.28 (ddd, H-6, J = 7.8, 7.6, 0.9); 7.56 (ddd, H-7, J = 8.3, 7.6, 1.0); 7.50 (dd, H-8, J = 8.3, 0.9); 7.03 (ddd, 1H, H-3', J = 15.6, 15.4, 7.6); 5.87 (dd, H-4', J = 15.6, 2.7); 5.31 (dd, H-1', J = 7.8, 4.7); 3.69 (s, 3H, $COOCH_3$); 2.89–2.77 (m, 2H, at C-2); 0.92 (s, 9H, $3CH_3$ of Si–C–C_3H_9); 0.14 (s, 3H, Si-CH_3); –0.11 (s, 3H, Si–CH_3).

NOE DF1: when proton at C-4' is irradiated, proton absorption at C-2' is enhanced by 2.8%. NOE DF_2: when a proton at C-3' is irradiated, absorptions of the proton at C-1', C-2', and C-4' are enhanced by 3.8, 3.71 and 1.89% respectively.

*Preparation of the diols **11a–c***

General procedure: the appropriate **10a–c** (1 equiv) in dry THF and pyridine (1:1) was added OsO_4 (1.1 equiv). After stirring for 6 h at room temperature, $NaHSO_3$ (4 times the amount of OsO_4) in water (10 mL) was added and stirring was continued for a further 3 h. Workup as described in the above followed by purification by MPLC (hexane–EtOAc; 3:2) gave the appropriate diols **11a–c** with the following data.

11a: colorless oil, yield = 77%, MS, *m/z*: 444 (M^+,1.6), 388 (43), 387 (100), 355 (11), 312 (26), 277 (22), 254 (25). HR-FAB mass: calc: 444.2081, found: 444.2086, for $C_{23}H_{32}N_2O_5Si$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 9.12 (br, 1H, N-H); 8.29 (d, H-3, J = 5.3); 7.89 (d, H-4, J = 5.3); 8.14 (dd, H-5, J = 7.8, 1.0); 7.31–7.29 (ddd, H-6, J = 7.8, 7.1, 1.0); 7.59–7.56 (ddd, H-7, J = 7.8, 7.1, 1.0) ; 7.51 (dd, H-8, J = 7.8, 1.0); 5.46–5.43 (t, H-1', J = 7.7); 4.02 (d, H-4', J = 2.0); 3.84–3.81 (m, 1H at C-3'); 3.75 (s, 3H, $COOCH_3$); 3.16 (br s, –OH); 2.60–2.54 (m, 1H at C-2'); 2.09–2.03 (m, 1H at C-2'); 0.94 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); 0.17 (s, 3H, Si–CH_3); –0.10 (s, 3H, Si–CH_3).

11b: total yield = 70%. First isomer of **11b**: white crystal (EtOAc), mp = 125–126.5 °C, HR-FAB mass: calcd 458.2238, found: 458.2212, for $C_{24}H_{34}N_2O_5Si$. Anal calc: C, 62.85; H, 7.47; N, 6.10. Found: C, 62.90; H, 7.50; N, 6.15. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.34 (d, H-3, J = 5.2); 7.95 (d, H-4, J = 5.2); 8.15 (dd, H-5, J = 7.6, 0.7); 7.34–7.30 (ddd, H-6, J = 7.9, 7.6, 1.0); 7.66–7.62 (ddd, H-7, J = 8.3, 7.9, 0.7); 7.50 (dd, H-8, J = 8.3, 1.0); 5.76 (m, 1H at C-1'); 4.28 (s, 3H, N–CH_3); 4.13 (m, 1H at C-3'); 4.10 (br s, 1H at C-4'); 3.78 (s, 3H, $COOCH_3$); 3.19 (br s, OH, D_2O exchange); 2.64–2.63 (m, 1H at C-2'); 2.05–2.03 (m, 1H at C-2'); 0.83 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.10 (s, 3H, Si–CH_3); –0.24 (s, 3H, Si–CH_3).

*Second isomer of **11b***: oil. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.36 (d, H-3, J = 5.2); 7.94 (d, H-4, J = 5.2); 8.15–8.13 (dd, H-5, J = 7.9, 0.9); 7.32–7.29 (ddd, H-6, J = 7.9, 7.4, 0.9); 7.65–7.61 (ddd, H-7, J = 8.3, 7.4, 0.9); 7.49 (dd, H-8, J = 8.3, 0.9); 5.83–5.80 (dd, H at C-1', J = 6.6, 2.1); 4.32–4.30 (m, 1H at C-3'); 4.27 (s, 3H, N–CH_3); 4.21 (br s, 1H at C-4'); 3.83 (s, 3H, $COOCH_3$); 2.50–2.40 (m, 2H at C-2'); 3.49 (br s, –OH); 3.19 (br s, –OH); 0.81 [s, 9H, $3CH_3$, Si–C–$C(CH_3)_3$]; –0.15 (s, 3H, Si–CH_3); –0.26 (s, 3H, Si–CH_3).

