Synthesis of the Indole Nucleoside Antibiotics Neosidomycin and SF-2140

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The indole nucleoside antibiotics neosidomycin **5** and SF-2140 **3** have been synthesized. Methyl 4-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranoside **8** was converted into methyl 1-chloro-1,4-dideoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranuronate **33** in five steps. Silver(I)-catalysed coupling of compound **33** with 3-(cyanomethyl)indole **20** gave stereoselectively an α-nucleoside which was converted into methyl 1-[3-(carbamoylmethyl)indol-1-yl]-1,4-dideoxy-α-D-*lyxo*-hexopyranuronate (neosidomycin, **5**). Coupling of compound **33** to 3-cyanomethyl-4-methoxyindole **23** by the sodium salt procedure, and subsequent deacylation, gave methyl 1-(3-cyanomethyl-4-methoxyindol-1-yl)-1,4-dideoxy-α-D-*lyxo*-hexopyranuronate (SF-2140, **3**). Neosidomycin, SF-2140, and their *O*-acyl derivatives adopt a conformation which differs from that of 1-(6-*O*-benzoyl-4-deoxy-2,3-*O*-pivaloyl-α-D-*lyxo*-hexopyranosyl)-3-(cyanomethyl)indole **29**, in which the methyl uronate grouping of the antibiotics is present at a lower oxidation level.

During the course of a screening programme, a novel nucleoside antibiotic, termed neosidomycin, was isolated from the fermentation broth of a strain of *Streptomyces hygroscopicus*. This compound, which possessed weak activity against gram-negative bacteria, was identified as a nucleoside of indole-3-acetamide, but the sugar unit could not be isolated in a pure state after hydrolysis. However, the relative configuration **1** was assigned to neosidomycin on the basis of NMR studies of the antibiotic and of, in particular, its di-*O*-acetyl derivative **2**, with the assumption that the sugar rings of compounds **1** and **2** adopt $^4C_1$ (D) conformations in solution. The absolute configuration of neosidomycin was not assigned.[1] Neosidomycin was the first example of a naturally occurring nucleoside containing the indole ring system.

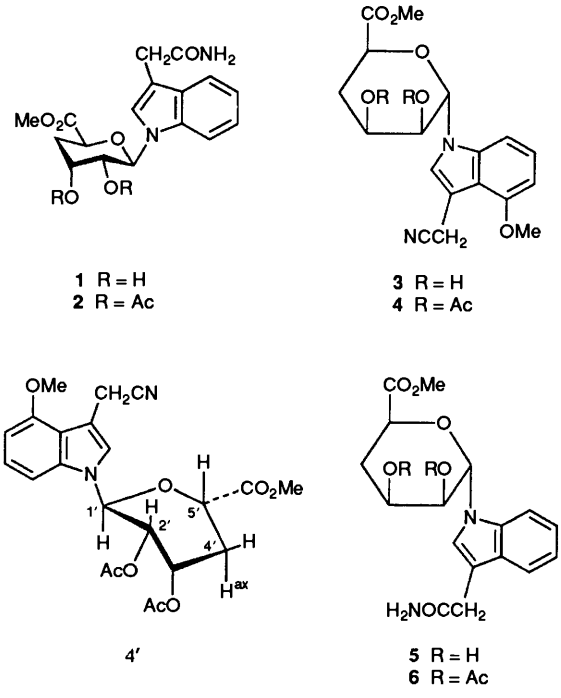
More recently, another indole nucleoside, with antiviral properties, has been described as a metabolite of an *Actinomadura* species isolated from a Japanese soil sample. This compound, termed SF-2140, was subjected to degradative, spectroscopic and X-ray crystallographic studies, as a result of which the structure **3** was determined for SF-2140, in which the 4-deoxyhexuronic acid unit has the D-*lyxo*-configuration. Since, however, the ^{1}H NMR data for compound **3** and its di-*O*-acetyl derivative **4** showed, in particular, large coupling constants $J_{1',2'}$ and $J_{4'ax,5'}$, it was suggested that, in solution, compounds **3** and **4** adopt twist-boat conformations ($^1S_5$) as indicated by structure **4'** in the case of the di-*O*-acetyl derivative. Interestingly, in the crystal structure, the methyl uronate ring of compound **3** adopts a $^1C_4$ (D) conformation.[2]

Since the ^{1}H NMR data for the di-*O*-acetyl derivatives of neosidomycin[1] and SF-2140[2] are virtually identical with regard to the sugar units (the large values of $J_{1',2'}$ and $J_{4'ax,5'}$ being important pieces of data in the assignment of structure **2** to neosidomycin diacetate[1]), the later workers suggested that the structures of neosidomycin and its di-*O*-acetyl derivative should be revised to **5** and **6** respectively.[2] It might be noted that since the absolute configuration of neosidomycin had not been determined, the original structure **1**[1] and the revised suggestion **5**[2] differ only in relative configuration at C-5'.

