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Synthesis of Ring C Modified Sesbanimide Analogues

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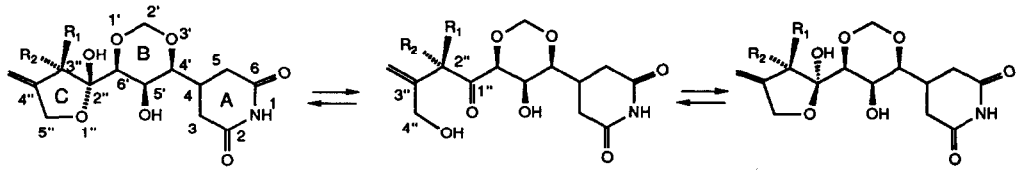
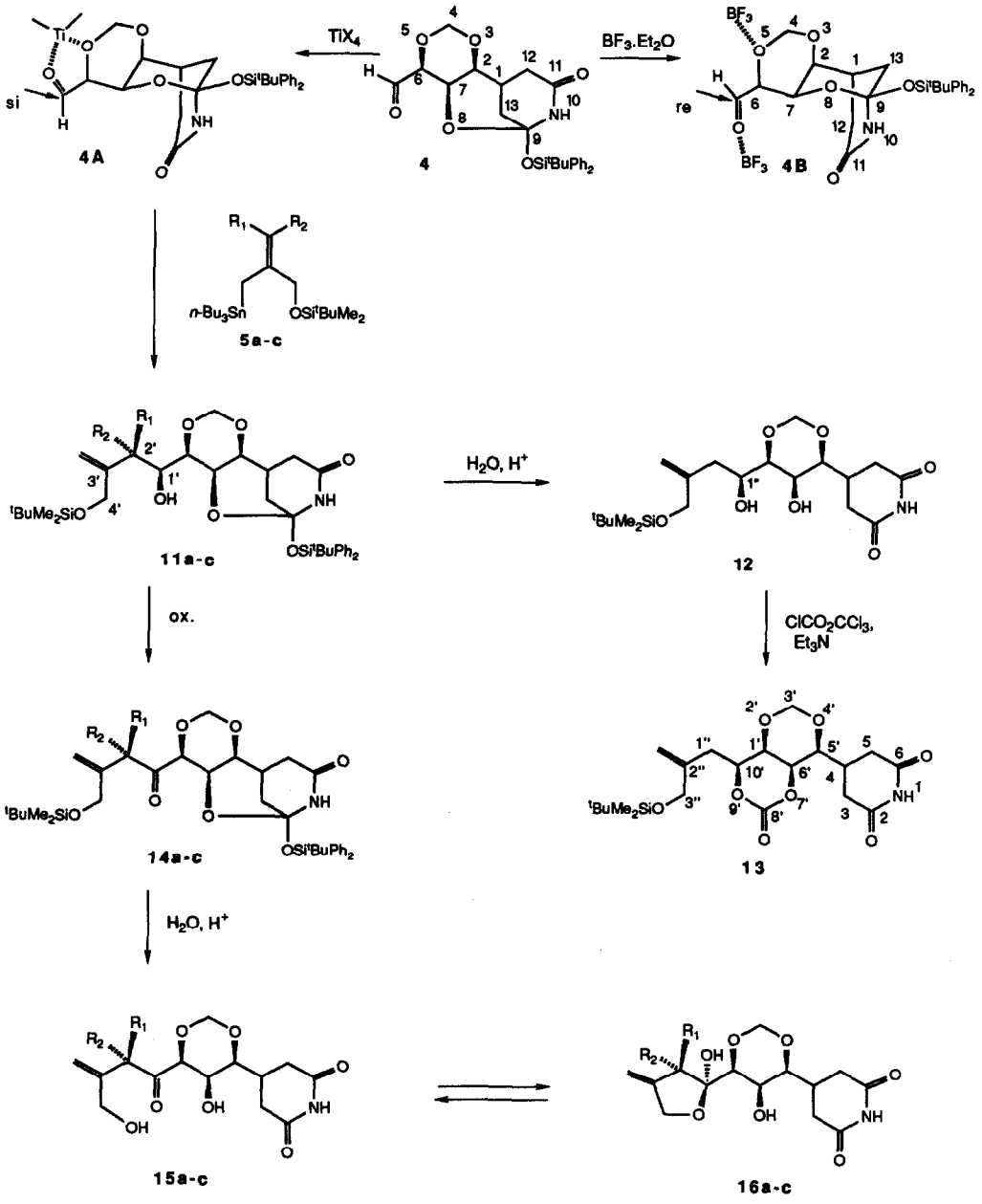
Abstract: *D-(+)-Xylose has been converted into C-ring modified analogues of (+)-sesbanimide A, via tricyclic aldehyde 4 as a central intermediate. The synthetic strategy involved the condensation of 4 with appropriate allylstannanes, as C-ring precursors, employing $TiCl_3(OiPr)$ as a highly effective electrophilic catalyst.*

The alkaloids (+)-sesbanimide A (**1a**) and sesbanimide B (**1b**) are two constituents of the seeds of *Sesbania drummondii*[1] and *Sesbania punicea*[2] which exhibit significant activity in antileukemic screening models. (+)-Sesbanimide A has been shown to be the most potent component of the seeds, while sesbanimide B is about ten times less active. The two alkaloids are isomeric and are distinguished only by the difference in the stereochemistry of the C(3'')-methyl substituent in ring C. This apparently minor structural variation not only results in a substantial difference in biological activity between the two compounds but also has a remarkable influence on the position of the hydroxy ketone $\rightleftharpoons$ hemiacetal equilibria involving their respective C rings (**1a** $\rightleftharpoons$ **2a** $\rightleftharpoons$ **3a**; **1b** $\rightleftharpoons$ **2b** $\rightleftharpoons$ **3b**). The NMR spectrum of sesbanimide A in $CDCl_3$ shows only the presence of the hemiacetal form **1a**, whereas that of sesbanimide B, in the same solvent, reveals it as a mixture of the isomeric forms **1b** and **3b**. In more polar solvents, the NMR spectra of **1a** and **1b** attest to the fact that the open hydroxy ketone forms (**2a** and **2b**), increase in both equilibria. The aforementioned biological activities of **1a** and **1b** coupled with their structural properties have led us to undertake the synthesis of **1a** analogues with modifications in the substitution-pattern at C-3'', for structure-activity relationship studies. In this communication, we present the synthesis of sesbanimide analogues **16a-c** (Scheme 1). The biological activity of these compounds will be reported elsewhere.



1 **2** **3**

a R_1 = Me, R_2 = H (+)-sesbanimide A
b R_1 = H, R_2 = Me sesbanimide B



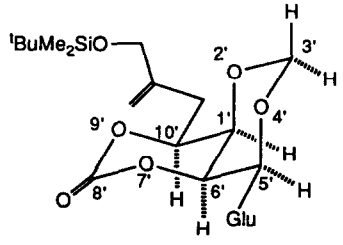
a. $R_1 = R_2 = H$, **b.** $R_1 = Et$, $R_2 = H$, **b'.** $R_1 = H$, $R_2 = Et$, **c.** $R_1 = R_2 = Me$

Scheme 1

We have recently reported[3] a strategy for the synthesis of the parent alkaloid (+)-sesbanimide A (**1a**), starting from D-(+)-xylose. According to this approach, D-(+)-xylose is converted, in thirteen steps, into an aldehyde intermediate **4**[3,4] (Scheme 1), which represents the masked AB ring moiety of the alkaloid molecule. Aldehyde **4** is capable of functioning as a general relay intermediate for the the synthesis of ring C analogues of sesbanimides, by condensation with suitable C-ring synthons. In the context of the synthesis of **1a**, it was observed that the aldehyde function in **4** could be most efficiently condensed with a C-ring synthon when the latter was employed as an allylstannane derivative and the condensation reaction was carried out under influence of $TiCl_3(O\textit{i}Pr)$[5] as an electrophilic catalyst[3].

The condensation of allylstannanes **5a-c** (described in the sequel, Scheme 2) with aldehyde **4** was carried out under influence of $TiCl_3(O\textit{i}Pr)$ at -78°C. In case of **5a** and **5c**, a single product was formed, while reaction of **5b** led to a mixture of two isomeric compounds (Scheme 1). It should be noted that nucleophilic attack at the aldehyde carbon of **4** can result in epimers at that centre. Although the stereochemistry at C(1') in the alcohol product is not crucial for the synthesis, since it is destroyed in the subsequent oxidation step, information on this point is of interest in the context of the stereochemical course of the coupling reaction. In our previous work[3,6], we had assigned the configuration at the developing C(1') chiral carbon on the basis of molecular models of the anticipated aldehyde-Lewis acid catalyst complexes and visualizing their reaction with a stannane or a silane nucleophile. Depending on the nature of the Lewis acid, a complex with the aldehyde (**4**) can assume conformations shown in **4A** and **4B**. Inspection of molecular models show that such complexes are sterically crowded to nucleophilic attack from the front-side (above the plane of the paper), so that the favoured mode for such a process would involve attack from the back-side (below the plane of the paper). This would imply an attack on the si-face of the carbonyl in **4A** and on the re-face in **4B**. Ample analogy for this stereochemical course for Lewis acid catalyzed nucleophilic attack on 2-alkoxycarbonyl compounds is found in the literature[7].