11c: total yield = 71%. First isomer of **11c**: white crystal (EtOAc), mp = 190–191 °C, MS, *m/z*: 534 (M^+, 1.1), 477 (93), 387 (14), 344 (10), 285 (72), 254 (31), 193 (20), 91 (100) . HR-FAB mass: calc: 543.2551, found: 543.2551, for $C_{30}H_{38}N_2O_5Si$. Anal calc: C, 67.38; H, 7.16; N, 5.23. Found: C, 67.26; H, 7.16; N, 5.38. ^{1}H-NMR (δ, $CDCl_3$, J = Hz, 60 °C) : 8.42 (d, H-3, J = 5.2); 7.96 (d, H-4, J = 5.2); 8.16 (dd, H-5, J = 7.9, 0.9); 7.32–7.28 (ddd, H-6, J = 7.9, 8.0, 0.6); 7.54–7.50 (ddd, H-7, J = 8.6, 8.0, 1.2); 7.34 (dd, H-8, J = 8.6, 0.6); 7.25–7.18 (m, 3H, H-3", 4", 5"); 6.93–6.91 (dd, 2H, H-2"; 6", J = 6.7); 6.20–6.16 (br d , H of CH_2–C_6H_5, J = 18.0); 5.91–5.88 (d, H of CH_2 of CH_2–C_6H_5, J = 18.0); 5.57–5.54 (dd, H at C-1', J = 7.6, 5.8); 4.08–4.06 (m, H at C-3' after D_2O exchange of OH gives dd; J = 5.8, 4.6); 3.81–3.80 (m, H at C-4'); 3.75 (s, 3H, $COOCH_3$); 2.82–2.70 (br s, –OH exchanged with D_2O); 2.17–2.13 (m, 2H at C-2'); 0.80 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.19 (s, 3H, Si–CH_3); –0.35 (s, 3H, Si–CH_3).

*Second isomer of **11c***: ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.39 (d, H-3, J = 5.2); 7.98 (d, H-4, J = 5.2); 8.17 (dd, H-5, J = 7.8, 1.0); 7.32–7.29 (dd, H-6, J = 7.8, 7.5); 7.54–7.51 (dd, H-7, J = 8.1, 7.5); 7.34 (dd, H-8, J = 8.1, 1.1); 7.26–7.17 (m, 3H, H-3", 4", 5" of benzene ring); 6.89 (d, 2H, H-2", 6" of bz, J = 6.6); 6.30 (br, 1H of $CH_2C_6H_5$); 5.83 (d, 1H of $CH_2C_6H_5$, J = 18.0); 5.57–5.54 (t, 1H at C-1', J = 7.1); 3.90 (m, 1H at C-3'); 3.72 (s, 4H: 1H at C-4' and $COOCH_3$); 2.31–2.25 (m, 1H at C-2'); 2.02 (m, 1H at C-2'); 0.82 (s, 9H, $3CH_3$ of Si–$C(CH_3)_3$); –0.23 (s, 3H, Si-CH_3); –0.27 (s, 3H, Si–CH_3).

*Preparation of the acetonides **12a–c***

General procedure: *p*-toluenesulphonic acid monohydrate (1 equiv) and 2,2-dimethoxypropane (5 equiv) were added to a solution of the appropriate **11a–c** (1 equiv) in dry acetone at 0 °C. The reaction mixture was heated under reflux for 1 h, then cold aqueous Na_2CO_3 (5%) was added to the cold reaction mixture, concentrated, extracted with $CHCl_3$ which was then washed (brine), dried ($MgSO_4$) and evaporated. The residue was purified by open column chromatography (SiO_2; EtOAc: hexane; 1:1) to give the appropriate acetonides **12a–c** as colorless oils with the following data. MPLC treatment of **12a** using hexane–EtOAc (2.5:1) afforded two oily compounds in a ratio of 2:1, respectively which differ only in their NMR spectra.

