SYNTHESIS OF CONFORMATIONALLY RESTRAINED, ß-SUBSTITUTED DERIVATIVES OF L-TRYPTOPHAN *VIA* LEWIS ACID-CATALYZED REACTION OF 2,3-AZIRIDINO-ß-D-LYXO-FURANOSIDES WITH 1-(TRIALKYLSILYL)INDOLES

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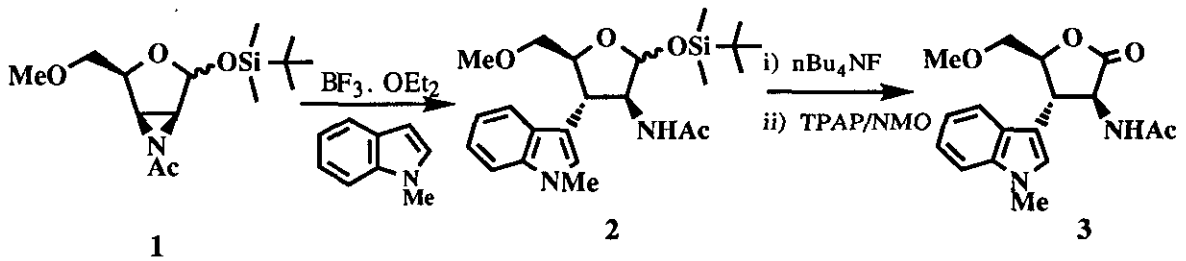
Abstract - Reaction of 1-(triisopropylsilyl)indole (or its 5-benzyloxy derivative) with *tert*-butyldimethylsilyl *N*-(*tert*-butyloxycarbonyl)-2,3-aziridino-2,3-dideoxy-5-*O*-methyl- (or benzyl-)-β-D-lyxofuranoside in the presence of boron trifluoride etherate gave, regio- and stereospecifically, the corresponding protected 2-amino-3-(3-indolyl)arabinofuranoside derivatives. These could be transformed, after desilylation, oxidation and removal of the Boc group, into 2-amino-3-(3-indolyl)arabinonolactone derivatives. The latter represent novel examples of conformationally restrained analogues of L-tryptophan as well as precursors of optically pure β-substituted L-tryptophans.

There has been much recent interest in the synthesis of stereochemically pure β-substituted tryptophan derivatives.[1,2] A prime example of such a derivative is β-methyltryptophan which, in addition to being found in nature,[3] is a structural unit of several biologically active compounds (e.g., telomycin,[4,5] streptonigrin,[6,7] lavendamycin[8]). The incorporation of modified tryptophan analogues, including β-substituted tryptophans,

This paper is dedicated to the memory of Professor Shun-ichi Yamada

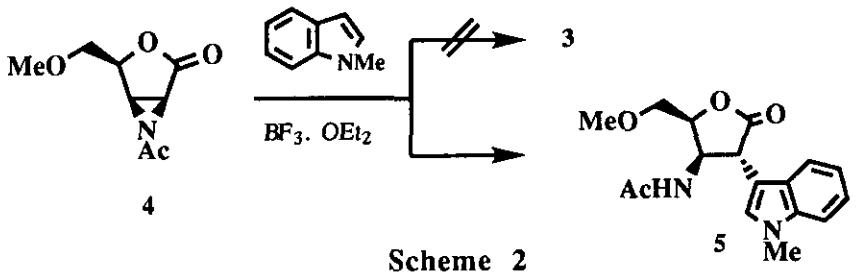
into bioactive peptides, can lead to products having higher potencies, selectivities and/or reduced metabolic degradation rates than the native peptides.[9] A special case of β-substituted tryptophans consists of those in which the β-substituent is in turn bonded to some other portion of the amino acid, resulting in the formation of conformationally restricted tryptophan derivatives.[10] These compounds may be pharmacologically interesting in their own right or may serve to replace the tryptophan residues of bioactive peptides to form, in turn, conformationally restricted peptides.

We have recently reported the synthesis of such a β-substituted, conformationally restricted tryptophan derivative in the form of the 2-amino-3-(3-indolyl)-γ-butyrolactone (**3**) (Scheme 1).[11] This compound was prepared by Lewis acid-catalyzed, regiospecific ring opening of the 2,3-aziridinolyxofuranoside (**1**) by



Scheme 1

1-methylindole to give **2** followed by desilylation and tetrapropylammonium perruthenate (TPAP)-mediated oxidation of the resulting anomeric hydroxyl group. Although it would at first seem evident that these last two steps could be eliminated if the 2,3-aziridino-γ-butyrolactone (**4**) was used as the starting material, this was shown not to be possible since reaction of **4** with 1-methylindole gave exclusively the product of aziridine ring opening at C-2 (i.e., compound (**5**)) instead of at C-3 (Scheme 2).

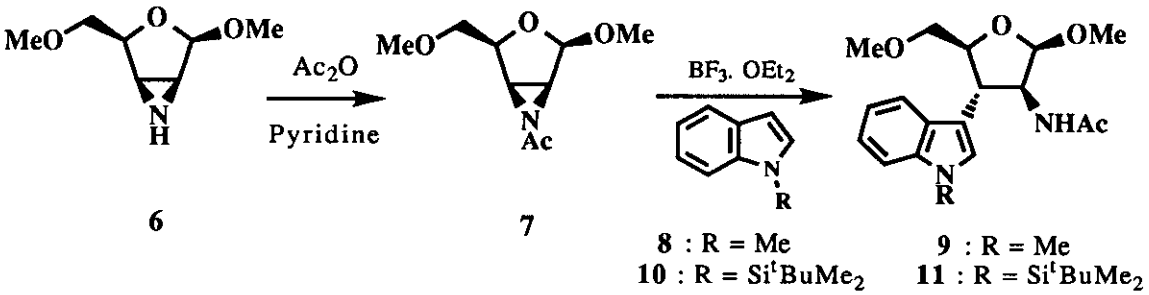


Scheme 2

While compound (**3**) has all the structural elements of a conformationally restrained tryptophan derivative, biological evaluation or further chemical modification of compounds formed *via* this reaction scheme are hampered by the presence of the two amine blocking groups whose removal would require reaction conditions

incompatible with the presence of the lactone ring. Moreover, in order to allow further derivatization of compounds of type (**3**), a blocking group other than methyl for the primary hydroxyl function was desired. We thus sought to adapt our methodology to substrates having protecting groups removable under mild conditions. The results of this systematic study are described herein.