Based on the aforementioned, it could be expected that the reaction of **4** with allylstannanes **5a-c**, in the presence of $TiCl_3(O\textit{i}Pr)$, should selectively lead to the **1'S** alcohols **11a-c**. In order to develop evidence for the proposed stereochemical course of the reaction, the product **11a** was selected for detailed examination. It was visualized that if **11a** was converted into a cyclic derivative, the orientation of the C(1')-hydroxyl could be analyzed (NMR) with facility in the rigid product. With this aim **11a** was subjected to hydrolytic studies. While attempts to specifically open the silyl ether function at C-9 led to simultaneous hydrolysis of the C(4')-silyl ether, we took advantage of the reaction intended to prepare an acetal, which, unexpectedly, gave the diol **12** in 68 % yield (vide experimental). Reaction of **12** with trichloromethyl chloroformate provided the crystalline carbonate **13**, in which the C(10')-O(9') bond is part of a cyclic structure. A detailed study of the NMR spectra of **13** allowed the assignment of an 1,3-diaxial relationship between the H6'-H10' protons. This assignment is attested by the following data: (i) there are only very small coupling constants (less then 1 Hertz) between H5' - H6'; H6' - H1' and between H1' - H10'; (ii) strong interactions (NOE difference) are observed between H6' and H10' and also between H1', $H3'_{ax}$ and H5'.



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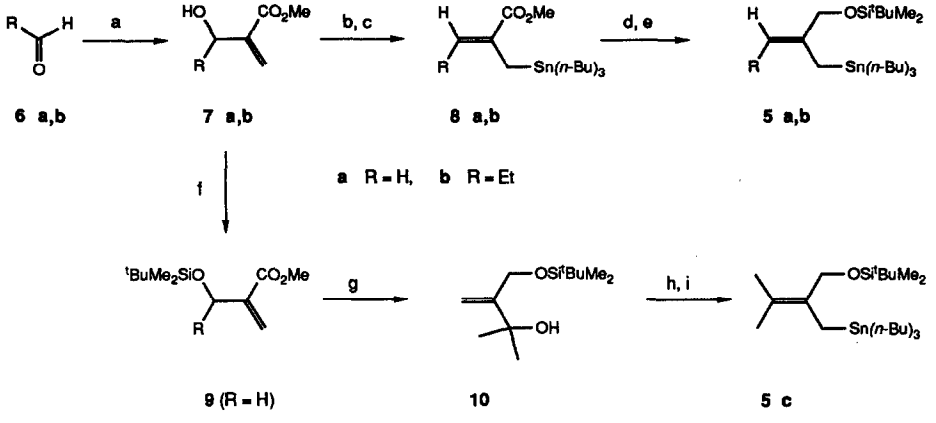
By extrapolation, the C(1'')-hydroxyl in **12** and the C(1')-hydroxyl in **11a** can now be assigned the S-configuration. The S orientations of the related hydroxyl groups in **11b**, **11b'** and **11c** (Scheme 1) are assigned by analogy[8].

The use of stannane **5b** in the condensation gives two different ethyl compounds **11b** and **11b'** that are epimeric at C(2'). The assignments of their structures and those of **14b,b'** and of **16b,b'** are based on the following information: (*i*) the ^{1}H NMR spectra of the epimeric pairs **11b,b'**, **14b,b'** and **16b,b'** exhibit characteristic differences which corresponded to those observed for the analogous compounds in the sesbanimide series[3,9]; (*ii*) the R_f values of the epimers show relatively large differences that again agree with those found in the sesbanimide series; (*iii*) the end product **16b** shows only one hemiacetal form (NMR) in $CDCl_3$ while **16b'** is a mixture of two hemiacetals in the same solvent. This behaviour parallels that of (+)-sesbanimide A and sesbanimide B[1b].

Oxidation of the alcohols **11a-c** with the Dess-Martin[10] reagent gave the corresponding ketones (**14a-c**). When the silyl ether groups in **14a-c** were deprotected by hydrolysis, the hydroxy ketones **15a-c** were formed which spontaneously cyclized to the hemiacetals corresponding to sesbanimide analogues **16a-c**.

For construction of the aforementioned sesbanimide analogues, new allylstannane derivatives were required. The requisite stannanes **5a-c** were prepared by the syntheses outlined in Scheme 2. The synthesis of **5a,b** followed a sequence of steps in which aldehydes **6a,b** were condensed with methyl acrylate in the presence of DABCO[11] to yield hydroxy esters **7a,b**. Acetylation of the hydroxy functions of **7a,b** and subsequent treatment with *n*-$Bu_3SnCuLiBr.DMS$ complex[12], led to allylstannane esters **8a,b** respectively. The synthesis of the desired reagents was completed by reduction of **8a,b** by DIBAH and protection of the generated alcohols as their silyl derivatives. The C-ring precursor **5c** could not, however, be prepared by the same route, since the DABCO catalyzed condensation of acetone with methyl acrylate could not be affected. To circumvent this difficulty, the hydroxy ester **7a** was silylated to **9** and the latter treated with excess of MeMgI (3 equiv.) to give tertiary alcohol **10**. Subsequently, **10** was acetylated and converted to the corresponding allylpalladium complex which upon reaction with tributyltindiethylaluminium, according to the Trost procedure[13], gave the desired stannane **5c**.



Reagents: (a) CH_2=$CHCO_2Me$, DABCO; (b) Ac_2O, H_2SO_4; (c) *n*-$Bu_3SnCuLiBr.DMS$; (d) DIBAH/THF; (e) $^tBuMe_2SiCl$, Et_3N, DMAP; (f) $^tBuMe_2SiCl$; (g) MeMgI (3 equiv.); (h) Ac_2O, pyr, DMAP; (i) *n*-Bu_3Sn-$AlEt_2$, $Pd(Ph_3P)_4$ (cat.).

Scheme 2

Experimental

General information. The glassware, used in the reactions with tricyclic silyl compounds, was washed with a solution of 3 % Et_3N in MeOH and dried at 150°C during at least 16 hours. All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The absorptions are given in cm^{-1}. All NMR spectra were run on a Bruker AC-200, Bruker WM-250, Bruker AMX-300 or Bruker WM-500 instrument. The chemical shifts (δ) are given in ppm. For the signals the following abbreviations are used: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Spin-spin coupling constants are given in Hertz. Fast atom bombardment (FAB) mass spectrometry was carried out on a VG Analytical ZAB-HFqQ mass spectrometer, an instrument with reverse geometry, fitted with a high field magnet, and coupled to a VG 11-250 data system. The samples for the electron impact (EI) mass spectra were introduced via the direct insertion probe into the ion source. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

methyl 2-methylene-3-hydroxypropanoate (7a)
The reaction is carried out following a methodology of Hoffmann and Rabe[11]. After 72 h a stirred mixture of methyl acrylate (50 ml, 560 mmol), paraformaldehyde **6a** (10.8 g, 360 mmol) and 1,4-diazabicyclo-[2.2.2]octane (DABCO, 4.40 g, 39 mmol) was diluted with ether (180 ml) and washed with H_2O (3 × 40 ml). The combined aqueous washes were extracted with ether (40 ml), the organic portions combined, washed with brine (40 ml), dried ($MgSO_4$) and filtered. The ether was removed *in vacuo* and the residue distilled through a 5 cm Vigreux column to give 10.1 g almost pure **7a** (24 %) as a clear colourless liquid. B.p. 60-61°C/1 mm. Hg. R_f = 0.22 (SiO_2, EtOAc/petroleum-ether 60-80 1/2). **IR** ($CHCl_3$): 3660-3300 (OH), 3030, 3000, 2955, 2870 (CH), 1715 (C=O), 1630 (C=C), 1440 (CH). **^{1}H NMR** (200 MHz, $CDCl_3$): 3.77 (s, 3H, CH_3O), 4.31 (m, 2H, CH_2O), 5.84 (q, 1H, J=1.3, HC=C), 6.25 (d, 1H, J=0.9, HC=C).

methyl 2-[(tri-*n*-butylstannyl)methyl]-2-propenoate (8a)
The reaction is carried out in analogy with a synthesis of J.L. Wood[12]. Concentrated H_2SO_4 (5 drops) was slowly added to a stirring mixture of alcohol **7a** (10.1 g, 87 mmol) and acetic anhydride (12.9 ml, 136 mmol). The reaction was immediately placed in an ice bath and after 5 min. stirring was continued at 20°C during 35 min. The mixture was diluted with H_2O (130 ml) and NaCl (4 g) was added. After extraction with CH_2Cl_2 (3 × 50 ml) the combined organic layers were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated. After distillation 10.2 g (74 %) of methyl 2-methylene-3-acetoxypropanoate was isolated. Colourless liquid. B.p. 65-66°C/3.0 mm. Hg. R_f = 0.42 (SiO_2, EtOAc/petroleum-ether 60-80 1/2). **IR** ($CHCl_3$): 3020, 2950 (CH), 1735, 1725 (C=O), 1630 (C=C). **^{1}H NMR** (200 MHz, $CDCl_3$): 2.09 (s, 3H, CH_3COO), 3.78 (s, 3H, CH_3O), 4.79 (d, 2H, J=0.9, CH_2O), 5.84 (m, 1H, HC=C), 6.36 (d, 1H, J=0.9, HC=C).