12a: total yield = 70 %. First isomer: MS, *m/z*: 484 (M^+, 6.3), 469 (24), 429 (13), 428 (46), 427 (100), 312 (62), 267 (12). HR-FAB mass: calc: 484.2394, found: 484.2395, for $C_{26}H_{36}N_2O_5Si$. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 9.09 (br, –NH); 8.34 (d, H-3, *J* = 5.4); 7.86 (d, H-4, *J* = 5.4); 8.14–8.13 (dd, H-5, *J* = 7.9, 0.6); 7.30–7.26 (ddd, H-6, *J* = 7.9, 7.4, 1.2); 7.58–7.54 (ddd, H-7, *J* = 8.3, 7.4, 0.6); 7.52–7.50 (dd, H-8, *J* = 8.3, 1.2); 5.45–5.42 (dd, 1H at C-1', *J* = 10.3, 2.7); 4.46–4.42 (m, 1H at C-3'); 4.11 (d, 1H at C-4', *J* = 8.1); 3.77 (s, 3H, $COOCH_3$); 2.44–2.38 (m, 1H at C-2'); 2.13–2.07 (m, 1H at C-2'); 1.50 (s, 3H, –O–C(CH_3)); 1.46 (s, 3H, –O–C(CH_3)); 0.92 (s, 9H, $3CH_3$ Si–C(CH_3)$_3$); 0.14 (s, 3H, Si–CH_3); –0.19 (s, 3H, Si–CH_3).

Second isomer of ***12a***: ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 9.23 (br, 1H, NH); 8.33 (d, H-3, *J* = 5.2); 7.86 (d, H-4, *J* = 5.2); 8.14–8.12 (dd, H-5, *J* = 8.0, 1.2); 7.30–7.27 (ddd, H-6, *J* = 8.0, 7.4, 1.2); 7.57–7.54 (ddd, H-7, *J* = 8.3, 7.4, 1.2); 7.52–7.50 (dd, H-8, *J* = 8.3, 1.2); 5.41–5.38 (t, 1H at C-1', *J* = 6.4); 4.27–4.23 (m, 2H at C-3' and C-4'); 3.64 (s, 3H, $COOCH_3$); 2.46–2.35 (m, 2H at C-2'); 1.40 (s, 3H, –O–C–CH_3); 1.35 (s, 3H, O–C–CH_3); 0.92 (s, 9H, Si–C(CH_3)$_3$); 0.13 (s, 3H, Si–CH_3); –0.14 (s, 3H, Si–CH_3).

12b: yield = 45%. HR-FAB mass: calc: 498.2551, found: 498.2555, for $C_{27}H_{38}N_2O_5Si$. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.39 (d, H-3, *J* = 4.9); 7.93 (d, H-4, *J* = 4.9); 8.15-8.13 (dd, H-5, *J* = 8.0, 1.0); 7.32–7.29 (ddd, H-6, *J* = 8.0, 7.8, 0.9); 7.64–7.61 (ddd, H-7, *J* = 8.5, 7.8, 1.0); 7.49 (dd, H-8, *J* = 8.5, 0.9); 5.72 (m, 1H at C-1'); 4.31 (s, 3H, N–CH_3); 4.28–4.26 (d, 1H at C-4', *J* = 9.5); 4.04–4.00 (m, 1H at C-3'); 3.62 (s, 3H, $COOCH_3$); 2.76–2.71 (m, 1H at C-2'); 2.57–2.52 (m, 1H at C-2'); 1.49 (s, 3H, O–C(CH_3)); 1.35 (s, 3H, O–C(CH_3)); 0.82 (s, 9H, of Si–C(CH_3)$_3$); –0.01 (br s, 3H, Si–CH_3); –0.17 (s, 3H, Si–CH_3).

12c: yield = 48%. MS, *m/z*: 574 (M^+, 0.3), 559 (23), 519 (50), 518 (100), 517 (58), 459 (32), 402 (34), 367 (12). ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz, 60 °C): 8.46 (d, H-3, *J* = 4.9); 7.94 (d, H-4, *J* = 4.9); 8.17–8.15 (dd, H-5, *J* = 7.6, 0.6); 7.31–7.28 (ddd, H-6, *J* = 7.6, 7.6, 1.2); 7.53–7.50 (ddd, H-7, *J* = 7.9, 7.6, 0.6); 7.34 (d, H-8, *J* = 7.9, 1.2); 7.23–7.19 (m, 3H, H-3", 4", 5"); 6.96 (d, 2H, H-2", 6", *J* = 7.0); 6.15–6.04 (br s, 1H of CH_2 of CH_2–C_6H_5); 5.84–5.80 (d, 1H of CH_2 of CH_2–C_6H_5; *J* = 18.0); 5.61–5.59 (dd, 1H at C-1'; *J* = 10.7, 2.3); 4.50–4.48 (m, 1H at C-3'); 4.02 (d, 1H at C-4', *J* = 8.0); 3.69 (s, 3H, $COOCH_3$); 2.54–2.50 (m, 1H at C-2'); 2.03–1.98 (m, 1H at C-2'); 1.46 (s, 3H, O–C(CH_3)); 1.44 (s, 3H, O–C(CH_3)); 0.76 (s, 9H, $3CH_3$ of Si–C(CH_3)$_3$); –0.25 (s, 3H, Si–CH_3); –0.45 (s, 3H, Si–CH_3).