The synthesis of tryptophan derivatives by reaction of unprotected indole with aziridine-2-carboxylates[12,13] or 2-cyanoaziridines[14] in the presence of zinc triflate or boron trifluoride etherate has been reported. These reactions were conducted in ether, dichloromethane or chloroform. In view of this, we began our study by reacting indole with the methyl *N*-acetyl-2,3-aziridinolyxofuranoside (**7**) (prepared by acetylation of aziridine (**6**)[15] using acetic anhydride-pyridine) (Scheme 3). However, regardless of the reaction conditions used (2-10 equiv. of indole ; ether, dichloromethane, chloroform or toluene as solvents ; 0 °C to rt ; 1-3 equiv. of boron trifluoride etherate or zinc triflate), there was no evidence of coupling of the indole with the aziridine. Instead, highly colored by-products were formed, probably arising from self-condensation/oxidation of indole.

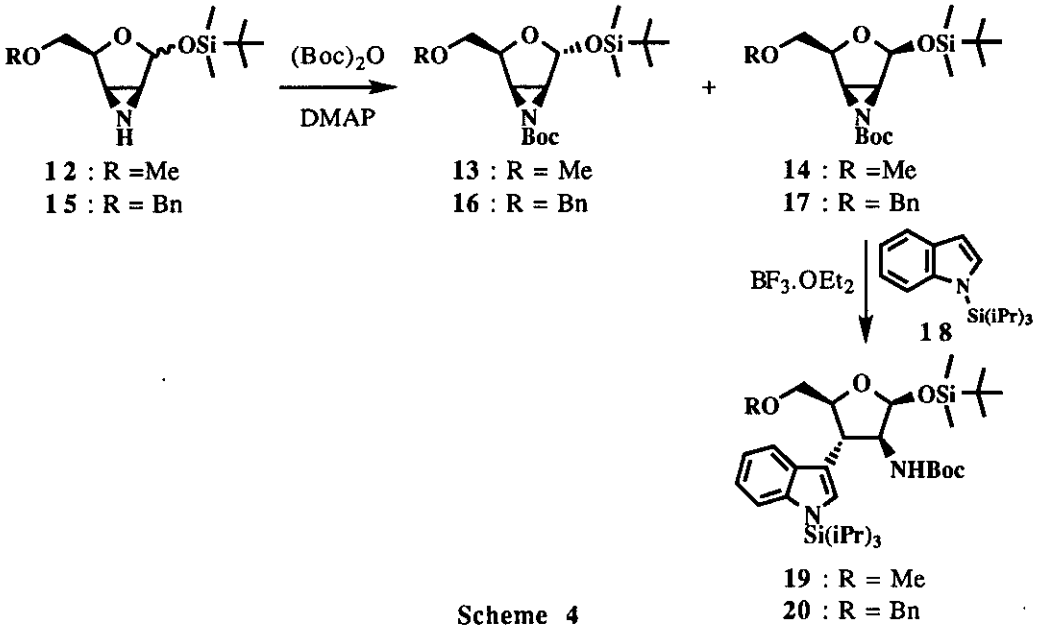


Scheme 3

That aziridine (**7**) can be coupled with an indole derivative was demonstrated by the formation of the 2-acetamido-3-[3-(1-methylindolyl)] derivative (**9**) when, by analogy with the reaction of Scheme 1, 1-methylindole (**8**) was used as the nucleophile. In this case, the highest yields of **9** (57%) were obtained at 0°C using ether as the solvent together with a large excess (7.7 equiv.) of **8** and 1.2-1.5 equiv. of boron trifluoride etherate. The use of chloroform as solvent gave a slightly lower yield of **9**. None of these conditions was successful in the case of unprotected indole, proving the need to protect the indole NH. However, use of *N*-acetyl and *N*-tosyl derivatives of indole also gave no coupling products with aziridine (**6**) using the aforementioned reaction conditions. In these cases, lack of reactivity is probably due to the electron-withdrawing properties of the *N*-blocking group, deactivating the C-3 position to nucleophilic attack. Finally, use of a silylated indole derivative in the form of *N*-(*tert*-butyldimethylsilyl)indole (**10**)[16] gave better results.

Thus, addition of excess **10** to a solution of aziridine (**7**) and boron trifluoride etherate in chloroform afforded, after 17.5 h at rt, the 3-(3-indolyl)arabinofuranoside (**11**) in 22% yield. The ^{1}H-NMR spectrum of **11** was very similar to that of compound (**3**) whose structure has been unambiguously established by derivatization and by NOESY experiments.[11] In particular, opening of the aziridine ring at C-3 gives rise to a characteristic 8-line resonance pattern for H-2 which simplifies to a 4-line signal after D_2O exchange due to the disappearance of the NH coupling. Furthermore, there was no evidence of epimerization of the anomeric methoxy group in this reaction, the H1-H2 coupling constant (4.5 Hz) being consistent for a *cis* arrangement of these protons.

Having shown that a trialkylsilyl-protected indole is suitable for these Lewis acid-catalyzed aziridine ring opening reactions, we then turned our attention to applying this reaction to an aziridine substrate having anomeric, amino, and eventually primary hydroxyl protecting groups suitable for facile derivatization to fully deprotected tryptophan analogues. For this purpose, the aziridine function of the *tert*-butyldimethylsilyl lyxofuranoside derivative (**12**)[15] was protected with a *tert*-butyloxycarbonyl (Boc) group by treatment with di-*tert*-butyl dicarbonate and DMAP in THF (Scheme 4). The resulting α- and β-anomers (compounds (**13**) and (**14**)), could be separated by chromatography. Similar treatment of the 5-*O*-benzyl aziridino derivative (**15**)[17] afforded the α- and β-anomers (**16** and **17**), respectively, also separable by chromatography.