We now describe the synthesis of compounds **3**–**6**, and confirm the structures of neosidomycin and SF-2140 as being **5** and **3** respectively.[3]

The absolute configuration of SF-2140 was assigned as indicated in structure **3** on the basis of molecular-rotation-difference data, but we felt that, as a preliminary to our synthetic work, it was desirable to confirm this assignment independently. Methyl 4-deoxy-α-D-*lyxo*-hexopyranoside **9** (Scheme 1) had been obtained, $[\alpha]_D$ +86° (*c* 1.0, water),† by sequential reduction and methanolysis of SF-2140 **3**. Rasmussen has described ready access to derivatives of compound **9** by free-radical deoxygenation of the D-mannose derivative to give compound **7** and, after deacylation, compound **8**.[4] Treatment of the protected triol **8** with aq. acetic acid gave the free triol **9** $[\alpha]_D$ +76° (*c* 0.5, water). Additionally, acetylation of triol **9** gave triacetate **10**, with ^{1}H NMR data in excellent agreement with those reported[2] for the equivalent material produced by degradation of SF-2140. Since the reported optical rotations of neosidomycin[1] and SF-2140[2] are very similar, the same absolute configuration can be assigned to neosidomycin.

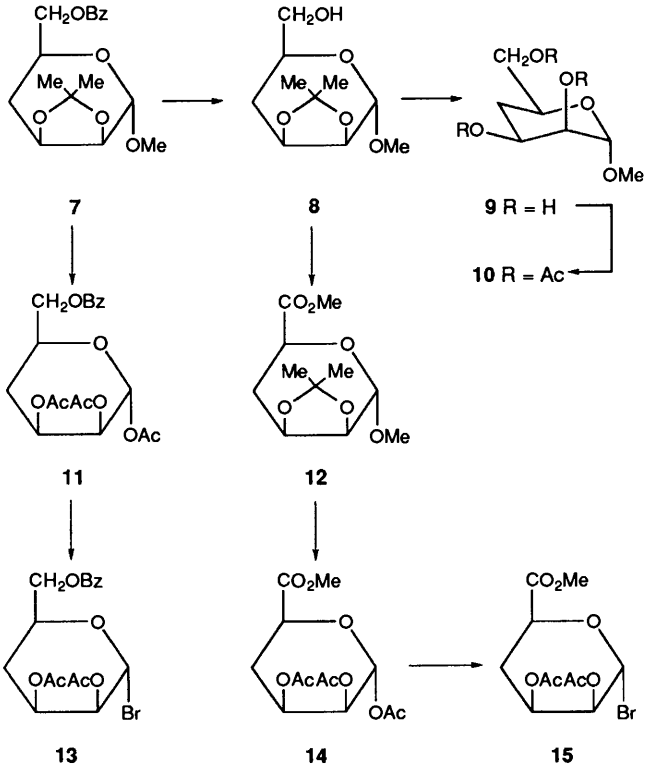
A well established method for the synthesis of *N*-glycosylindoles is the 'indole-indoline' method, originally developed by Preobrazhenskaya *et al.*,[5] and also employed by others,[6] including for the related situation of the synthesis of 1-(β-D-ribofuranosyl)indole-3-acetic acid.[7] In this method, the indole is



† Optical-rotation values are now reported in units of 10^{-1} deg cm^2 g^{-1}.

reduced to the corresponding indoline (2,3-dihydroindole), which is then linked to a peracylated sugar unit, and the *N*-glycosylated indoline is then oxidised to the *N*-glycosylindole.