Preparation of ***13a–c***

General procedure: lithium borohydride (6 equiv) was added to a solution of the appropriate acetonides **12a–c** (1 equiv) in diethyl ether and the mixture was stirred at room temperature for 7 h under argon. NH_4OH (14%) was added and the organic layer was separated. The aqueous layer was saturated with NaCl, extracted with ether, and the combined organic layers were washed (brine), dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by MPLC with EtOAc: hexane (2:1) to give the appropriate primary alcohols **13a–c** as pale to colorless oils with the following data.

13a: total yield = 78%. HR-FAB mass: calc: 256.2445, found: 256.2444, for $C_{25}H_{36}N_2O_4Si$. First isomer: ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 9.13 (br, –NH); 8.33 (d, H-3, *J* = 5.2); 7.86 (d, H-4, *J* = 5.2); 8.14–8.12 (dd, H-5, *J* = 7.8, 0.9); 7.30–7.27 (ddd, H-6, *J* = 8.1, 7.8, 1.0); 7.57–7.54 (ddd, H-7, *J* = 8.3, 8.1, 0.9); 7.50–7.48 (dd, H-8, *J* = 8.3, 1.0); 5.38–5.36 (t, 1H at C-1', *J* = 12.9); 4.04–4.00 (m, 1H at C-3'); 3.74–3.71 (ddd, 1H at C-4', *J* = 11.8, 8.1, 4.4); 3.67–3.64 (dd, 1H at C-5', *J* = 11.9, 7.8); 3.56–3.53 (dd, 1H at C-5'; *J* = 11.8, 8.0); 2.36–2.31 (m, 1H at C-2'); 2.23–2.18 (m, 1H at C-2'); 1.37 (s, 3H, O–C–CH_3); 1.35 (s, 3H, O–C–CH_3); 0.92 (s, 9H, $3CH_3$ of Si–C(CH_3)$_3$); 0.13 (s, 3H, (Si–CH_3)); –0.13 (s, 3H, Si-CH_3).

Second isomer of ***13a***: ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 9.14 (br, 1H, NH); 8.28 (d, H-3, *J* = 5.4); 7.89 (d, H-4, *J* = 5.4); 8.15–8.13 (dd, H-5, *J* = 8.1, 1.2); 7.31–7.28 (ddd, H-6, *J* = 8.1, 7.7, 1.2); 7.59–7.56 (ddd, H-7, *J* = 8.3, 7.7, 1.2); 7.52–7.50 (dd, H-8, *J* = 8.3, 1.2); 5.46–5.43 (dd, 1H at C-1', *J* = 8.1, 1.2); 5.04 (br s, OH); 3.89–3.86 (m, 1H at C-3'); 3.84–3.80 (m, 2H at C-4', C-5'); 3.78–3.74 (dd, 1H at C-5', *J* = 12.2, 8.0); 2.37–2.32 (m, 1H at C-2'); 2.21–2.15 (m, 1H at C-2') 1.41 (s, 3H, O–C–CH_3); 1.29 (s, 3H, O–C–CH_3); 0.92 (s, 9H, Si–C(CH_3)$_3$); 0.15 (s, 3H, Si–CH_3); –0.08 (s, 3H, Si–CH_3).

13b: yield = 79%. UV (max, MeOH, nm): 216, 237, 262, 289, 345, 359. MS, *m/z*: 470 (M^+, 0.8), 455 (09), 413 (50), 209 (25), 149 (13), 75 (68), 57 (100). HR-FAB mass: calc: 470.2602, found: 470.2608, for $C_{26}H_{38}N_2O_4Si$. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz): 8.35 (d, H-3, *J* = 5.2); 7.98 (d, H-4, *J* = 5.2); 8.16–8.14 (dd, H-5, *J* = 7.8, 1.2); 7.33–7.30 (ddd, H-6, *J* = 7.8, 7.4, 0.8); 7.66–7.62 (ddd, H-7, *J* = 8.3, 7.4, 1.2); 7.50 (dd, H-8, *J* = 8.3, 0.8); 5.85 (m, 1H at C-1'); 4.23 (s, 3H, N-CH_3); 3.87–3.85 (m, 1H at C-3'); 3.76 (m, 2H, H-4', 5'); 3.65–3.62 (dd, H at C-5', *J* = 11.8, 6.4); 2.38 (m, 2H at C-2'); 1.45 (s, 3H, O–C–CH_3); 1.42 (s, 3H, O–C–CH_3); 0.83 (s, 9H, Si–C(CH_3)$_3$); –0.12 (s, 3H, Si–CH_3); –0.48 (s, 3H, Si–CH_3).