At 0°C *n*-BuLi (7.6 ml, 12.2 mmol, 1.6 M solution in hexanes) was slowly added to a solution of diisopropylamine (1.80 ml, 12.8 mmol) in THF (12.2 ml). After 6 min. *n*-Bu_3SnH (3.30 ml, 12.3 mmol) was added dropwise in 6 min. The solution turned bright yellow and the white teflon stir bar turned blue. After 15 min. the mixture was cooled to -78°C and solid copper(I)bromide-dimethyl sulfide complex (2.50 gr, 12.2 mmol) was added at once to give a dark coloured solution. After 10 min. dimethyl sulfide (895 µl, 12.2 mmol) was slowly added. 20 Min. later the acetate (1.60 gr, 10.1 mmol) in THF (10 ml) was slowly added and after stirring for 45 min. at -78°C the reaction was quenched with saturated aqueous NH_4Cl (50 ml) directly followed by concentrated NH_4OH (5 ml), warmed to room temperature and stirred under a slow stream of air until the aqueous phase became bright transparent blue (about 10 h). After extraction with petroleum-ether 40-60 (4 × 25 ml) the combined extracts were filtered through $MgSO_4$ and concentrated *in vacuo* (at 25°C) to give a light yellow liquid. After flash chromatography (SiO_2, petroleum-ether 40-60/EtOAc 25/0 → 25/1) stannane **8a** (2.0 gr, 50 %) was isolated as a colourless liquid. **IR**: to avoid contamination of the IR cell the compound was not characterized by IR. **^{1}H NMR** (200 MHz, $CDCl_3$ + 0.4 % pyridine): 0.6-1.1 (m, 15H, CH_3-CH_2-), 1.1-1.7 (m, 12H, -CH_2-CH_2-Sn), 1.97 (d, 2H, J=0.8, 1.82 and 2.11 one set of ^{119}Sn sidebands, Sn-CH_2-C=C), 3.73 (s, 3H, CH_3O), 5.29 (d, 1H, J=1.3, HC=C), 5.81 (d, 1H, J=1.5, HC=C).

***tert*-butyldimethyl[[2-[(tri-*n*-butylstannyl)methyl]-2-propenyl]oxy]silane (5a)**
To a solution of ester **8a** (2.00 g, 5.1 mmol) in dry THF (50 ml) at -78°C was added DIBAH (10.7 ml, 13.0 mmol, 20 wt. % solution in toluene) in 2 min. After 10 min. the temperature was raised to 20°C and 3.5 h later methanol (13 ml) was carefully added followed by pentane (77 ml) and $MgSO_4$ (100 mg). After stirring for 2 h the thick white precipitate was filtered and washed several times (with pentane/ether 10/1) until a dry white powder was left. The combined filtrates were concentrated *in vacuo* (30°C) and the alcohol, together with some

toluene, was directly used. The crude alcohol was dissolved in dry CH_2Cl_2 (50 ml) followed by Et_3N (1.05 ml, 7.5 mmol), *tert*-butyldimethylsilyl chloride (994 mg, 6.6 mmol) and 4-dimethylaminopyridine (62 mg, 0.5 mmol). After 6 h the solvents were evaporated *in vacuo* and H_2O (70 ml) was added. After extraction with petroleum-ether 40-60 (3 × 50 ml) the organic layers were dried (Na_2SO_4), filtered and evaporated to give a colourless residue that was purified by chromatography (50 g Al_2O_3 activity I, pH 9.5, petroleum-ether 40-60) to give pure **5a** (1.31 g, 54 % for two steps) as a clear colourless liquid. The product was stabilized with catalytic amounts of Et_3N and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide and kept under nitrogen at -30°C. **IR**: to avoid contamination of the IR cell the compound was not characterized by IR. **^{1}H NMR** (200 MHz, $CDCl_3$ + 0.4 % pyridine): 0.07 (s, 6H, CH_3Si), 0.6-1.1 (m, 24H, *tert*-BuSi and CH_3-CH_2-), 1.1-1.7 (m, 12H, -CH_2-CH_2-Sn), 1.72 (s, 2H, Sn-CH_2-C=C, at 1.87 one ^{119}Sn sideband visible), 3.97 (s, 2H, -C=C-CH_2-OSi), 4.59 (d, 1H, J=1.0, HC=C), 4.78 (q, 1H, J=2.0, HC=C). **MS** (FAB), *m/z* (% intensity): parent ion not observed, 419 ([$C_{22}H_{48}OSi^{120}Sn$ - (C_4H_9)]$^+$, 100 %), 417 ([$C_{22}H_{48}OSi^{118}Sn$ - (C_4H_9)]$^+$, 82 %), 415 ([$C_{22}H_{48}OSi^{116}Sn$ - (C_4H_9)]$^+$, 46 %), 291 (44 %), 289 (37 %), 287 (25 %), 251 (27 %), 249 (27 %), 247 (18 %), 235 (34 %), 233 (30 %), 231 (20 %), 195 (32 %), 193 (32 %), 191 (23 %), 179 (67 %), 177 (75 %), 175 (60 %), 73 (83 %).

methyl 2-[(tri-*n*-butylstannyl)methyl]-2-pentenoate (8b)

A mixture of propionaldehyde (40 ml, 0.55 mol) and methyl acrylate (50 ml, 0.55 mol) was stirred with DABCO (2.4 g, 21 mmol) for 7 days. Then it was washed with 6 N. HCl (20 ml) and 2 N. NaOH (2 × 20 ml). The combined aqueous washes were extracted once with ether. The combined organic layers were concentrated *in vacuo* and the residue added to an ice cold solution of 100 ml acetic anhydride with 1 ml concentrated H_2SO_4. The mixture was allowed to warm up to room temperature and stirred overnight. Water (200 ml) and ether (400 ml) were added, the layers separated and the water layer extracted with ether (2 × 100 ml). The organic layers were dried ($MgSO_4$) and concentrated. Fractional vacuum distillation gave 44.8 g (44 %) of a colourless liquid (b.p. 85-90°C/6.0 mm. Hg). **IR** ($CHCl_3$): 2960, 2920, 2825 (CH), 1730-1690 (C=O), 1600 (C=C), 1430, 1410 (CH). **^{1}H NMR** (200 MHz, $CDCl_3$): 0.90 (t, 3H, J=7.4, CH_3C-), 1.6-1.9 (m, 2H, -CH_2-), 2.08 (s, 3H, CH_3COO), 3.77 (s, 3H, CH_3O), 5.56 (m, 1H, -CH-O-), 5.76 (s, 1H, HC=C), 6.29 (s, 1H, HC=C). **MS** (EI): 187 ($C_9H_{15}O_4$, [M+H]$^+$, 1.3 %), 157 (4 %), 155 (10 %), 144 (12 %), 143 (68 %), 127 (9 %), 126 (51 %), 115 (52 %), 112 (12 %), 111 (47 %), 95 (15 %), 83 (15 %), 67 (17 %), 43 (100 %).

To a solution of diisopropylamine (0.72 ml, 5.14 mmol) in THF (5 ml) at 0°C was added dropwise *n*-BuLi (3.04 ml, 1.6 M in hexane) and after stirring for 5 min. *n*-Bu_3SnH (1.32 ml, 5.14 mmol) was added dropwise. After 15 min from complete addition, the reaction mixture was cooled to -78°C, solid copper(I)bromide-dimethyl sulfide complex (1 g, 5 mmol) was added and the mixture stirred for 20 min.. Then a solution of the acetate (745 mg, 4.0 mmol) in THF (4 ml) was added, the mixture was stirred for 4 h, allowed to warm to about -15°C and quenched with saturated $NaHCO_3$ (8 ml). After vigorous stirring for 30 min. the reaction mixture was filtered, the filtrate separated and the water layer extracted with ether (3 ×). The combined organic layers were washed with aqueous HCl (10 %) and brine, dried (Na_2SO_4) and concentrated to yield 1.5 g residue. Column chromatography (SiO_2, petroleum-ether 40/60) gave 0.65 g (43 %) **8b**. **^{1}H NMR** (200 MHz, $CDCl_3$): 0.6-1.0 (m, 15H, CH_3-CH_2-C-C-Sn), 1.05 (t, 3H, J=7.5, CH_3-C-C=C), 1.2-1.6 (m, 12H, -CH_2-CH_2-Sn), 1.88 (s, 2H, Sn-CH_2-C=C, at 1.73 and 2.03 two ^{119}Sn sidebands visible), 2.0-2.2 (m, 2H, C-CH_2-C=C), 3.71 (s, 3H, CH_3O), 6.41 (t, 1H, J=7.1, HC=C). **MS** (EI), *m/z* (% intensity): parent ion not observed, 361 ([$C_{19}H_{38}O_2{}^{120}Sn$ - (C_4H_9)]$^+$, 100 %), 360 (36 %), 359 ([$C_{19}H_{38}O_2{}^{118}Sn$ - (C_4H_9)]$^+$, 74 %), 358 (29 %), 357 ([$C_{19}H_{38}O_2{}^{116}Sn$ - (C_4H_9)]$^+$, 41 %), 247 (5 %), 245 (4 %), 243 (2 %), 179 (13 %), 177 (12 %), 175 (8 %), 151 (8 %), 149 (6 %), 147 (4 %).