The application of this method to the synthesis of neosidomycin and SF-2140 would require the methyl uronate **14**, and this was readily obtained from compound **8**[4] by oxidation using Sharpless' ruthenium-based system,[8] which gave the methyl ester **12** (Scheme 1) in 72% yield after methylation



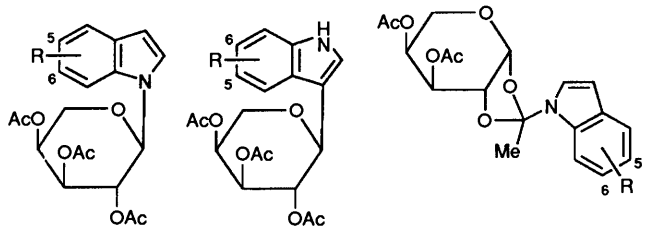
Scheme 1

with diazomethane. Acetolysis of compound **12** led rapidly to the 2,3-di-*O*-acetyl derivative, and then more slowly to the tri-*O*-acetyl compound **14**. This proved difficult to separate from the di-*O*-acetyl derivative, and prolonged reaction time led to decomposition products, so that compound **14** was obtainable in only modest yield. As a result of this complication, acetolysis of compound **7** was also carried out, which led much more cleanly to the tri-*O*-acetyl derivative **11**, isolated as a crystalline solid in 62% yield.

Commercial 3-(cyanomethyl)indole **20** was used as the indolic component. However, although reduction to the indoline proceeded cleanly using pyridine–borane in trifluoroacetic acid (TFA),[9] attempted coupling of the indoline with triacetates **11** and **14**, under a variety of conditions,[5–7] gave no more than trace amounts of product.

N-Glycosylindoles can also be obtained by the interaction of a peracylated glycosyl halide with an indole in the presence of silver salts, but other products can also be formed, as is illustrated by the interaction of 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide with the appropriate indole in the presence of silver oxide to give varying amounts of *N*-glycosylindoles **16**, 3-glycosylindoles **17**, and 1,2-*O*-(indol-1-yl)ethylidene compounds **18**.[10]

To investigate the applicability of this approach to our situation, the glycosyl bromides **13** and **15** were prepared (Scheme 1) from the corresponding acetates **11** and **14**, respectively. Both bromides **13** and **15** were of limited stability and were used immediately. Interaction of compound **13** with 3-(cyanomethyl)indole **20** in the presence of silver oxide and

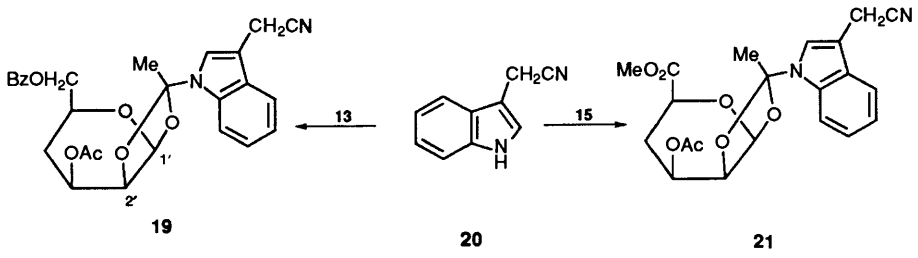


molecular sieves in dry benzene[10] led to the isolation of a single product, to which the structure **19** (Scheme 2) was assigned by ^{1}H NMR spectroscopy. In particular, compound **19** showed signals at δ 5.54 and 4.33 assignable to 1′-H and 2′-H, respectively. The equivalent signals in the (indol-1-yl)ethylidene derivatives **18** occur at δ 5.42–5.57 and 4.06–4.25,[10] whereas, in the spectrum of neosidomycin diacetate **6**, 1′-H and 2′-H resonate at δ 6.50 and 5.37, respectively. Similar use of glycosyl bromide **15** was equally unrewarding, with compound **21** being the only product isolable, and in low yield.