12 : R =Me
15 : R = Bn

13 : R = Me
16 : R = Bn

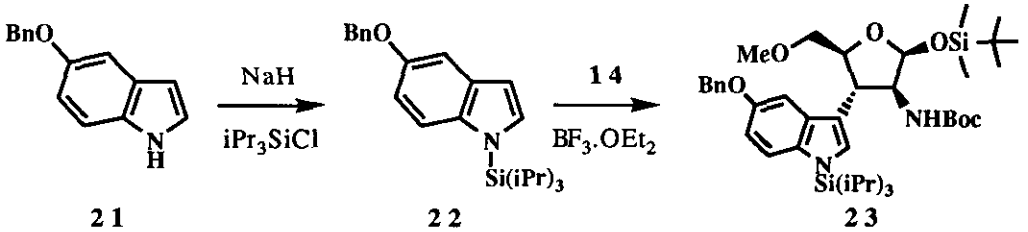
14 : R =Me
17 : R = Bn

19 : R = Me
20 : R = Bn

Scheme 4

The initial investigation of the reactions of *N*-Boc aziridines (**14** and **17**) with (*tert*-butyldimethylsilyl)indole (**10**) gave disappointing results, the yields of coupling products being in both cases almost negligible, regardless of the solvent used for the reaction (ether or chloroform). Better results were obtained when **14** and **17** were reacted with 1-(triisopropylsilyl)indole (**18**),[18] producing compounds (**19** and **20**), respectively, in 30% and 25% yields. The superiority of indole (**18**) over indole (**10**) probably arises from the ability to conduct reactions with the former in the absence of any added solvent. Thus, mild heating of a mixture of **18** and aziridines (**14** or **17**) before addition of the Lewis acid produced homogeneous solutions which remained so upon cooling to rt. This was not the case with analogous reactions involving indole (**10**) which required the use of a solvent (e.g., chloroform or ether) to achieve dissolution of the reactants. Such solvents apparently had detrimental effects on yields. It should also be noted that neither of the α-anomers (**13** or **16**) reacted with indole (**18**), in the absence or presence of solvent, to give the expected coupling products. The large steric hindrance provided by the *tert*-butyldimethylsilyl groups of **13** and **16**, situated, in contrast to β-anomers (**14** and **17**), on the same face as the attacking nucleophile, may account for this failure.

The possibility of using a substituted indole derivative in these reactions was next investigated. In particular, the incorporation of a 5-benzyloxyindole moiety on the 2-aminobutyrolactone ring would give access, after hydrogenolysis, to rigid 5-hydroxytryptophan analogues of potential pharmacological interest. For this purpose, 5-benzyloxy-1-triisopropylsilylindole (**22**) was prepared by treating 5-benzyloxyindole (**21**) with sodium hydride in DMF and then with triisopropylsilyl chloride (Scheme 5). Reaction of **22** and aziridine



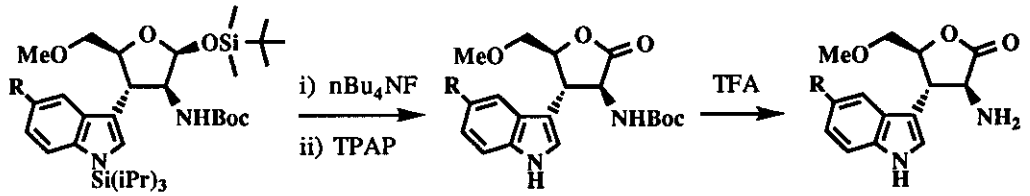
21 **22** **23**

Scheme 5

derivative (**14**) in chloroform in the presence of boron trifluoride etherate then gave the expected C3-C3 coupled product (**23**), though in lower yield than those observed for unsubstituted indole (**18**).

Finally, the transformation of the 5-methoxy adducts (**19** and **23**) into *N*-deprotected, constrained tryptophan analogues of type (**3**) was studied. Thus, both silyl protecting groups of compound (**19**) were removed simultaneously by treatment with tetrabutylammonium fluoride in THF at -20 °C (Scheme 6). The intermediate

furanose derivative, isolated only by extractive procedures, was immediately oxidized to lactone (**24**) by the action of catalytic TPAP (and 4-methylmorpholine *N*-oxide as co-oxidant)[19] in acetonitrile. Removal of the *N*-Boc blocking group of **24** was achieved using trifluoroacetic acid in dichloromethane at



19 : R = H
23 : R = OBn

24 : R = H
26 : R = OBn

25 : R = H
27 : R = OBn

Scheme 6

rt, affording the desired 2-amino-γ-butyrolactone (**25**). Spectroscopic data for **25** were completely consistent with the assigned structure. In particular, the ^{1}H-NMR spectrum clearly showed both amine signals, the indolic proton being observed as a singlet at 8.49 ppm while the primary amino group gave rise to a broad two-proton singlet at 1.78 ppm. The IR spectrum of **25** showed the characteristic lactone carbonyl absorption at 1772 cm^{-1}. Similarly, treatment of the benzyloxyindolyl derivative (**23**) with the same sequence of reagents (tetrabutylammonium fluoride, TPAP/NMO, and finally trifluoroacetic acid) gave, without any extensive purification of the intermediates, the corresponding 2-aminobutyrolactone (**27**).

In conclusion, the Lewis acid-catalyzed coupling of *N*-alkylsilylindole derivatives with *tert*-butyldimethylsilyl 2,3-aziridino-β-D-lyxofuranoside derivatives provides a new route to compounds which may be considered as novel examples of conformationally constrained tryptophan derivatives. The various blocking groups chosen for each substrate (trialkylsilyl, Boc, benzyl) allow their selective removal and thus the possibility of further elaboration or functionalization of the coupling products. Finally, since we have previously shown that the 2-amino-γ-butyrolactone ring can easily be opened by alcohols to give esters of β-substituted amino acids,[20,21] then compounds (**25** and **27**) may be formally considered as precursors of β-substituted L-tryptophan derivatives.