13c: yield = 82%. UV (max, MeOH, nm): 202, 213, 238, 289, 339, 354. MS, *m/z*: no M^+ peak, 531 (05), 489 (49), 431 (08), 402 (09), 254 (11), 91 (100). HR-FAB mass: calc: 546.2915, found: 546.2926, for $C_{32}H_{42}N_2O_4Si$. ^{1}H-NMR (δ, $CDCl_3$, *J* = Hz, 60 °C): 8.40 (d, H-3, *J* = 4.9); 7.99 (d, H-4, *J* = 4.9); 8.17–8.15 (dd, H-5; *J* = 7.9, 1.3); 7.31–7.28 (ddd, H-6, *J* = 7.9, 7.5, 1.0); 7.53–7.50 (ddd, H-7, *J* = 8.5, 7.5, 1.3); 7.33 (dd, H-8; *J* = 8.5, 1.0); 7.24–7.17 (m, 3H, H-3", 4", 5"); 6.94–6.93 (d, 2H, H-2", 6"; *J* = 7.3); 6.02 (br d, 2H of CH_2 of CH_2–C_6H_5); 5.55–5.52 (dd, 1H at C-1', *J* = 8.8, 5.5); 3.61 (m, 2H, H-3', 5'); 3.47 (m, 2H, H-4', 5'); 2.84 (br s, OH); 2.60 (m, 1H at C-2'); 2.22 (m, 1H at C-2'); 1.29 (s, 3H, O–C–CH_3); 1.20 (s, 3H, O–C–CH_3); 0.79 (s, 9H, Si–C(CH_3)$_3$); –0.12 (s, 3H of Si–CH_3); –0.43 (br s, 3H of Si–CH_3).

Preparation of ***14a–c***

General procedure: Tetra(*n*-butyl)ammonium fluoride (1 M, 2 equiv) in THF (containing small amounts of water) was added to a solution of the appropriate **13a–c** (1 equiv) in THF at room temperature under argon. After stirring for 1.5 h, NH_4Cl was added and the reaction mixture was washed with EtOAc. The aqueous layer was saturated with NaCl, extracted with EtOAc, and the combined organic layers were washed, and dried ($MgSO_4$). The products were separated on MPLC with EtOAc:hexane (2:1) as colorless oils of the following data.

14a: yield = 70%. UV (max, MeOH, nm): 207, 241, 250, 289, 302, 315. MS, *m/z*: 342 (M^+, 4.9), 327 (5.7), 253 (4.2), 211 (9.4), 198 (100), 168 (32), 140 (14). HR-FAB mass: calc: 342.1580, found: 342.1581, for $C_{19}H_{22}N_2O_4$. ^{1}H-NMR (δ,

$CDCl_3$, J = Hz): 9.47 (br, –NH); 8.31 (d, H-3, J = 5.4); 7.89 (d, H-4, J = 5.4); 8.13 (dd, H-5, J = 7.4, 1.0); 7.30–7.27 (ddd, H-6, J = 7.8, 7.4, 1.0); 7.58–7.55 (ddd, H-7, J = 8.3, 7.8, 1.2); 7.52–7.50 (dd, H-8, J = 8.3, 1.0); 5.52–5.51 (dd, 1H at C-1', J = 7.3, 2.7); 4.35 (br s, OH at C-1'); 4.24–4.20 (m, 1H at C-3'); 4.01–3.98 (m, 1H at C-4'); 3.84–3.80 (dd, 1H at C-5', J = 12.0, 4.7); 3.80–3.77 (dd, 1H at C-5', J = 12.0, 4.1); 2.46–2.41 (m, 1H at C-2'); 2.39–2.34 (m, 1H at C-2'); 1.52 (s, 3H, O–C–CH_3); 1.41 (s, 3H, O–C–CH_3).