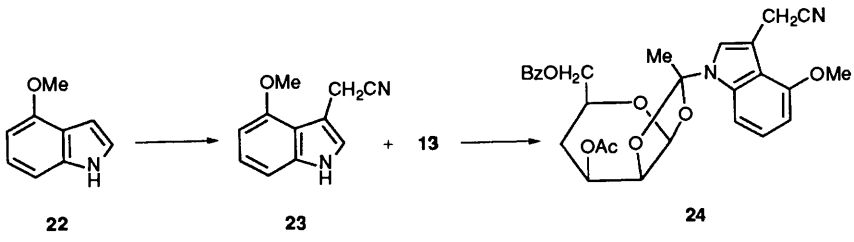
Preobrazhenskaya and coworkers found that nitroindoles gave greater proportions of the (indol-1-yl)ethylidene products **18b**, **18c** than was found for indole itself.[10] We reasoned that an electron-donating methoxy group, as is found in SF-2140, might increase the possibility of obtaining the *N*-glycosylindole. Thus (Scheme 3) we prepared 4-methoxyindole **22** from 2-methoxy-6-nitrotoluene using a combination of literature procedures,[11,12] and converted it into 3-cyanomethyl-4-methoxyindole **23** as described by Govindachari *et al.*[13] However, reaction of nitrile **23** with glycosyl bromide **13** once again gave only an (indol-1-yl)ethylidene product **24** (1′-H, δ 5.53; 2′-H, δ 4.33).

It seemed likely that, if the acetyl group at O-2 of glycosyl bromides **13** and **15** were to be replaced with a bulkier acyl group, then the formation of (indol-1-yl)alkylidene products might be suppressed in favour of the desired *N*-glycosylindoles. This argument has precedent in the use of 2-*O*-pivaloyl groups to suppress the formation of orthoesters during Koenigs–Knorr syntheses of 1,2-*trans* glycosides,[14] including a case in which a glucosiduronate is the glycosyl donor.[15] To investigate this idea, 2,3-*O*-isopropylidene compound **7** was hydrolysed to diol **25** (Scheme 4) with aq. TFA, and this was then pivaloylated using pivaloyl chloride in pyridine. It was observed by TLC that the first pivaloylation occurred much more rapidly than did the second, the slow reaction presumably being that of the axial hydroxy group at O-2. The dipivaloyl derivative **26** could be obtained in 76% yield as a crystalline solid. Acetolysis of methyl glycoside **26** gave 1-*O*-acetyl derivative **27** in high yield, and this could be converted, using HBr–HOAc, into the unstable glycosyl bromide **28**, which was immediately treated with 3-(cyanomethyl)indole **20** and silver oxide in benzene at reflux. From this reaction could be isolated one UV-active product, albeit in low yield, the ^{1}H NMR spectrum of which indicated clearly that it was the *N*-glycosylindole **29**. In particular can be noted the signals for 1′-H and 2′-H at δ 6.00 and 5.74 respectively, distinguishing compound **29** from the (indol-1-yl)ethylidene compounds referred to above, but which are typical of the signals expected for *O*-acylated nucleosides. However, it was also clear from coupling-constant data (*e.g.*, $J_{1',2'}$ 4.1, $J_{3',4'ax}$ 9 Hz), that compound **29** had a clear preference for a $^4C_1$ chair conformation, and did not display the tendency to exist as a twist-boat as was noted above for the cases of the di-*O*-acetyl derivatives of neosidomycin and SF-2140 (compounds **4** and **6**), in which C-6′ is at the uronate level of oxidation.

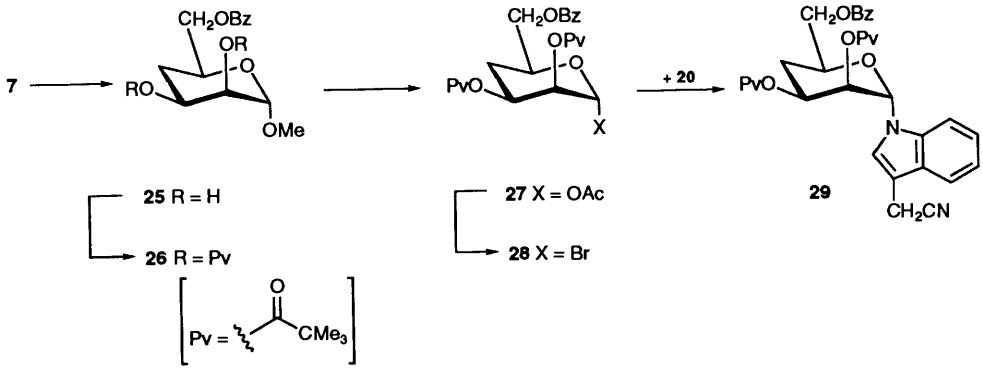
We then proceeded to apply this approach to the synthesis of