EXPERIMENTAL

General - Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as films or as KBr pellets with a Nicolet 205 FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined on Bruker 250 MHz or 300 MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with uv light (254 nm) and with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-400 mesh) at medium pressure (200 mbar). Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

Methyl *N*-Acetyl-2,3-aziridino-2,3-dideoxy-5-*O*-methyl-β-D-lyxofuranoside (7) - A solution of aziridine (**6**)[15] (294 mg, 1.85 mmol) in anhydrous pyridine (19 mL) and acetic anhydride (3 mL) was left for 60 h at 4 °C. The solvents were then removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate). A small quantity (< 10%) of the minor α-anomer of **7** was first eluted, followed by the major β-anomer (**7**) (236 mg, 64%) which was isolated as an oil. IR (film) 3568, 1700, 1691 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 2.18 (s, 3H, Ac), 3.32 (dd, 1H, $J_{2,3}$ = 4.7 Hz, $J_{3,4}$ = 1.9 Hz, H-3), 3.39 (dd, $J_{2,3}$ = 4.7 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 3.42 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.65 (dd, 2H, $J_{4,5a}$ = $J_{4,5b}$= 6.2 Hz, $J_{5a,5b}$ = 1.6 Hz, H-5), 4.11 (dt, 1H, $J_{4,5a}$ = $J_{4,5b}$= 6.2 Hz, $J_{3,4}$ = 1.9 Hz, H-4), 5.02 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 23.5, 41.5, 41.8, 57.4, 59.4, 72.0, 75.4, 103.0, 118.5. Anal. Calcd for $C_9H_{15}NO_4$. 0.1 H_2O : C, 53.25 ; H, 7.50 ; N, 6.90. Found : C, 53.14 ; H, 7.49 ; N, 6.54.

Methyl 2-Acetamido-2,3-dideoxy-5-*O*-methyl-3-*C*-[3-(1-methylindolyl)]-β-D-arabinofuranoside (9) - A solution of compound (**7**) (26.5 mg, 0.13 mmol) and 1-methylindole (0.18 mL, 1.02 mmol) in anhydrous ether (120 µL) was treated dropwise at 0 °C under argon with boron trifluoride etherate (24 µL, 0.19 mmol). The reaction mixture was stirred for 30 min at 0 °C and ethyl acetate (5 mL) was then added followed by saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, the aqueous phase was extracted with ethyl acetate (3 x 5 mL), the organic extracts were combined and dried over Na_2SO_4. Removal

of the solvents under reduced pressure left a residue which was purified by column chromatography on silica gel (ethyl acetate-heptane 1:4 followed by ethyl acetate) affording compound (**9**) in 57% yield (25 mg) as an oil. IR (film) 3310, 1655 cm^{-1}. CIMS m/z 333 (MH^+). ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.86 (s, 3H, NHCOC<u>H</u>$_3$), 3.39 (s superimposed on m, 4H, OCH_3, H-3), 3.47 (s, 3H, OCH_3), 3.52 (ddd, 2H, $J_{5a,5b}$ = 10.5 Hz, $J_{4,5a}$ = 5.9 Hz, $J_{4,5b}$ = 2.5 Hz, H-5), 3.74 (s, 3H, NCH_3), 4.14 (ddd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5a}$ = 5.9 Hz, $J_{4,5b}$ = 2.5 Hz, H-4), 4.96 (m, 2H, H-1, H-2), 5.82 (d, 1H, J = 8.4 Hz, exchangeable with D_2O, N<u>H</u>Ac), 7.10-7.30 (m, 4H, ArH, NCH=C), 7.56 (d, 1H, J = 7.2 Hz, ArH). *Anal. Calcd for* $C_{18}H_{24}N_2O_4$: C, 65.06 ; H, 7.23 ; N, 8.43. Found : C, 65.26 ; H, 7.20 ; N, 8.60.

Methyl 2-Acetamido-2,3-dideoxy-3-*C*-{3-[1-(*tert*-butyldimethylsilyl)indolyl]}-5-*O*-methyl-β-D-arabinofuranoside (11) - A solution of aziridine (**7**) (47 mg, 0.23 mmol) in anhydrous chloroform (200 µL) was treated at rt under an argon atmosphere with boron trifluoride etherate (35 µL, 0.27 mmol) and the mixture was stirred for 15 min. Indole (**10**) (166 mg, 0.72 mmol) was then added and stirring was continued for 17.5 h. At the end of the reaction period, the mixture was diluted with ethyl acetate (5 mL) and made basic by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, the aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were dried over Na_2SO_4. Removal of the solvents under reduced pressure left an oil which was purified by column chromatography on silica gel using ethyl acetate as eluent, affording compound (**11**) as a solid in 22% yield (22 mg) ; mp 70-75 °C (decomp). IR (film) 3444, 3325, 1660 cm^{-1}. EIMS m/z 432 (M^+), 373 (M^+-CH_3CONH_2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.59 (s, 3H, $SiCH_3$), 0.60 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.89 (s, 3H, NCH_3), 3.42 (s, 3H, OCH_3), 3.48 (s superimposed on m, 4H, OCH_3, H-3), 3.56 (ddd, 2H, $J_{5a,5b}$ = 10.6 Hz, $J_{4,5a}$ = 5.9 Hz, $J_{4,5b}$ = 2.3 Hz, H-5), 4.13 (ddd, $J_{3,4}$ = 9.6 Hz, $J_{4,5a}$ = 5.9 Hz, $J_{4,5b}$ = 2.3 Hz, H-4), 4.97 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 5.04 (ddd, 1H, $J_{2,3}$ = 11.5 Hz, $J_{2,NH}$ = 9.2 Hz, $J_{1,2}$ = 4.5 Hz, H-2), 5.79 (d, 1H, $J_{NH,2}$ = 9.2 Hz, exchangeable with D_2O, NH), 7.15 (m, 2H, ArH), 7.25 (s, 1H, NCH=C), 7.50 (d, 1H, J = 7.2 Hz, ArH), 7.57 (d, 1H, J = 7.2 Hz, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : - 3.8, 19.6, 26.4, 40.2, 54.9, 55.7, 59.5, 74.7, 84.0, 101.8, 113.2, 114.3, 118.6, 119.8, 121.7, 129.1, 131.1, 141.8, 169.8. Anal. Calcd for $C_{23}H_{36}N_2O_4Si$. 1.5 H_2O : C, 59.86 ; H, 8.45 ; N, 6.07. Found : C, 60.11 ; H, 8.09 ; N, 5.76.