***tert*-butyldimethyl[[2-[(tri-*n*-butylstannyl)methyl]-2-pentenyl]oxy]silane (5b)**

To a solution of ester **8b** (650 mg, 1.55 mmol) in THF (25 ml) at -78°C was added dropwise over 2 min. a solution of DIBAH (3.87 ml, 1.0 M solution in toluene). The reaction mixture was allowed to warm up to room temperature and after stirring for 3 h quenched with MeOH (2 ml), diluted with pentane (10-15 ml) and seeded with $MgSO_4$. After stirring for 45 min. hyflo was added, the suspension filtered and the precipitate triturated with a mixture of ether/pentane. The filtrate was concentrated and the residue was directly transformed into its silyl ether by dissolving it in dichloromethane (15 ml) at room temperature and adding respectively Et_3N (0.32 ml, 2 mmol), 4-dimethylaminopyridine (15 mg) and *tert*-butyldimethylsilyl chloride (280 mg, 1.8 mmol). After completion of the reaction (18 h) the mixture was carefully concentrated to a small volume and diluted with water (15 ml). Extraction with petroleum-ether 40/60 (3 × 15 ml), washing of the combined ether layers with brine, drying (Na_2SO_4) and concentration gave a residue, which was purified by chromatography (Al_2O_3

activity I, pH 9.5, petroleum-ether 40-60) to give 720 mg (92 %) **5b**. **^{1}H NMR** (300 MHz, $CDCl_3$): 0.06 (s, 6H, CH_3Si), 0.7-1.1 (m, 15H, CH_3-CH_2-C-C-Sn), 0.91 (s, 9H, *tert*-BuSi), 0.97 (t, 3H, J=7.5, CH_3-C-C=C), 1.2-1.6 (m, 12H, -CH_2-CH_2-Sn), 1.70 (s, 2H, Sn-CH_2-C=C, at 1.60 and 1.80 two ^{119}Sn sidebands visible), 1.97 (quint, 2H, C-CH_2-C=C), 3.93 (d, 2H, J=1.1, CH_2-OSi), 5.09 (t, 1H, J=6.8, HC=C). **MS** (EI), *m/z* (% intensity): parent ion not observed, 447 ($[C_{24}H_{52}OSi^{120}Sn$ - $(C_4H_9)]^+$, 44 %), 445 ($[C_{24}H_{52}OSi^{118}Sn$ - $(C_4H_9)]^+$, 32 %), 443 ($[C_{24}H_{52}OSi^{116}Sn$ - $(C_4H_9)]^+$, 18 %), 365 (39 %), 363 (30 %), 361 (20 %), 291 (57 %), 289 (40 %), 287 (24 %), 257 (45 %), 235 (100 %), 233 (73 %), 231 (42 %), 209 (16 %), 207 (13 %), 195 (20 %), 193 (18 %), 191 (18 %), 179 (80 %), 177 (75 %), 175 (45 %), 127 (23 %), 121 (20 %), 75 (58 %), 73 (39 %).

methyl 2-methylene-3-(*tert*-butyldimethylsilyloxy)propanoate (9)
A mixture of alcohol **7a** (7.3 g, 62 mmol), *tert*-butyldimethylsilyl chloride (9.94 g, 66 mmol), Et_3N (10 ml, 72 mmol) and 4-dimethylaminopyridine (620 mg, 5 mmol) in dry CH_2Cl_2 (60 ml) was stirred 2 h at room temperature. The reaction mixture was extracted with H_2O (3 × 30 ml). The combined H_2O layers were washed back with CH_2Cl_2 (30 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was dissolved in a small amount ether/pentane, filtered (SiO_2), and the SiO_2 washed with the same eluent. The solvents were removed by distillation through a Vigreux column and the residue distilled to give 11.0 g (78 %) pure **9** as a colourless liquid. B.p. 70-72°C/2 mm. Hg. **IR** ($CHCl_3$): 3000, 2950, 2930, 2880, 2850 (CH), 1715 (C=O), 1630 (C=C). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.09 (s, 6H, CH_3Si), 0.92 (s, 9H, *tert*-BuSi), 3.76 (s, 3H, CH_3O), 4.37 (t, 2H, J=2.0, CH_2-OSi), 5.92 (q, 1H, J=2.0, HC=C), 6.26 (q, 1H, J=2.0, HC=C).

2-methyl-3-methylene-4-(*tert*-butyldimethylsilyloxy)-2-butanol (10)
Under nitrogen, dry ether (8 ml) was added to dry magnesium turnings (2.91 g, 120 mmol) at room temperature, followed by 3 ml of a solution of methyl iodide in ether (7.84 ml, 120 mmol methyl iodide in 21.6 ml dry ether). After the start of the reaction the rest of the methyl iodide solution was added at such a rate that the mixture refluxed gently and finally the mixture was refluxed for an hour to dissolve most of the magnesium. Dry ether (28 ml) was added and the mixture cooled in an ice bad. Ester **9** (9.21 g, 40 mmol) dissolved in dry ether (24 ml) was added slowly in about 15 min. After 2 h at room temperature the mixture was poured in ice water, carefully neutralized with ice cold dilute HCl, the layers separated and the aqueous solution extracted with ether (2 ×). The combined ether extracts were washed with brine, dried (Na_2SO_4) and evaporated to give 9.3 g of a crude oil containing at least three compounds (R_f = 0.54, 0.42 and 0.20, SiO_2, EtOAc/petroleum-ether 60-80 1/2). Careful distillation gave 3.4 g (37 %) product as a colourless liquid. B.p. 72-74°C/1.0 mm. Hg. R_f = 0.54 (SiO_2, EtOAc/petroleum-ether 60-80 1/2). **IR** ($CHCl_3$): 3590, 3600-3200 (OH), 2970, 2950, 2920, 2880, 2850 (CH), 1710 (C=C). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.09 (s, 6H, CH_3Si), 0.90 (s, 9H, *tert*-BuSi), 1.37 (s, 6H, 2 × CH_3-), 3.13 (bs, 1H, OH), 4.32 (s, 2H, CH_2-OSi), 5.01 (d, 1H, J=1.2, HC=C), 5.04 (s, 1H, HC=C).

***tert*-butyldimethyl[[2-[(tri-*n*-butylstannyl)methyl]-3-methyl-2-butenyl]oxy]silane (5c)**
A mixture of alcohol **10** (3.22 g, 14 mmol), pyridine (11.22 ml, 140 mmol), acetic anhydride (11.22 ml, 119 mmol) and DMAP (171 mg, 1.4 mmol) was stirred for 72 h at room temperature. The solvents were evaporated, petroleum-ether 40-60 (50 ml) and cold H_2O (20 ml) were added and the mixture neutralized with a cold $NaHCO_3$ solution. The organic layer was isolated, washed with H_2O, saturated $CuSO_4$, H_2O, brine, dried (Na_2SO_4) and carefully evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum-ether 40-60/EtOAc 20/1 → 10/1) to give 2.30 g (60 %) of a colourless volatile liquid. Further purification of the acetate was difficult. It contained about 20 % of an unknown product and was used without further purification in the next step. **IR** ($CHCl_3$): 2980, 2950, 2925, 2880, 2850 (CH), 1720 (C=O), 1255 (C-O). **^{1}H NMR** (200 MHz, $CDCl_3$): 0.08 (s, 6H, CH_3Si), 0.92 (s, 9H, *tert*-BuSi), 1.57 (s, 6H, 2 × CH_3-), 1.99 (s, 3H, CH_3COO), 4.18 (s, 2H, CH_2-OSi), 5.08 (d, 1H, J=1.0, HC=C), 5.22 (d, 1H, J=1.0, HC=C).