Scheme 2



Scheme 3



Scheme 4

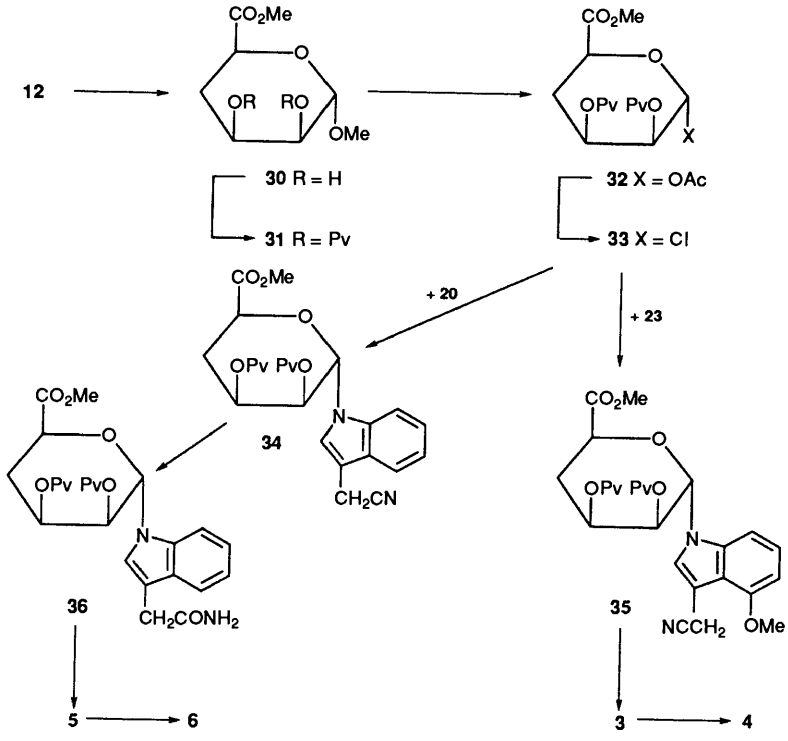
neosidomycin and SF-2140. We were, however, keen to obtain higher yields in the coupling reactions. We felt that one major reason for the low yields in the reactions described above was the instability of the glycosyl bromides, and that a glycosyl chloride might be a more appropriate reactant. The required chloride **33** could be prepared (Scheme 5) from the methyl uronate **12** by a high yielding sequence of hydrolysis to the diol **30**, pivaloylation to give compound **31**, acetolysis to yield acetate **32**, and treatment of this with dichloromethyl methyl ether and anhydrous zinc chloride.[16] The α-configuration of the chloride **33**, of relevance in some later discussion, was established by NOE measurements, in which irradiation of either 3-H or 5-H caused enhancement of the other signal, but in neither case was any enhancement observed of the 1-H signal.

We also felt that use of soluble silver salts would also enhance the yields in coupling reactions.[17] Accordingly, chloride **33** was treated with 3-(cyanomethyl)indole **20** in dichloromethane, in the presence of silver triflate and 2,6-dimethylpyridine (2,6-lutidine), from which reaction compound **34** could be isolated in 36% yield, although again after extensive chromatography. One major by-product, difficult to separate by chromatography, was the glycose formed by hydrolysis of compound **33**, a sample of which was independently prepared by ammonolysis of acetate **32**. The ^{1}H NMR spectrum of compound **34** confirmed its structure, and also indicated that this compound adopted the same conformation as did neosidomycin, SF-2140, and their di-*O*-acetyl derivatives. Chemical-shift and coupling-constant data for the sugar rings of compound **34**, di-*O*-acetyl-SF-2140 **4**[2] and di-*O*-acetylneosidomycin **6**[1] are collected in Table 1.

In an effort to increase further the yield of the coupling, and to simplify the isolation of product, we considered the application of the sodium-salt glycosylation procedure introduced by Revankar, Robins and their co-workers.[18] In this procedure, there is less certainty as to whether a 2-*O*-acyl group will ensure, *via* participation, a nucleoside with 1′,2′-*trans*-stereochemistry, or whether the reaction will proceed by direct inversion.[18] In our situation, direct inversion on the α-chloride **33** would lead to the unwanted β-anomer of the product. However, there are cases reported,[19–21] including examples involving sodium salts of pyrrolo[2,3-*d*]pyrimidines[20] and pyrroles,[21] where acyloxy participation seems to dominate the reaction pathway.