***tert*-Butyldimethylsilyl *N*-(*tert*-Butyloxycarbonyl)-2,3-aziridino-2,3-dideoxy-5-*O*-methyl-α-(and β)-D-lyxofuranoside (13 and 14)** - To a solution of compound (**12**) (447 mg, 1.7 mmol) and 4-

dimethylaminopyridine (45 mg, 0.36 mmol) in THF (10 mL) was added dropwise at rt a solution of di-*tert*-butyl dicarbonate (873 mg, 4.0 mmol) in THF (5 mL) and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, the oily residue was dissolved in ethyl acetate (20 mL), brine (10 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL), the organic extracts were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The remaining crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 4:1). The α-anomer (**13**) was eluted first and isolated as an oil in 33% yield (201 mg). IR (film) 2956, 1727 cm^{-1}. CIMS m/z 360 (MH^+), 260 (MH^+-Boc). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.11 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 3.14 (d, 1H, $J_{2,3}$ = 4.5 Hz, H-2), 3.27 (dd, 1H, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 1.6 Hz, H-3), 3.42 (s, 3H, OCH_3), 3.62 (d, 2H, $J_{4,5a} = J_{4,5b}$ = 6.1 Hz, H-5), 4.19 (dt, 1H, $J_{4,5a} = J_{4,5b}$ = 6.1 Hz, $J_{3,4}$ = 1.6 Hz, H-4), 5.37 (s, 1H, H-1). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -4.3, 17.9, 25.7, 27.9, 41.6, 44.8, 59.4, 71.5, 75.3, 81.5, 96.3, 160.3. Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.79 ; H, 9.25 ; N, 3.90. Found : C, 56.69 ; H, 9.29 ; N, 3.96.

Continued elution of the column afforded the β-anomer (**14**), isolated as an oil (275 mg, 45%) which slowly crystallized, mp 34-36 °C. $[\alpha]_D^{22}$ -26.1° (c 1.94, $CHCl_3$). IR (film) 2978, 1724 cm^{-1}. EIMS m/z 359 (M^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.16 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.45 (s, 9H, $OC(CH_3)_3$), 3.18 (dd, 1H, $J_{2,3}$ = 4.9 Hz, $J_{1,2}$ = 1.3 Hz, H-2), 3.22 (dd, 1H, $J_{2,3}$ = 4.9 Hz, $J_{3,4}$ = 1.7 Hz, H-3), 3.65 (d, 2H, $J_{4,5a} = J_{4,5b}$ = 6.1 Hz, H-5), 3.97 (dt, 1H, $J_{4,5a} = J_{4,5b}$ = 6.1 Hz, $J_{3,4}$ = 1.7 Hz, H-4), 5.34 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -4.4, 18.2, 25.8, 27.9, 42.1, 44.3, 59.6, 71.9, 75.3, 81.4, 97.0, 161.0. Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.79 ; H, 9.25 ; N, 3.90. Found : C, 56.76 ; H, 9.48 ; N, 3.64.

***tert*-Butyldimethylsilyl *N*-(*tert*-Butyloxycarbonyl)-2,3-aziridino-5-*O*-benzyl-2,3-dideoxy-α-(and β-)-D-lyxofuranoside (16 and 17)** - To a solution of compound (**15**) (388 mg, 1.16 mmol) and 4-dimethylamino-pyridine (46 mg, 0.4 mmol) in THF (5 mL) was added dropwise at rt a solution of di-tert-butyl dicarbonate (582 mg, 2.66 mmol) in THF (5 mL). The reaction mixture was stirred for 2 days and then worked up in the same manner as for the preparation of **13** and **14**. The resulting crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 20:1). The first compound eluted was the α-anomer (**16**), obtained in 30% yield (151 mg) as an oil which slowly crystallized, mp 51-53 °C. $[\alpha]_D^{22}$ +13.5° (c 1.54, $CHCl_3$). IR (film) 3439, 1724 cm^{-1}. CIMS m/z 436 (MH^+), 336 (MH^+-Boc). ^{1}H-NMR (250 MHz,

$CDCl_3$) δ : 0.15 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 3.16 (d, 1H, $J_{2,3}$ = 4.5 Hz, H-2), 3.33 (dd, 1H, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 1.5 Hz, H-3), 3.73 (d, 2H, $J_{4,5a} = J_{4,5b}$ = 6.1 Hz, H-5), 4.26 (dt, 1H, $J_{4,5a} = J_{4,5b}$ = 6.1 Hz, $J_{3,4}$ = 1.5 Hz, H-4), 4.66 (s, 2H, $PhC\underline{H}_2$), 5.38 (s, 1H, H-1), 7.10-7.35 (m, 5H, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -4.3, 17.9, 25.7, 27.9, 41.7, 44.9, 63.1, 73.5, 75.5, 81.5, 96.3, 127.6, 127.7, 128.3, 138.9, 160.3. Anal. Calcd for $C_{23}H_{37}NO_5Si$: C, 63.45 ; H, 8.51 ; N, 3.22. Found : C, 63.22 ; H, 8.71 ; N, 3.04.