Following a methodology of Trost[13] *n*-BuLi (1.93 ml of a 1.6 M solution in hexanes, 3.1 mmol) was added (in 10 min.) to a solution of diisopropylamine (434 µl, 3 mmol) in THF (3 ml) under a nitrogen atmosphere at 0°C. After 10 min. the solution was cooled to -78°C and *n*-Bu_3SnH (815 µl, 3.0 mmol) was slowly (10 min.) added. After 20 min. a solution of Et_2AlCl (1.67 ml, 1.8 M solution, 3.0 mmol) in toluene was added with stirring. After 60 min. $Pd[P(C_6H_5)_3]_4$ (24 mg, 0.02 mmol) dissolved in dry THF (1.5 ml) was added (to give a clear light-red solution) directly followed by the allylacetate (540 mg, ≈ 2 mmol) dissolved in THF (1.5 ml). The cooling bath was removed, the reaction mixture stirred at room temperature for 40 h, cooled in an ice bath and

10 % ammonia (10 ml) was added. The water layer was extracted with petroleum-ether 40-60 (3 ×), the combined organic layers washed with brine, dried (Na_2SO_4), filtered and concentrated to give 1.2 gram of an oil. Chromatography (Al_2O_3 activity I, pH 9.5, pentane) gave 420 mg colourless liquid. The product was contaminated with about 20 % of an unknown stannane that did not interfere in the coupling reactions. A small sample was further purified (with considerable loss of the acid labile stannane) by chromatography (SiO_2, petroleum-ether 40-60 → petroleum-ether 40-60/EtOAc 20/1 + 1 % pyridine. Chromatography was started when the eluent contained pyridine). **IR**: to avoid contamination of the IR cell the compound was not characterized by IR. **^{1}H NMR** (200 MHz, $CDCl_3$): 0.07 (s, 6H, CH_3Si), 0.60-1.10 (m, 24H, *tert*-BuSi and CH_3-CH_2-), 1.10-1.70 (m, 18H, -CH_2-CH_2-Sn and CH_3-C=C), 1.69 (s, 2H, Sn-CH_2-C=C, at 1.84 one ^{119}Sn sideband visible), 4.07 (s, 2H, -C=C-CH_2-OSi). **MS** (FAB), *m/z* (% intensity): parent ion not observed, 447, ($[C_{24}H_{52}OSi^{120}Sn - (C_4H_9)]^+$, 18 %), 445 ($[C_{24}H_{52}OSi^{118}Sn - (C_4H_9)]^+$, 18 %), 443 ($[C_{24}H_{52}OSi^{116}Sn - (C_4H_9)]^+$, 11 %), 365 (37 %), 363 (29 %), 361 (17 %), 315 (100 %), 313 (78 %), 311 (46 %), 291 (52 %), 289 (43 %), 287 (26 %), 251 (27 %), 249 (24 %), 247 (15 %), 235 (31 %), 233 (26 %), 231 (17 %), 195 (30 %), 193 (28 %), 191 (18 %), 179 (53 %), 177 (72 %), 175 (53 %), 73 (60 %).

(1R,2S,6R,7R,9S)-(-)-9-(*tert*-Butyldiphenylsilyloxy)-6-[(1S)-1-hydroxy-3-methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]tridecan-11-one (11a)

A solution of aldehyde **4**[4] (66 mg, 0.14 mmol) and Et_3N (6 µl, 4 µmol) in CH_2Cl_2 (1.5 ml) was slowly added to a suspension of titanium trichloride isopropoxyde[5] (96 mg, 0.45 mmol) in CH_2Cl_2 (1.5 ml) at -78°C. After 3 min. stannane **5a** (120 mg, 0.25 mmol) was slowly added and the clear pale yellow solution turned red-brown. After stirring 4 h at -78°C, Et_3N (1.50 ml) was added, followed by a mixture of saturated $NaHCO_3$ (6 ml), Na_2CO_3 (3 ml), ether (15 ml) and H_2O (3 ml) to give a colourless mixture. After stirring for 1 h the layers were separated and the water layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and evaporated. The crude product was chromatographed (Al_2O_3 activity I, pH 9.5, EtOAc/petroleum-ether 60-80 1/3 → 2/1) to give 93 mg colourless oil containing some of an unknown stannane. This oil was chromatographed again (SiO_2, EtOAc/petroleum-ether 60-80 1/2 → 2/1) to give 53 mg (35 mmol, 57 %) of a glassy compound m.p. 57-63°C. R_f = 0.27 (SiO_2, EtOAc/petroleum-ether 40-60 2/1, detection with anisaldehyde gives a blue colour). $[\alpha]_D$ -3.5° (c 0.90, CH_2Cl_2). **IR** ($CHCl_3$): 3390, 3360 (NH), 2990, 2950, 2930, 2880, 2850 (CH), 1665 (C=O, amide), 1460, 1445, 1425, 1405 (CH). **^{1}H NMR** (250 MHz, $CDCl_3$, COSY): 0.07 (s, 6H, CH_3Si), 0.91 (s, 9H, *tert*-BuSi), 1.04 (s, 9H, *tert*-BuSi), 1.50 (dd, 1H, J=12.5, J=2.5, H_{13a}), 2.0-2.3 (m, 5H, H_1, H_{12a}, H_{13b}, 2 × $H_{2'}$), 2.53 (dd, 1H, J=19.1, J=7.2, H_{12b}), 3.01 (d, 1H, J=2.6, OH), 3.23 (bs, 1H, H_2), 3.38 (dd, 1H, J=7.2, J=1.8, H_6), 3.54 (s, 1H, H_7), 3.69 (m, 1H, $H_{1'}$), 4.09 (s, 2H, $H_{4'}$), 4.65 (AB, 1H, J_{AB}=6.2, H_{4ax}), 4.84 (bs, 1H, =CH_a), 5.03 (AB, 1H, J_{AB}=6.2, H_{4eq}), 5.16 (d, 1H, J=1.6, =CH_b), 6.17 (bs, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.76 (m, 4H, aromatic H). **MS** (FAB): $C_{36}H_{54}NO_7Si_2$, $[M+H]^+$: calcd. 668.3439, obsd. 668.3443.

(1R,2S,6R,7R,9S)-(-)-9-(*tert*-Butyldiphenylsilyloxy)-6-[(1S,2R)-1-hydroxy-2-ethyl-3-methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]-tridecan-11-one (11b) and (1R,2S,6R,7R,9S)-(+)-9-(*tert*-butyldiphenylsilyloxy)-6-[(1S,2S)-1-hydroxy-2-ethyl-3-methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]tridecan-11-one (11b')

A solution of aldehyde **4**[4] (105 mg, 0.22 mmol) in CH_2Cl_2 (2.0 ml) was slowly added to a suspension of titanium trichloride isopropoxyde (230 mg, 1.7 mmol) in CH_2Cl_2 (2.5 ml) at -78°C. After 5 min. stannane **5b** (230 µl, 0.48 mmol) was slowly added. No direct colour change was observed, but after 2 h of stirring at -65 to -60°C the mixture turned dark red-brown. The reaction was followed with TLC (SiO_2, EtOAc/petroleum-ether 1/1) and after 4 h the cooling bath was removed and a mixture of ether (15 ml), saturated $NaHCO_3$ (15 ml) and triethylamine (2 ml) was added to the reaction mixture. The resulting mixture was stirred vigorously for 20 min., the layers were separated and the water layer extracted with ether (3 ×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated. Flash chromatography (SiO_2, EtOAc/petroleum-ether 1/1) gave a mixture of two diastereomeric alcohols as colourless foams.

1'S,2'S epimer 11b'. Yield 54 mg (36 %). R_f = 0.50 (SiO_2, EtOAc/petroleum-ether 1/1). $[\alpha]_D$ +3.5° (c 2.55, $CHCl_3$). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.07 (s, 6H, CH_3Si), 0.90 (s, 9H, *tert*-BuSi), 0.7-0.95 (m, 5H, CH_3CH_2), 1.04 (s, 9H, *tert*-BuSi), 1.52 (dd, 1H, J=13.4, J=2.8, H_{13a}), 2.1-2.3 (m, 4H, H_1, H_{12a}, H_{13b}, $H_{2'}$), 2.54 (dd, 1H, J=18.6, J=7.1, H_{12b}), 3.05 (d, 1H, J = 6.8, OH), 3.15 (bs, 1H, H_2), 3.39 (m, 1H, H_6), 3.5-3.6 (m, 1H, $H_{1'}$), 3.58 (s, 1H, H_7), 3.98 (AB, 1H, J_{AB}=14.1, $H_{4'a}$), 4.21 (AB, 1H, J_{AB}=14.2, $H_{4'b}$), 4.59 (AB, 1H, J_{AB}=6.1, H_{4ax}), 4.80 (s, 1H, =CH_a), 4.98 (AB, 1H, J_{AB}=6.1, H_{4eq}), 5.15 (d, 1H, J=1.1,

$=CH_b$), 6.20 (s, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.7-7.8 (m, 4H, aromatic H).
1'S,2'R epimer 11b. Yield 23 mg (15 %). R_f = 0.14 (SiO_2, EtOAc/petroleum-ether 1/1). $[\alpha]_D$ -3.7° (c 1.07, $CHCl_3$). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.07 (s, 6H, CH_3Si), 0.91 (s, 9H, *tert*-BuSi), 0.75-0.95 (m, 5H, CH_3CH_2), 1.03 (s, 9H, *tert*-BuSi), 1.58 (dd, 1H, J=16.3, J=7.5, H_{13a}), 2.1-2.3 (m, 4H, H_1, H_{12a}, H_{13b}, $H_{2'}$), 2.47 (dd, 1H, 18.7, J=7.2, H_{12b}), 3.11 (s, 1H, OH), 3.24 (s, 1H, H_2), 3.54-3.71 (m, 3H, H_6, H_7, $H_{1'}$), 3.98 (AB, 1H, J_{AB}=14.5, $H_{4'a}$), 4.08 (AB, 1H, J_{AB}=14.6, $H_{4'b}$), 4.65 (AB, 1H, J_{AB}=6.1, H_{4ax}), 4.89 (bs, 1H, $=CH_a$), 5.05 (AB, 1H, J_{AB}=6.0, H_{4eq}), 5.21 (bs, 1H, $=CH_b$), 6.25 (s, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.7-7.9 (m, 4H, aromatic H).