When the indole **20** was converted into its sodium salt and allowed to react with α-chloride **33** in acetonitrile, a nucleoside product could be isolated in an improved yield (44%), and after a much simpler work-up. However, NMR examination indicated that, although compound **34** was the major component, smaller amounts of an isomer were also present, which could not be separated chromatographically. The assignment of this isomer as the β-anomer (**34β**) is discussed below. It was found that the relative amounts of the two anomers produced were temperature-dependent; operation at 0 °C led to a ratio of 6:1 in favour of compound **34**, whilst reactions at higher temperatures led to more of the β-isomer (at 50 °C, ratio 2:1).

In the case of 3-cyanomethyl-4-methoxyindole **23**, reaction with chloride **33** in the presence of silver triflate did not yield the desired product **35**; the only nucleoside product isolated, in low yield, had spectroscopic data which led us to conclude tentatively that it was a *C*-glycosylindole. However, use of the



Scheme 5

Table 1 Selected ^{1}H NMR data for carbohydrate portions of some indol-1-yl glycosides

Compound	δ_H						Coupling constant (J/Hz)						
	1′-H	2′-H	3′-H	4′-H^{ax}	4′-H^{eq}	5′-H	1′,2′	2′,3′	3′,4′$_{ax}$	3′,4′$_{eq}$	4′$_{ax}$,4′$_{eq}$	4′$_{ax}$,5	4′$_{eq}$,5
34[a]	6.56	5.38	5.67	2.51	2.57	4.63	9.7	2.9	3.0	3.6	15.1	6.9	2.1
35[a]	6.49	5.35	5.66	2.51	2.55	4.63	9.7	2.9	2.9	3.6	15.0	6.9	2.0
36[a]	6.54	5.33	5.63	2.49	2.59	4.68	9.5	2.8	3.0	3.6	15.2	7.6	1.5
4[b]	6.44	5.38	5.57	2.38	2.62	4.57	9.6	3.2	2.8	3.8	15.0	6.8	2.2
6[c]	6.50	5.37	5.54	2.38	2.67	4.61	9.5	3.1	2.9	3.7	15.0	6.6	2.1

[a] Spectrum recorded at 360 MHz. [b] Data from ref. 2 (200 MHz). [c] Data from ref. 1 (originally assigned structure **2**), field strength not specified.

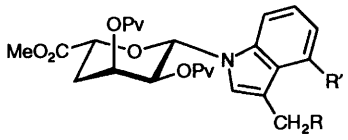
sodium salt procedure led to the desired reaction; again an isomer of compound **35** was also produced, but in this series the product **35** was crystalline and the epimer **35β** was easily removed by crystallisation. The ^{1}H NMR data for the sugar ring of compound **35** are given in Table 1, and again the structural and conformational similarity with the diacetates of neosidomycin and SF-2140 is apparent.

Treatment of compound **35** with lithium hydroxide in methanol[22] followed by diazomethane led to SF-2140 **3** in 76% yield. We were unable to obtain our synthetic material in crystalline form, as reported,[2] but on acetylation crystalline di-*O*-acetyl derivative **4** was obtained, m.p. 104 °C. This value represents a discrepancy with the reported value[2] of 114 °C; however, when we acetylated a sample of natural SF 2140 (kindly provided by Dr. T. Mayama, Meiji Seika, Kaisha Ltd., Yokohama), we obtained a diacetate of m.p. 105 °C, which showed no depression on admixture with synthetic material. The ^{1}H NMR spectra of both samples of diacetates **4** were completely superposable.

For the synthesis of neosidomycin, it was necessary to convert the nitrile group of compound **34** into an amide, and after some experimentation it was found that this was best accomplished by the use of hydrated nickel acetate in glacial acetic acid at reflux, a method we have employed earlier in another situation.[23] Since the sample of nitrile **34** used contained small amounts of the β-anomer (ratio **34**:**34β**, 6:1) the product **36** (67%) also contained its β-anomer, which again proved inseparable by chromatography. The ^{1}H NMR data for the amide **36** are also included in Table 1. Treatment of anomers **36** + **36β** with methanolic lithium hydroxide, followed by diazomethane, gave neosidomycin **5**, the ^{1}H NMR spectrum of which was in agreement with that reported for the natural material,[1] but again the minor β-isomer was also present. Acetylation of the synthetic product **5** gave the 2′,3′-di-*O*-acetyl derivative **6**, still inseparable from the minor β-anomer. The ^{1}H NMR spectrum of synthetic product **6** was in very close agreement with that reported for material prepared by acetylation of the natural product (see Table 1).