Continued elution of the column afforded the β-anomer (**17**) in 34% yield (172 mg) as an oil, $[\alpha]_D^{22}$ -22.7° (c 1.53, $CHCl_3$). IR (film) 1722 cm^{-1}. EIMS m/z 435 (M^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.16 (s, 3H, $Si(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 3.18 (dd, 1H, $J_{2,3}$ = 4.9 Hz, $J_{1,2}$ = 1.3 Hz, H-2), 3.26 (dd, 1H, $J_{2,3}$ = 4.9 Hz, $J_{3,4}$ = 1.8 Hz, H-3), 3.82 (ddd, 2H, $J_{5a,5b}$= 9.5 Hz, $J_{4,5a} = J_{4,5b}$ = 6.2 Hz, H-5), 4.02 (dt, 1H, $J_{4,5a} = J_{4,5b}$ = 6.2 Hz, $J_{3,4}$ = 1.8 Hz, H-4), 4.61 (s, 2H, $PhC\underline{H}_2$), 5.35 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1), 7.26-7.35 (m, 5H, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -4.9, -4.0, 18.2, 25.8, 27.9, 42.1, 44.4, 69.5, 73.7, 75.4, 81.4, 96.9, 127.6, 127.8, 128.4, 138.2, 161.1. Anal. Calcd for $C_{23}H_{37}NO_5Si$. 0.2 H_2O : C, 62.92 ; H, 8.52 ; N, 3.19. Found : C, 62.81 ; H, 8.32 ; N, 3.47.

***tert*-Butyldimethylsilyl 2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,3-dideoxy-3-*C*-{3-[1-(triisopropylsilyl)-indolyl]}-5-*O*-methyl-β-D-arabinofuranoside (19)** - A mixture of aziridine (**14**) (234 mg, 0.65 mmol) and 1-(triisopropylsilyl)indole (**18**) (1.01 g, 3.7 mmol) was treated at rt under an argon atmosphere with boron trifluoride etherate (120 µL, 0.95 mmol). The reaction mixture was stirred for 4 h at rt and then worked up as for compound (**11**). The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 9:1) affording compound (**19**) as an oil in 30% yield (123 mg), $[\alpha]_D^{22}$ -55.5° (c 0.87, $CHCl_3$). IR (film) 3455, 1715 cm^{-1}. EIMS m/z 632 (M^+), 532 (M^+-Boc). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.17 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.96 (s, 9H, $SiC(CH_3)_3$), 1.14 (d, 18H, J = 7.5 Hz, $Si[CH(C\underline{H}_3)_2]_3$), 1.26 (s, 9H, $OC(CH_3)_3$), 1.69 (m, 3H, J = 7.5 Hz, $Si[C\underline{H}(CH_3)_2]_3$), 3.30 (m, 1H, H-3), 3.35 (s, 3H, OCH_3), 3.55 (ddd, 2H, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5a}$ = 7.0 Hz, $J_{4,5b}$ = 2.5 Hz, H-5), 4.18 (ddd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{4,5a}$ = 7.0 Hz, $J_{4,5b}$ = 2.5 Hz, H-4), 4.58 (ddd, 1H, $J_{2,3}$ = 9.4 Hz, $J_{2,NH}$ = 9.4 Hz, $J_{1,2}$ = 4.0 Hz, H-2), 4.74 (d, 1H, $J_{2,NH}$ = 9.4 Hz, exchangeable with D_2O, NH), 5.44 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 7.12 (m, 2H, ArH), 7.23 (s, 1H, NCH=C), 7.46 (d, 1H, J = 7.9 Hz, ArH), 7.60 (d, 1H, J = 7.9 Hz, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -5.1, -4.1, 12.9, 14.2, 18.2, 25.8, 28.3, 40.2, 58.3, 59.1, 75.5,

79.1, 83.5, 96.1, 113.7, 118.6, 119.6, 121.6, 128.9, 130.9, 141.8, 155.4. Anal. Calcd for $C_{34}H_{60}N_2O_5Si_2$: C, 64,56 ; H, 9,49; N, 4,43. Found : C, 64,51 ; H, 9,41 ; N, 4.34.

***tert*-Butyldimethylsilyl 2-[*N*-(*tert*-Butyloxycarbonyl)amino]-5-*O*-benzyl-2,3-dideoxy-3-*C*-{3-[1-(tri-isopropylsilyl)indolyl]}-β-D-arabinofuranoside (20)** - A mixture of aziridine (**17**) (174 mg, 0.4 mmol) and 1-(triisopropylsilyl)indole (**18**) (505 mg, 2.1 mmol) was treated dropwise at rt with boron trifluoride etherate (65 µL, 0.51mmol). The reaction mixture was stirred for 4 h at rt and then worked up in the same manner as for **11**. The resulting crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 9:1), affording compound (**20**) in 25% yield (71 mg) as an oil, $[\alpha]_D^{22}$ -28.5° (c 2.38, $CHCl_3$). IR (film) 3452, 1717 cm^{-1}. CIMS m/z 709 (MH^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.15 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.14 (d, 18H, J = 7.2 Hz, $Si[CH(C\underline{H}_3)_2]_3$), 1.30 (s, 9H, $OC(CH_3)_3$), 1.68 (m, 3H, $Si[C\underline{H}(CH_3)_2]_3$), 3.35 (dd, 1H, $J_{3,4}$ = 11.5 Hz, $J_{2,3}$ = 10.5 Hz, H-3), 3.65 (ddd, 2H, $J_{5a,5b}$ = 10.3Hz, $J_{4,5a}$ = 6.5 Hz, $J_{4,5b}$ = 2.6 Hz, H-4), 4.24 (ddd, 1H, $J_{3,4}$ = 11.5 Hz, $J_{4,5a}$ = 6.5 Hz, $J_{4,5b}$ = 2.6 Hz, H-4), 4.32-4.51 (m, 3H, $PhC\underline{H}_2$, H-2), 4.76 (d, 1H, $J_{2,NH}$ = 9.5 Hz, exchangeable with D_2O, NH), 5.45 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-1), 7.05-7.13 (m, 3H, ArH, NCH=C), 7.21-7.30 (m, 5H, ArH), 7.46 (d, 1H, J = 7.4 Hz, ArH), 7.58 (d, 1H, J = 7.4 Hz, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -5.1, -4.1, 12.9, 18.2, 18.7, 25.9, 28.4, 40.5, 58.4, 73.2, 73.4, 79.2, 83.6, 96.1, 104.8, 114.2, 118.8, 119.7, 120.6, 121.6, 127.5, 127.8, 128.3, 128.9, 131.2, 141.8, 155.4. Anal. Calcd for $C_{40}H_{64}N_2O_5Si_2$: C, 67.80 ; H, 9.04 ; N, 3.95. Found : C, 67.63 ; H, 8.93 ; N, 3.91.