(1R,2S,6R,7R,9S)-(+)-9-(*tert*-Butyldiphenylsilyloxy)-6-[(1S)-1-hydroxy-2,2-dimethyl-3--methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]-tridecan-11-one (11c)
A sufficient amount of titanium trichloride isopropoxyde[5] was washed twice (in the reaction vessel, under nitrogen) with dry pentane and after drying *in vacuo* at room temperature 220 mg dry catalyst was left. The catalyst was dissolved in dry CH_2Cl_2 (1600 µl, necessary to dissolve all the catalyst) and 555 µl of this solution was removed to leave 143 mg (0.67 mmol, > 4 eq.) of the catalyst in 1045 µl CH_2Cl_2. The solution was cooled to -78°C and aldehyde **4** (72 mg, 0.15 mmol) in CH_2Cl_2 (500 µl) was slowly added. After 5 minutes stannane **5c** (200 mg, > 0.26 mmol) was added slowly to the pale yellow solution to give a very intense brown-red colour. After 15 min. the temp. was raised to -65°C, 5 h later the cooling bath was removed and immediately a mixture of ether (15 ml), saturated $NaHCO_3$ (15 ml) and Et_3N (600 µl) was added to the still intense coloured solution that discoloured directly. The layers were separated and the water layer was extracted with ether (3 ×). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), filtered and evaporated to give a crude product that contained a small amount of unreacted aldehyde and stannane. Flash chromatography (SiO_2, EtOAc/petroleum-ether 40-60 1/2 + 0.1% pyridine) gave the product. After concentration and addition of some pentane the product (86 mg, 0.12 mmol, 82 %) crystallized as white needles (m.p. 126-128°C). A pure sample was obtained by crystallization from pentane. M.p. 127-129°C. R_f = 0.35 (SiO_2, EtOAc/petroleum-ether 40-60 1/1). $[\alpha]_D$ +9.2° (c 0.72, CH_2Cl_2). **IR** ($CHCl_3$): 3570 (OH), 3390 (NH), 2990, 2950, 2930, 2880, 2850 (CH), 1665 (C=O, amide), 1460, 1445, 1425, 1405 (CH). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.06 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.95 (s, 12H, *tert*-BuSi and CH_3-), 1.03 (s, 9H, *tert*-BuSi), 1.10 (s, 3H, CH_3-), 1.47 (dd, 1H, J=13.3, J=3.7, H_{13a}), 2.03-2.25 (m, 3H, H_1, H_{12a}, H_{13b}), 2.45 (m, 1H, H_{12b}), 2.50 (bs, 1H, OH), 3.21 (bs, 1H, H_2), 3.48 (s, 1H, H_7), 3.51 and 3.62 (2 × d, 2 × 1H, J=4.9, H_6 and $H_{1'}$), 4.23 and 4.37 (AB, 2H, J_{AB}=15.2, 2 × $H_{4'}$), 4.65 (AB, 1H, J_{AB}=6.2, H_{4ax}), 4.93 (bs, 1H, $=CH_a$), 4.99 (AB, 1H, J_{AB}=6.2, H_{4eq}), 5.30 (d, 1H, J=1.0, $=CH_b$), 6.53 (s, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.75 (m, 2H, aromatic H), 7.86 (m, 2H, aromatic H). **MS** (FAB): $C_{38}H_{58}NO_7Si_2$, $[M+H]^+$: calcd. 696.3752, obsd. 696.3703.

4-[(4S,5R,6R)-5-Hydroxy-6-((1S)-1-hydroxy-3-methylene-4-(*tert*-butyldimethylsilyloxy)-butyl)-1,3-dioxan-4-yl]-2,6-piperidinedione (12)
p-Methoxybenzaldehyde (18 µl, 148 µmol) was dissolved in 1,2-dichloroethane (800 µl). From this solution 240 µl (44 µmol) was added to a mixture of alcohol **11a** (23 mg, 34 µmol), pyridinium *p*-toluenesulfonate (3 mg) and *p*-TsOH.H_2O (1 mg) in 1,2-dichloroethane (1.8 ml) and refluxed gently under nitrogen for 60 min. The reaction was followed by TLC. After cooling pyridine (5 µl) was added, the solvent evaporated and the residue chromatographed (SiO_2, EtOAc + 0.2 % pyridine) to give diol **12** (10 mg, 23 µmol, 68 %) as a colourless oil. **^{1}H NMR** (250 MHz, $CDCl_3$): 0.08 (s, 6H, CH_3Si), 0.90 (s, 9H, *tert*-BuSi), 2.25-3.00 (m, 7H, H_3, H_4, H_5, $H_{2''}$), 3.29 (d, 1H, J=8.0, $H_{4'}$), 3.44 (d, 1H, J=3.5, OH), 3.57 (d, 1H, J=4.0, $H_{6'}$), 3.67 (d, 1H, OH, J=6.0), 3.81 (d, 1H, J=6.3, $H_{5'}$), 4.01 (m, 1H, $H_{1''}$), 4.11 (s, 2H, $H_{4''}$), 4.72 (AB, 1H, J_{AB}=6.2, $H_{2'ax}$), 4.97 (s, 1H, $=CH_a$), 5.14 (d, 1H, J=1.2, $=CH_b$), 5.19 (AB, 1H, J_{AB}=6.2, $H_{2'eq}$), 8.06 (1H, NH_1).

4-[(1R,5S,6R,10S)-10-(2-Methylene-3-(*tert*-butyldimethylsilyloxy)propyl)-8-oxo-2,4,7,9--tetraoxabicyclo[4.4.0]decan-5-yl]-2,6-piperidinedione (13)
To a stirring solution of diol **12** (9 mg, 21 µmol), 2,4,6-trimethylpyridine (200 µl, 1.5 mmol) and a catalytic amount of DMAP in $CHCl_3$ (500 µl), trichloromethyl chloroformate (16 µl, 130 µmol) in $CHCl_3$ (100 µl) was added at -50°C. The temp. was raised to 20°C and after 24 h water (50 µl) was added, the solution coevaporated with toluene (2 ×) and the residue washed with pentane. Flash chromatography (SiO_2, EtOAc/petroleum ether 60-80 2/1 → EtOAc) followed by trituration with pentane gave 6.8 mg (15 µmol, 70 %) **13** as a white solid. M.p. 87-89°C. R_f = 0.56 (SiO_2, EtOAc, detection with *p*-anisaldehyde reagent). **IR**

($CHCl_3$): 3370 (NH), 3020, 2950, 2925, 2845 (CH), 1755 (C=O, carbonate), 1705 (C=O, imide), 1250 (CH). **^{1}H NMR** (250 MHz, $CDCl_3$, COSY, NOE): 0.06 (s, 6H, CH_3Si), 0.89 (s, 9H, *tert*-BuSi), 2.3-3.0 (m, 7H, H_3, H_4, H_5, $H_{1'a}$), 3.46 (d, 1H, J=8.1, $H_{5'}$), 3.94 (s, 1H, $H_{1'}$), 4.09 (AB, 2H, J_{AB}=13.5, $H_{3'b}$), 4.29 (s, 1H, $H_{6'}$), 4.65 (m, 1H, $H_{10'}$), 4.74 (AB, 1H, J_{AB}=6.4, $H_{3'ax}$), 4.99 (s, 1H, $=CH_a$), 5.18 (AB, 1H, J_{AB}=6.4, $H_{3'eq}$), 5.19 (s, 1H, $=CH_b$), 8.05 (1H, NH_1). A NOE difference experiment showed a strong interaction between $H_{6'}$ and $H_{10'}$ (irradiation at $H_{6'}$). A second NOE experiment showed strong interactions of $H_{1'}$ with $H_{3'ax}$ and $H_{5'}$ (irradiation at $H_{1'}$). **MS** (FAB): $C_{21}H_{33}NO_8SiNa$, $[M+Na]^+$: calcd. 478.1873, obsd. 478.1863.