14b: yield = 68%. UV (max, MeOH, nm): 202, 216, 237, 289, 356. MS, *m/z*: 356 (M^+, 0.5), 341 (2.5), 225 (3.9), 220 (2.8), 212 (100). HR-FAB mass: calc: 356.1737, found: 356.1728, for $C_{20}H_{24}N_2O_4$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.38 (d, H-3, J = 5.2); 7.95 (d, H-4, J = 5.2); 8.15–8.13 (dd, H-5, J = 7.8, 1.9); 7.33–7.30 (ddd, H-6, J = 7.8, 7.6, 1.0); 7.65–7.62 (ddd, H-7, J = 8.3, 7.6, 1.8); 7.49 (dd, H-8, J = 8.3, 1.0); 5.81–5.79 (dd, 1H at C-1', J = 8.0, 3.6); 4.28–4.25 (m, 1H at C-3'); 4.18 (s, 3H, N–CH_3); 4.09–4.05 (m, 1H at C-4'); 3.86–3.83 (dd, 1H at C-5', J = 11.8, 4.9); 3.79–3.76 (dd, 1H at C-5', J = 11.9, 4.0); 2.49–2.45 (m, 1H at C-2'); 2.22–2.16 (m, 1H at C-2'); 1.47 (s, 3H, O–C–CH_3); 1.39 (s, 3H, O–C–CH_3).

14c: yield = 71%. UV (max, MeOH, nm): 206, 210, 237, 287, 339, 353. HR-FAB mass: calc: 432.2050, found: 432.2038, for $C_{26}H_{28}N_2O_4$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz, 60 °C): 8.39 (d, H-3, J = 5.2); 7.96 (d, H-4, J = 5.2); 8.17–8.16 (dd, H-5, J = 8.0, 0.9); 7.32–7.29 (ddd, H-6, J = 8.0, 7.5, 1.0); 7.56–7.52 (ddd, H-7, J = 8.5, 7.5, 0.9); 7.39 (dd, H-8, J = 8.5, 1.0); 7.22–7.17 (m, 3H, H-3", 4", 5"); 6.93–6.91 (dd, 2H, H-2", 6", J = 5.8, 2.1); 5.90 (d, 1H of CH_2–C_6H_5, J = 17.7); 5.79 (d, 1H of CH_2–C_6H_5, J = 18.0); 5.45–5.43 (dd, 1H at C-1', J = 9.2); 5.07 (br s, –OH at C-1'); 4.40–4.36 (m, 1H at C-3'); 3.77–3.73 (m, 1H at C-4'); 3.70–3.65 (ddd, 2H of C-5', J = 13.1, 10.1, 1.8); 2.12–2.07 (m, 1H at C-2'); 1.94 (br s, –OH at C-5'); 1.86–1.80 (m, 1H at C-2'); 1.46 (s, 3H, O–C–CH_3); 1.45 (s, 3H, O–C–CH_3).

*Preparation of **15a–c** by oxidation with MnO_2*

General procedure: a solution of the appropriate **14a–c** in $CHCl_3$ was stirred with active MnO_2 [28] (10 times the weight of the starting material) at room temperature overnight until the starting material was no longer detectable by TLC (hexane: EtOAc, 1:1). The reaction mixture was filtered through celite, then washed several times with $CHCl_3$. The combined chloroformic solution was evaporated and the yellow residue was separated by flash column chromatography (EtOAc:hexane, 1:1) to afford **15a–c** as yellow oils with the following data.

15a: yield = 60%. UV (max, MeOH, nm): 217, 252, 262, 285, 308, 381. MS, *m/z*: 340 (M^+, 32), 325 (80), 282 (93), 265 (100), 251 (96), 235 (72), 212 (96). HR-FAB mass: calc: 340.1416, found: 340.1439, for $C_{19}H_{20}N_2O_4$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 10.31 (br s, NH); 8.51 (d, H-3, J = 4.9); 8.16 (d, H-4, J = 4.9); 8.15 (d, H-5, J = 8.3, 0.9); 7.35–7.26 (ddd, H-6, J = 8.3, 7.3, 1.0); 7.62–7.59 (ddd, H-7, J = 8.0, 7.3, 1.0); 7.57–7.56 (dd, H-8, J = 8.0, 1.0); 4.66–4.62 (m, 1H at C-3'); 4.04–4.01 (m, 1H at C-4'); 3.92–3.88 (ddd, 1H at C-5', J = 12.0, 4.4, 2.4); 3.83–3.77 (m, 2H, H-5', 2'); 3.75–3.70 (dd, 1H at C-2', J = 16.8, 4.6); 2.59–2.56 (t, OH, J = 6.3 exchanged with D_2O); 1.46 (s, 6H, $2CH_3$ of –$C(CH_3)_2$).