5-Benzyloxy-1-(triisopropylsilyl)indole (22) - To a suspension of sodium hydride (109 mg of a 50% dispersion in oil, 2.27 mmol) in anhydrous DMF (10 mL) was added dropwise at 0 °C under argon a solution of 5-benzyloxyindole (**21**, 415 mg, 1.86 mmol) in DMF (3 mL). After gas evolution had ceased, the solution was allowed to stir at rt for 30 min and it was then cooled again to 0 °C before the addition of triisopropylsilyl chloride (0.8 mL, 3.72 mmol). The reaction mixture was stirred for 60 h at rt, water (20 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 10 mL). The organic phases were combined, washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure left a crude product which was purified by column chromatography on silica gel (heptane-ethyl acetate 20:1), affording compound (**22**) as a pale yellow solid in 83% yield (585 mg), mp 60-63 °C. EIMS m/z 379 (M^+). ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.15 (d, 18H, J = 7.5 Hz, $SiCH(C\underline{H}_3)_2$),

1.67 (m, 3H, J = 7.5 Hz, SiC<u>H</u>), 5.09 (s, 2H, PhC<u>H</u>$_2$), 6.54 (d, 1H, J = 3.0 Hz, N-CH=C<u>H</u>), 6.88 (dd, 1H, J = 8.8 and 2.2 Hz, ArH), 7.16 (d, 1H, J = 2.2 Hz, ArH), 7.22 (d, 1H, J = 3.0 Hz, NC<u>H</u>=CH), 7.33-7.49 (m, 6H, ArH). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 12.8, 18.1, 70.6, 103.6, 104.6, 111.9, 114.4, 127.5, 127.7, 128.5, 131.9, 135.9, 137.8, 153.4. Anal. Calcd for $C_{24}H_{33}NOSi$: C, 75.99 ; H, 8.71 ; N, 3.69. Found : C, 75.65, H, 8.92 ; N, 3.81.

***tert*-Butyldimethylsilyl 2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,3-dideoxy-3-*C*-{3-[5-(benzyloxy)-1-(tri-isopropylsilyl)indolyl]}-5-*O*-methyl-β-D-arabinofuranoside (23)** - To a mixture of aziridine (**14**) (116 mg, 0.32 mmol) and 5-benzyloxy-1-(triisopropylsilyl)indole (**22**) (321 mg, 0.85 mmol) in chloroform (150 µL) was added dropwise at rt boron trifluoride etherate (51 µL, 0.40 mmol). The solution was stirred for 18 h at rt and then worked up in the same manner as for compound (**11**). The resulting crude product was purified by preparative tlc on silica gel (heptane-ethyl acetate 4:1), affording compound (**23**) as an oil in 22% yield (138 mg), $[\alpha]_D^{22}$ -12.3° (c 0.88, $CHCl_3$). IR (film) 3451, 1716 cm^{-1}. CIMS m/z 739 (MH^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.16 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.96 (s, 9H, $SiC(CH_3)_3$), 1.12 (d, 18H, J = 7.5 Hz, $Si[CH(C\underline{H}_3)_2]_3$), 1.32 (s, 9H, $OC(CH_3)_3$), 1.66 (m, 3H, $Si[C\underline{H}(CH_3)_2]_3$), 3.24 (m, 1H, H-3), 3.35 (s, 3H, OCH_3), 3.50 (ddd, 2H, $J_{5a,5b}$ = 10.6 Hz, $J_{4,5a}$ = 2.7 Hz, $J_{4,5b}$ = 6.3 Hz, H-5), 4.15 (ddd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{4,5a}$ = 2.7 Hz, $J_{4,5b}$ = 6.3 Hz, H-4), 4.55 (ddd, 1H, $J_{2,3}$ = 11.5 Hz, $J_{2,NH}$ = 9.4 Hz, $J_{2,1}$ = 4.2 Hz, H-2), 4.74 (d, 1H, $J_{2,NH}$ = 9.4 Hz, exchangeable with D_2O, NH), 5.10 (s, 2H, PhC<u>H</u>$_2$), 5.43 (d, 1H, $J_{1,2}$ = 4.2 Hz, H-1), 6.87 (d, 1H, J = 7.8 Hz, ArH), 7.13-7.49 (m, 8H, ArH, NCH=C). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : -5.1, -4.1, 12.9, 18.2, 18.5, 25.9, 28.4, 40.2, 58.2, 59.4, 70.9, 75.5, 81.1, 83.4, 96.1, 111.9, 113.5, 114.8, 127.8, 127.9, 128.7, 129.8, 131.5, 136.9, 137.9, 153.3, 155.4, 178.9. Anal. Calcd for $C_{41}H_{66}N_2O_6Si_2$: C, 66.67 ; H, 8.94 ; N, 3.79. Found : C, 66.91 ; H, 8.83 ; N, 3.91.