(1R,2S,6R,7R,9S)-(-)-9-(*tert*-Butyldiphenylsilyloxy)-6-(1-oxo-3-methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]tridecan-11-one (14a)

To a mixture of alcohol **11a** (132 mg, 0.19 mmol) and pyridine (16 µl, 0.20 mmol) in CH_2Cl_2 (2.0 ml) Dess-Martin periodinane[10] (200 mg, 0.47 mmol, 2.3 eq.) was added at once. After 4 h at room temperature pyridine (32 µl, 0.40 mmol) was added directly followed by ether (20 ml), petroleum-ether 40-60 (10 ml) and a mixture of saturated bicarbonate and sodium thiosulfate (1/4, 20 ml). After stirring for 30 min. the water layer was separated and extracted with ether/petroleum-ether 40-60 (2/1, 30 ml).The combined organic layers were washed with bicarbonate/thiosulfate (1/4) and brine. After drying (Na_2SO_4) and filtration the solvents were evaporated and the residue purified by flash chromatography (SiO_2, EtOAc/petroleum-ether 40-60 1/1) to give 103 mg (0.15 mmol, 79 %) of a colourless oil that solidified on standing to give a white powder with m.p. 85-89°C. R_f = 0.24 (SiO_2, EtOAc/petroleum-ether 40-60 1/1), 0.34 (SiO_2, EtOAc/petroleum ether 40-60 2/1, detection with anisaldehyde gives a red-brown colour). $[\alpha]_D$ -24.7° (c 1.93, CH_2Cl_2). **IR** ($CHCl_3$): 3390, 3360 (NH), 3070, 2990, 2950, 2930, 2850, 2770 (CH), 1715 (C=O), 1665 (C=O, amide), 1457, 1445, 1425, 1405 (CH). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.03 (s, 6H, CH_3Si), 0.88 (s, 9H, *tert*-BuSi), 1.01 (s, 9H, *tert*-BuSi), 1.55 (m, 1H, H_{13a}), 2.1-2.4 (m, 3H, H_1, H_{12a}, H_{13b}), 2.48 (AB, 1H, J_{AB}=16.8, $H_{2'a}$), 2.52 (dd, 1H, J=18.6, J=6.6, H_{12b}), 3.28 (AB, 1H, J_{AB}=16.8, $H_{2'b}$), 3.35 (bs, 1H, H_2), 3.9-4.1 (m, 4H, 2 × $H_{4'}$, H_6, H_7), 4.66 (AB, 1H, J_{AB}=6.3, H_{4ax}), 4.69 (bs, 1H, $=CH_a$), 5.08 (AB, 1H, J_{AB}=6.3, H_{4eq}), 5.12 (d, 1H, J=1.5, $=CH_b$), 6.04 (bs, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.6-7.8 (m, 4H, aromatic H). **MS** (FAB): $C_{36}H_{52}NO_7Si_2$, $[M+H]^+$: calcd. 666.3282, obsd. 666.3288.

(1R,2S,6R,7R,9S)-(-)-9-(*tert*-Butyldiphenylsilyloxy)-6-[(2R)-1-oxo-2-ethyl-3-methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]tridecan-11-one (14b)

To a solution of alcohol **11b** (18 mg, 26 µmol) and pyridine (4 µl) in CH_2Cl_2 (1 ml) was added Dess-Martin[10] periodinane (30 mg, 70 µmol). After stirring for 3 h at room temperature, a mixture of ether (5 ml), petroleum-ether (2.5 ml), 10 % sodium thiosulfate (4 ml) and saturated bicarbonate (1 ml) was added. After 30 min. of vigorous stirring, the layers were separated, the water layer extracted with ether (3 ×) and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated to give 16.5 mg (92 %) **14b**. R_f = 0.14 (SiO_2, EtOAc/petroleum-ether 40-60 1/1, the R_f value is identical to that of starting material, the product gave a red colour upon spraying of the TLC plate with anisaldehyde reagent, whereas the starting material gave a purple colour). $[\alpha]_D$ -45.5° (c 0.83, $CHCl_3$). **IR** ($CHCl_3$): 3390, 3360 (NH), 3000, 2950, 2925, 2850 (CH), 1725 (C=O), 1665 (C=O, amide), 1455, 1420, 1405 (CH). **^{1}H NMR** (250 MHz, $CDCl_3$): 0.07 (s, 6H, CH_3Si), 0.72 (t, 3H, J=7.4, CH_3C-), 0.94 (s, 9H, *tert*-BuSi), 1.00 (s, 9H, *tert*-BuSi), 1.2-1.9 (m, 3H, -CH_2-, H_{13a}), 2.1-2.3 (m, 3H, H_1, H_{12a}, H_{13b}), 2.48 (dd, 1H, J=18.9, J=6.9, H_{12b}), 3.13 (t, 1H, J=7.2, $H_{2'}$), 3.36 (s, 1H, H_2), 4.01 (s, 1H, H_7), 4.08 (AB, 1H, J_{AB}=15.3, $H_{4'a}$), 4.09 (d, 1H, J=2.0, H_6), 4.30 (AB, 1H, J_{AB}=15.3, $H_{4'b}$), 4.66 (AB, 1H, J_{AB}=6.3, H_{4ax}), 4.79 (bs, 1H, $=CH_a$), 5.05 (AB, 1H, J_{AB}=6.3, H_{4eq}), 5.20 (bs, 1H, $=CH_b$), 6.29 (bs, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.6-7.9 (m, 4H, aromatic H). **MS** (FAB): $C_{38}H_{56}NO_7Si_2$, $[M+H]^+$: calcd. 694.3595, obsd. 694.3588.

(1R,2S,6R,7R,9S)-(+)-9-(*tert*-Butyldiphenylsilyloxy)-6-[(2S)-1-oxo-2-ethyl-3-methylene-4-(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.0^{2,7}]tridecan-11-one (14b')

Alcohol **11b'** (50 mg, 70 µmol) was oxidized as described for **11b**. Yield 44 mg (88 %) **14b'**. R_f = 0.54 (SiO_2, EtOAc/petroleum-ether 40-60 1/1). $[\alpha]_D$ +54.7° (c 0.80, $CHCl_3$). **IR** ($CHCl_3$): 3390, 3360 (NH), 2950, 2925, 2850 (CH), 1730 (C=O), 1665 (C=O, amide), 1460, 1435, 1425, 1405 (CH).**^{1}H NMR** (300 MHz, $CDCl_3$): 0.07 (s, 6H, CH_3Si), 0.90 (s, 9H, *tert*-BuSi), 0.9 (m, 3H, CH_3-), 0.99 (s, 9H, *tert*-BuSi), 1.35 (dd, 1H, J=12.4, J=2.9, H_{13a}), 1.79 and 1.96 (2 × m, 2 × 1H, -CH_2-), 2.08 (dd, 1H, J=12.4, J=1.6, H_{13b}), 2.20-2.30 (m, 2H, H_1, H_{12a}), 2.48 (dd, 1H, J=18.7, J=7.2, H_{12b}), 3.16 (t, 1H, J=7.2, $H_{2'}$), 3.35 (s, 1H, H_2), 4.08 (m, 3H, H_7, $H_{4'}$), 4.42 (d, 1H, J=2.1, H_6), 4.63 (AB, 1H, J_{AB}=6.3, H_{4ax}), 4.97 (s, 1H,

$=CH_a$), 5.06 (AB, 1H, J_{AB}=6.2, H_{4eq}), 5.21 (s, 1H, $=CH_b$), 6.23 (s, 1H, NH_{10}), 7.2-7.5 (m, 6H, aromatic H), 7.6-7.9 (m, 4H, aromatic H). MS (FAB): $C_{38}H_{56}NO_7Si_2$, $[M+H]^+$: calcd. 694.3595, obsd. 694.3603.

(1R,2S,6R,7R,9S)-(-)-9-(*tert*-Butyldiphenylsilyloxy)-6-(1-oxo-2,2-dimethyl-3-methylene-4--(*tert*-butyldimethylsilyloxy)butyl]-3,5,8-trioxa-10-azatricyclo[7.3.1.$0^{2,7}$]tridecan-11-one (14c)