15b: yield = 60%. UV (max, MeOH, nm): 218, 288, 375. Ms, *m/z*: 354 (M^+, 2.2), 339 (4.9), 296 (5.1), 265 (9.9), 225 (28), 208 (15), 181 (100). HR-FAB mass: calcd: 354.1580, found: 354.1564, for $C_{20}H_{22}N_2O_4$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.48 (d, H-3, J = 4.9); 8.15 (d, H-4, J = 4.9); 8.16–8.15 (dd, H-5, J = 7.4, 1.8); 7.36–7.33 (ddd, H-6, J = 7.9, 7.4, 0.9); 7.67–7.64 (ddd, H-7, J = 8.2, 7.9, 1.8); 7.54–7.52 (dd, H-8, J = 8.2, 0.9); 4.61–4.57 (m, 1H at C-3'); 4.04–4.01 (m, 1H at C-4'); 3.94 (s, 3H, N–CH_3); 3.91–3.87 (m, 1H at C-5'); 3.83 and 3.76 (m, 2H, H-2', 5'); 3.70–3.65 (dd, 1H at C-2', J = 16.2, 7.6); 2.35–2.32 (dd, OH, J = 7.4 exchanged with D_2O); 1.44 (s, 3H, C–CH_3); 1.41 (s, 3H, C–CH_3).

15c: yield = 63%. UV (max, MeOH, nm): 217, 288, 369. HR-FAB mass: calc: 430.1893, found: 430.1873, for $C_{26}H_{26}N_2O_4$. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.46–8.45 (d, H-3, J = 4.9); 8.15–8.14 (d, H-4, J = 4.9); 8.18–8.16 (dd, H-5, J = 7.8, 1.2); 7.36–7.32 (ddd, H-6, J = 7.8, 7.4, 0.9); 7.61–7.58 (ddd, H-7, J = 8.6, 7.4, 1.2); 7.52–7.50 (dd, H-8, J = 8.6, 0.9); 7.17–7.14 (m, 3H, H-3", 4", 5"); 6.83–6.81 (ddd, 2H, H-2"; 6", J = 7.5, 4.1, 1.0); 5.82–5.81 (d, 2H of CH_2–C_6H_5, J = 4.2); 4.42–4.38 (m, 1H at C-3'); 3.88–3.85 (m, 1H at C-4'); 3.79–3.76 (m, 1H at C-5'); 3.68–3.64 (m, 1H at C-5'); 3.45–3.40 (dd, 1H at C-2'; J = 17.1, 6.5); 3.32–3.28 (dd, 1H at C-2'; J = 17.1, 5.8); 2.13 (br s, –OH); 1.41 (s, 3H, C–CH_3); 1.34 (s, 3H, C–CH_3).

*Acetonide removal [29] of **15a–c***

General procedure: to the appropriate **15a–c** in methanol (6 mL) HCl (10%, 5 mL) was added and the resulting mixture was heated in a water bath at 80 °C for 15 min. Acetone and methanol were slowly distilled off under reduced pressure. A mixture of methanol (5 mL) and HCl (10%, 5 mL) were added and the mixture was kept at room temperature overnight. $CHCl_3$ and solid Na_2CO_3 were added and the organic layer was separated. The aqueous layer was saturated with NaCl, extracted with $CHCl_3$:MeOH (9:1), dried ($MgSO_4$) and after evaporating of the solvent the residue was separated by MPLC with EtOAc:MeOH (95:5) to afford **16a–c** as yellow oils of the following data.

16a: yield = 60%. UV (max, MeOH, nm): 217, 234, 242, 251, 259, 284, 307, 380. EIMS: *m/z*: 300 (M^+, 2.8), 282 (7.1), 251 (7.6), 239 (7.4), 221 (13), 211 (38), 182 (32), 168 (100), 167 (89), 140 (70). HR-FAB mass: calc: 300.1110, found: 300.1105, for $C_{16}H_{16}N_2O_4$. ^{13}C-NMR (δ, CD_3OD, DEPT): C-1 = 137.2; C-3 = 138.5; C-4 = 120.1; C-5 = 122.6; C-6 = 121.6; C-7 = 130.3; C-8 = 113.4; C-10 = 136.3; C-11 = 133.3; C-12 = 121.6; C-13 = 143.4; C-1' = 203.4; C-2' = 43.1; C-3' = 69.5; C-4' = 75.4; C-5' = 64.3. ^{1}H-NMR (δ, $CDCl_3$, J = Hz): 8.47 (d, H-3, J = 5.2); 8.32 (d, H-4, J = 5.2); 8.23 (dd, H-5, J = 7.8, 0.8); 7.33–7.29 (ddd, H-6, J = 7.8, 7.6, 1.0); 7.61–7.58 (ddd, H-7, J = 8.3, 7.6, 0.8); 7.71 (dd, H-8, J = 8.3, 1.0); 4.44–4.41 (m, 1H at C-3'); 3.75–3.73 (ddd, 1H at C-5', J = 8.8, 3.4); 3.70–3.63 (m, 3H, H-5', 4', 2'); 3.54–3.51 (dd, 1H at C-2', J = 15.9, 4.3).