2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,3-dideoxy-3-*C*-(3-indolyl)-5-*O*-methyl-D-arabinono-lactone (24) - A solution of compound (**19**) (111 mg, 0.175 mmol) in anhydrous THF (10 mL) was cooled to -78 °C, tetrabutylammonium fluoride (173 mg, 0.55 mmol) was added and the reaction mixture was stirred for 45 min. The solution was then warmed to -20 °C and saturated aqueous NH_4Cl (10 mL) was added. The phases were separated, the aqueous phase was extracted with ethyl acetate (3 x 5 mL), the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and the solvents were removed under reduced

pressure. The residual yellow oil was dissolved in acetonitrile (2 mL) and the solution was added to a mixture of freshly activated, powdered 4 Å molecular sieves (93 mg), 4-methylmorpholine *N*-oxide (45.3 mg, 0.39 mmol) and tetrapropylammonium perruthenate (6.7 mg, 0.02 mmol) in acetonitrile (2 mL). After the reaction mixture was stirred for 45 min at rt, the solvent was removed under reduced pressure and the residue was filtered through a thin (2 cm) pad of silica gel (heptane-ethyl acetate 1:1). Evaporation of the filtrate *in vacuo* left crude **24** (73 mg) as a brown oil which could be used in the following step without further purification. An analytical sample of **24** was obtained by purification of an aliquot of the crude material by preparative tlc on silica gel (heptane-ethyl acetate 2:1). IR (film) 3362, 1780, 1702, 1698 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.36 (s, 9H, $OC(CH_3)_3$), 3.43 (s, 3H, OCH_3), 3.65 (ddd, 2H, $J_{5a,5b}$ = 10.6 Hz, $J_{4,5a}$ = 3.5 Hz, $J_{4,5b}$ = 1.7 Hz, H-5), 3.94 (m, 1H, H-3), 4.54 (m, 1H, H-4), 4.78 (m, 1H, H-2), 5.10 (br d, 1H, $J_{2,NH}$ = 7.1 Hz, exchangeable with D_2O, NH), 7.11-7.26 (m, 3H, ArH, NCH=C), 7.40 (d, 1H, J = 7.1 Hz, ArH), 7.58 (d, 1H, J = 7.1 Hz, ArH), 8.53 (s, 1H, exchangeable with D_2O, indole NH). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 31.0, 40.4, 59.6, 68.5, 71.1, 77.6, 82.0, 110.5, 111.8, 118.9, 120.2, 122.8, 123.2, 140.2, 173.7. HRCIMS calcd for $C_{19}H_{25}N_2O_5$ m/z 361.1763, found 361.1758.

2-Amino-2,3-dideoxy-3-*C*-(3-indolyl)-5-*O*-methyl-D-arabinonolactone (25) - To a solution of the crude compound (**24**) (50 mg) in dichloromethane (5 mL), was added trifluoroacetic acid (0.5 mL) and the solution was stirred for 1 h at rt. Saturated, aqueous $NaHCO_3$ (5 mL) was then added, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The organic extracts were combined, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, affording compound (**25**) as an oil in 30% yield (based on **19**) (14 mg), $[\alpha]_D^{22}$ -6.9° (c 1.0, $CHCl_3$). IR (film) 3397, 1772 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.78 (brs, 2H, exchangeable with D_2O, NH_2), 3.41 (s, 3H, OCH_3), 3.59 (t, 1H, $J_{2,3} = J_{3,4}$ = 11.0 Hz, H-3), 3.60 (ddd, 2H, $J_{5a,5b}$ = 11.5 Hz, $J_{4,5a}$ = 4.6 Hz, $J_{4,5b}$ = 1.5 Hz, H-5), 4.10 (d, $J_{2,3}$ = 11.0 Hz, H-2), 4.70 (ddd, 1H, $J_{3,4}$ = 11.0 Hz, $J_{4,5a}$ = 4.6 Hz, $J_{4,5b}$ = 1.5 Hz, H-4), 7.14-7.26 (m, 3H, ArH, NCH=C), 7.40 (d, 1H, J = 7.0 Hz, ArH), 7.63 (d, 1H, J = 7.0 Hz, ArH), 8.49 (br s, 1H, exchangeable with D_2O, indole NH). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 43.7, 57.1, 59.1, 70.1, 80.8, 110.7, 117.4, 118.5, 119.7, 121.8, 122.4, 125.9, 136.4, 176.5. HRCIMS calcd for $C_{14}H_{17}N_2O_3$ m/z 261.1239, found 261.1237.

2-Amino-3-*C*-{3-[5-(benzyloxy)indolyl]}-2,3-dideoxy-5-*O*-methyl-D-arabinonolactone (27) - Following the same procedure used for the transformation of **19** into **25**, compound (**23**) (165 mg, 0.22 mmol) was treated successively with tetrabutylammonium fluoride, tetrapropylammonium perruthenate and finally trifluoroacetic acid, affording compound (**27**) as a white solid in 43 % yield (35 mg) after purification of the crude material by column chromatography on silica gel (dichloromethane-ethanol 95:5), mp 154-156 °C. $[\alpha]_D^{22}$ -1.8° (c 0.5, MeOH). IR (KBr) 3382, 1779 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.79 (br s, 2H, exchangeable with D_2O, NH_2), 3.39 (s, 3H, OCH_3), 3.53 (pseudo t, 1H, $J_{2,3} = J_{3,4} = 10.7$ Hz, H-3), 3.58 (ddd, 2H, $J_{5a,5b} = 11.5$ Hz, $J_{4,5a} = 4.5$ Hz, $J_{4,5b} = 1.7$ Hz, H-5), 4.01 (d, 1H, $J_{2,3} = 10.7$ Hz, H-2), 4.62 (ddd, 1H, $J_{3,4} = 10.7$ Hz, $J_{4,5a} = 4.5$ Hz, $J_{4,5b} = 1.7$ Hz, H-4), 5.10 (s, 2H, $PhC\underline{H}_2$), 6.95-7.45 (m, 9H, ArH, NCH=C), 8.35 (br s, 1H, exchangeable with D_2O, indole NH).^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 44.0, 57.5, 59.6, 71.1, 71.3, 81.2, 102.6, 110.7, 112.5, 113.7, 122.8, 123.0, 127.6, 128.0, 128.7, 132.1, 137.5, 153.5, 177.0. HRCIMS calcd for $C_{21}H_{23}N_2O_4$ m/z 367.1658, found 367.1633.

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