To a mixture of alcohol **11c** (49 mg, 0.07 mmol) and pyridine (6 µl) in dry THF (1 ml) Dess-Martin reagent[10] (71 mg, 0.17 mmol, 2.4 eq.) was added at once. After 2 h at room temperature ether (10 ml) and a mixture of saturated bicarbonate and sodium thiosulfate (1/4, 10 ml) was added. After stirring for 30 min. the water layer was separated and extracted with ether (2 ×). The combined organic layers were washed with bicarbonate/thiosulfate (1/4) and brine. After drying (Na_2SO_4) and filtration the solvents were evaporated and the residue purified by flash chromatography (EtOAc/petroleum-ether 40-60 1/2 + 0.1 % pyridine) to give 42 mg (88 %) of the oxidized product that solidified as white needles by adding pentane. A pure sample was obtained by crystallization from pentane. M.p. 120-122°C. R_f = 0.35 (SiO_2, EtOAc/petroleum-ether 40-60 1/1, detection with anisaldehyde gives a red-brown colour). $[a]_D$ -30.9° (c 0.85, CH_2Cl_2). **IR** ($CHCl_3$): 3390 (NH), 2990, 2950, 2930, 2850 (CH), 1715 (C=O), 1665 (C=O, amide), 1455, 1445, 1425, 1405 (CH). **^{1}H NMR** (300 MHz, $CDCl_3$): 0.066 (s, 3H, CH_3Si), 0.070 (s, 3H, CH_3Si), 0.92 (s, 9H, *tert*-BuSi), 1.006 (s, 9H, *tert*-BuSi), 1.205 (s, 3H, CH_3-), 1.212 (s, 3H, CH_3-), 1.40 (dd, 1H, J=12.2, J=2.7, H_{13a}), 2.1-2.3 (m, 3H, H_1, H_{12a}, H_{13b}), 2.50 (dd, 1H, J=18.6, J=7.1, H_{12b}), 3.29 (d, 1H, J=1.4, H_2), 4.05 (s, 1H, H_7), 4.21 (AB, 2H, J_{AB}=15.4, $H_{4'}$), 4.40 (d, 1H, J=1.9, H_6), 4.59 (AB, 1H, J_{AB}=6.3, H_{4ax}), 4.93 (s, 1H, $=CH_a$), 5.02 (AB, 1H, J_{AB}=6.3, H_{4eq}), 5.23 (s, 1H, $=CH_b$), 6.32 (s, 1H, NH_{10}), 7.3-7.5 (m, 6H, aromatic H), 7.76 (m, 2H, aromatic H), 7.83 (m, 2H, aromatic H). MS (FAB): $C_{38}H_{56}NO_7Si_2$, $[M+H]^+$: calcd. 694.3595, obsd. 694.3621.

(-)-4-[(4S,5R,6R)-5-Hydroxy-6-[1-oxo-3-methylene-4-hydroxy)butyl]-1,3-dioxan-4-yl]-2,6--piperidinedione (16a)

34 mg (50 µmol) **14a** was stirred 5 h in AcOH/THF/H_2O (3/2/1, 500 µl) at room temperature. The solvents were evaporated *in vacuo*, the residue dried and purified by flash chromatography (SiO_2, EtOAc/petroleum-ether 40-60 1/1 → 5/1) to give 11 mg (70 %) of a glassy compound. $[\alpha]_D$ -0.1° (c 0.45, $CHCl_3$ + 5 % CH_3OH), -22.0° (c 0.45, CH_3OH). The IR and ^{1}H NMR spectra are identical to that described by Wanner et. al.[6a]. MS: $C_{14}H_{17}NO_6$, $[M-(H_2O)]^+$: calcd. 295.1056, obsd. 295.1038.

(+)-4-[(4S,5R,6R)-5-Hydroxy-6-[(2R,3R)-2-hydroxy-3-ethyl-4-methylenetetrahydrofuran-2--yl]-1,3-dioxan-4-yl]-2,6-piperidinedione (16b)

A solution of silylether **14b** (16.5 mg, 24 µmol) in a mixture of AcOH/THF/H_2O (3/1/1, 2.0 ml) was stirred for 4 h at room temperature. Toluene was added, the mixture coevaporated and the residue chromatographed (SiO_2, EtOAc) to give 8 mg (99 %) **16b** as a white foam. R_f = 0.28 (SiO_2, EtOAc). $[\alpha]_D$ +6.7° (c 0.30, $CHCl_3$). **^{1}H NMR** (250 MHz, $CDCl_3$): one closed form is observed, 1.04 (t, 3H, J=7.5, CH_3C-), 1.60 (m, 1H, $-CH_{2a}$-), 1.75 (m, 1H, $-CH_{2b}$-), 2.3-2.7 (m, 4H, H_{3a}, H_4, H_{5a}, $H_{3'}$), 2.79 (ddd, 1H, J=16.5, J=4.4, J=1.2, H_{3b}), 2.90 (ddd, 1H, J=16.9, J=4.0, J=1.4, H_{5b}), 3.32 (d, 1H, J=8.1, $H_{4'}$), 3.55 (s, 1H, OH), 3.67 (d, 1H, J=6.3, $H_{6'}$), 3.97 (d, 1H, J=6.2, $H_{5'}$), 4.22 (s, 1H, OH), 4.37 (dd, 1H, J=12.6, J=0.8, $H_{5'',a}$), 4.53 (dd, 1H, J=12.6, J=2.0, $H_{5'',b}$), 4.75 (AB, 1H, J_{AB}=6.2, $H_{2'ax}$), 5.01 (d, 1H, J=2.3, $=CH_a$), 5.04 (d, 1H, J=2.3, $=CH_b$), 5.22 (AB, 1H, J_{AB}=6.2, $H_{2'eq}$), 7.95 (bs, 1H, NH_1). **MS** (EI): $C_{16}H_{21}NO_6$, $[M-(H_2O)]^+$: calcd. 323.1369, obsd. 323.1362.

(+)-4-[(4S,5R,6R)-5-Hydroxy-6-[(2R,3S)-2-hydroxy-3-ethyl-4-methylenetetrahydrofuran-2--yl]-1,3-dioxan-4-yl]-2,6-piperidinedione (16b')

A solution of silylether **14b'** (29 mg, 40 µmol) in a mixture of AcOH/THF/H_2O (3/1/1, 2.0 ml) was stirred for 4 h at room temperature. Toluene was added and the mixture coevaporated. The residue was chromatographed (SiO_2, EtOAc) to give 10 mg (72 %) **16b'** as a white foam. R_f = 0.22 (SiO_2, EtOAc). $[\alpha]_D$ +5.3° (c 0.49, $CHCl_3$). **^{1}H NMR** (250 MHz, $CDCl_3$): two closed forms are observed in a nearly 1:1 mixture, 0.95 and 1.08 (t, 3H, J=7.3 and J=7.5, CH_3C-), 1.55-1.68 (m, 2H, $-CH_2$-), 2.3-2.5 (m, 3H, H_{3a}, H_{5a}, $H_{3'}$), 2.55-2.7 (m, 1H, H_4), 2.73-3.1 (m, 2H, H_{3b}, H_{5b}), 3.32 and 3.40 (2 × d, 1H, J=8.0 and J=8.1, $H_{4'}$), 3.63 (d, 1H, J=7.6, $H_{6'}$), 4.03 and 4.08 (s and d, 1H, J=9.5, $H_{5'}$), 4.4-4.6 (m, 2H, $H_{5''}$), 4.75 and 4.79 (2 × AB, 1H, J_{AB}=6.2 and J_{AB}=6.2, $H_{2'ax}$), 5.06 (bs, 2H, $=CH_2$), 5.19 and 5.22 (2 × AB, 1H, J_{AB}=6.2 and J_{AB}=6.2, $H_{2'eq}$), 8.21 and 8.24 (bs, 1H, NH_1). **MS** (EI): $C_{16}H_{21}NO_6$, $[M-(H_2O)]^+$: calcd. 323.1369, obsd. 323.1373.

(+)-4-[(4S,5R,6R)-5-Hydroxy-6-[2-hydroxy-3,3-dimethyl-4-methylenetetrahydrofuran-2-yl]-1,3-dioxan-4-yl]-2,6-piperidinedione (16c)

Ketone **14c** (71 mg, 0.10 mmol) dissolved in a mixture of AcOH/THF/H_2O (3/2/1, 3.0 ml) and CF_3COOH (3 µl) was stirred for 7 h at room temperature. The solvents were evaporated *in vacuo* and this was repeated with toluene. After drying (0.05 mm. Hg) the solid residue was chromatographed (SiO_2, EtOAc/petroleum-ether 40-60 1/1 → 5/1). The product was dissolved (THF/CH_2Cl_2 1/1), filtered, the solvents evaporated and the residue dried *in vacuo* to give 31 mg (89 %) crystalline material (m.p. 215-218°C). Recrystallization from hot CH_2Cl_2 followed by slow evaporation of a part of the solvent at room temperature gave very small hexagonal platelets, m.p. 218-219°C. $[\alpha]_D$ -30.9° (c 0.85, CH_2Cl_2). **^{1}H NMR** (250 MHz, $CDCl_3$ + some drops CD_3OD, one closed form observed): 1.01 (s, 3H, CH_3-), 1.18 (s, 3H, CH_3-), 2.2-2.45 (m, 2H, H_{3a}, H_{5a}), 2.45-2.60 (m, 1H, H_4) 2.68 (dd, 1H, J=16.6, J=2.8, H_{3b}), 2.85 (dd, 1H, J=16.9, J=2.5, H_{5b}), 3.30 (d, 1H, J=8.1, $H_{4'}$), 3.65 (s, 1H, $H_{6'}$), 3.97 (s, 1H, $H_{5'}$), 4.45 (s, 2H, $H_{5''}$), 4.70 (AB, 1H, J_{AB}=6.2, $H_{2'ax}$), 4.83 (d, 1H, J=1.9, $=CH_a$), 4.85 (d, 1H, J=2.4, $=CH_b$), 5.10 (AB, 1H, J_{AB}=6.2, $H_{2'eq}$). Also in CD_3OD only one closed form is observed. **MS** (FAB): $C_{16}H_{23}NO_7Na$, $[M+Na]^+$: calcd. 364.1372, obsd. 364.1381.

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