*Natural alkaloid **3***: UV (max, MeOH, nm): 216, 234, 243, 251, 260, 284, 307, 380. EIMS, *m/z*: 300 (M^+, 26), 282 (23), 264 (82), 247 (38), 239 (33), 221 (34), 211 (100), 210 (87), 182 (30), 168 (93), 167 (59), 140 (28). HR-FAB mass: calc: 300.1110, found: 300.1102, for $C_{16}H_{16}N_2O_4$. ^{13}C-NMR (δ, CD_3OD, DEPT): C-1 = 137.3; C-3 = 138.5; C-4 = 120.1; C-5 = 122.6; C-6 = 121.6; C-7 = 130.3; C-8 = 113.4; C-10 = 136.3; C-11 = 133.3; C-12 = 121.6; C-13 = 143.4; C-1' = 203.6; C-2' = 43.1; C-3' = 76.2; C-4' = 70.3 ; C-5' = 64.7. ^{1}H-NMR (δ, CD_3OD, J = Hz): 8.46 (d, H-3, J = 5.2); 8.30 (d, H-4, J = 5.2); 8.21 (dd, H-5, J = 8.0, 1.0); 7.31 (ddd, H-6, J = 8.0, 8.0, 1.0);

7.59 (ddd, H-7, J = 8.3, 8.0, 1.1); 7.70 (d, H-8, J = 8.3); 4.34 (m, 1H at C-3'); 3.82 (dd, 1H at C-5', J = 10.7, 3.3); 3.68–3.60 (m, 4H, H-5', 4' and 2H at C-2').

16b: yield = 61%. UV (max, MeOH, nm): 205, 220, 247, 289, 373. Low FAB mass: 315 (M^+, 18), 307 (28), 289 (15), 155 (29), 154 (100), 137 (60), 136 (66), 120 (10), 107 (18). HR-FAB mass: calc: 314.1267, found: 314.1285, for $C_{17}H_{18}N_2O_4$. ^{1}H-NMR (δ, CD_3OD, J = Hz); 8.42 (d, H-3, J = 4.9); 8.29 (d, H-4, J = 4.9); 8.25–8.23 (dd, H-5, J = 7.6, 1.0); 7.35–7.32 (ddd, H-6, J = 7.6, 7.0, 1.8); 7.67–7.65 (m, 2H, H-7, 8); 4.35–4.32 (m, 1H at C-3'); 3.89 (s, 3H, N-CH_3); 3.71–3.69 (ddd, 1H at C-5', J = 8.9, 3.7); 3.67–3.61 (m, 2H, H-4', 5'); 3.58–3.54 (dd, 1H at C-2'; J = 15.3, 4.5); 3.52–3.47 (dd, 1H at C-2'; J = 15.2, 9.1).

16c: yield = 63%. UV (max, MeOH, nm): 217, 289, 339, 360. MS, *m/z*: 390 (M^+, 0.6), 373 (5.8), 313 (10), 257 (11), 255 (12), 91 (100). HR-FAB mass: calc: 390.1581, found: 390.1594, for $C_{23}H_{22}N_2O_4$. ^{1}H-NMR (δ, CD_3OD, J = Hz, 60 °C): 8.42 (d, H-3, J = 4.9); 8.31 (d, H-4, J = 4.9); 8.28–8.26 (dd, H-5, J = 7.9, 1.8); 7.37–7.34 (ddd, H-6, J = 7.9, 7.9, 1.8); 7.62–7.61 (m, 2H, H-7, 8); 7.17–7.13 (m, 3H, H-3", 4", 5"); 6.81–6.79 (dd, 2H, H-2", 6"; J = 7.5, 2.2); 5.83–5.80 (d, 1H of CH_2–C_6H_5; J = 17.1); 5.77–5.74 (d, 1H of CH_2–C_6H_5; J = 16.7); 4.18–4.15 (m, 1H at C-3'); 3.66–3.63 (dd, 1H at C-5'; J = 11.2, 5.0); 3.60–3.56 (dd, 1H at C-5'; J = 11.2, 6.2); 3.53–3.50 (m, 1H at C-4'); 3.23–3.18 (dd, 1H at C-2'; J = 16.2, 8.6); 3.01–2.97 (dd, 1H at C-2'; J = 16.2, 4.4).

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