In conclusion, we make some comments concerning the identity of the minor isomers from the sodium salt glycosylations, which we have described above as being the β-anomers. Although the formation of such products would not be unexpected under these reaction conditions,[18] we were surprised to find that these minor products all showed large values for both the coupling constants $J_{1',2'}$ and $J_{4'ax,5'}$ ($J_{1',2'}$ 9.2–9.5, $J_{4'ax,5'}$ 10.8–12.0 Hz for **34β**, **36β** and **6β**). Smaller values for $J_{1',2'}$ would be expected for a β-isomer in a chair conformation. We therefore considered the possibility that these minor products might be epimers at C-5′ (see structure **37**), this epimerisation being induced by the basic reaction conditions of the sodium salt couplings. Large values for the couplings $J_{1',2'}$ and $J_{4'ax,5'}$ would be predictable for compounds of type **37** in a $^1C_4$ (L) conformation.

This explanation seems unlikely, however, on the basis of



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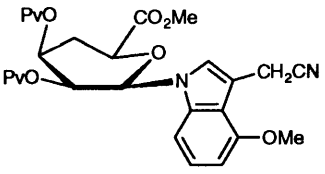

35β

NMR experiments. When a sample of compound **35** (pure α-anomer) was dissolved in a solution of $NaOCD_3$ in CD_3OD, and a series of spectra were recorded, the following changes were observed. The couplings $J_{4',5'}$ disappeared from the signals for both protons at C-4', both signals collapsing to double doublets; the signals for 5'-H, the methoxy group of the uronic ester, and the methylene protons α- to the nitrile were all lost. However, no signals for the minor isomer appeared. Thus, exchange of 5'-H is occurring, but without any epimerisation, a result which implies that the α-nucleosides, in their twist-boat conformations, are more stable than their 5'-epimers (in conformation **37** or any alternative). In a complementary experiment, a sample of compound **35** enriched in the minor isomer **35β** was treated in the same way. The signals due to anomer **35** changed in the way described above. The signals for the sugar ring of the minor isomer decreased in intensity, and extra signals appeared, although it was not possible to analyse these in detail. However, it was clear that the minor isomer was not being transformed into compound **35**.

We thus must conclude that the minor isomers are indeed β-anomers, and that the large values observed for $J_{1',2'}$ must reflect a conformation other than a $^4C_1$ chair, most likely the twist-boat ($^OS_2$) indicated for structure **35β**, where the large $J_{1',2'}$ coupling is due to eclipsing of the two hydrogen atoms.

Experimental

IR spectra were recorded using Perkin-Elmer 257 or 157 G instruments, and mass spectrometry was carried out using VG updated MS9 and VG 2AB-E spectrometers. NMR spectra were recorded on Bruker WP 200 SY and WH 360 spectrometers, with $CDCl_3$ as solvent unless otherwise stated. *J*-Values are given in Hz. Specific rotations were measured using a Bendix-NPL 143D automatic polarimeter (path length 1 cm).

Column chromatography was carried out using Kieselgel H type 60 (Merck); an external pressure was applied to the top of columns. TLC was carried out using precoated aluminium-backed plates (Merck, Kieselgel HF_{254} type 60). Light petroleum refers to material of boiling range 40–60 °C. Organic extracts were dried over sodium sulfate.

Methyl 4-*Deoxy*-α-D-lyxo-*hexopyranoside* **9**.—A solution of the isopropylidene compound **8**[4] (0.5 g) in acetic acid–water (4:1; 20 cm^3) was heated under reflux for 20 min. Evaporation gave a light-coloured oil, which was preadsorbed onto silica and applied to a silica column, which was eluted with diethyl ether–methanol (20:1) to give triol **9**[2] (0.4 g, 98%) as an oil, $[\alpha]_D$ +76 (*c* 0.5, water) {lit.,[2] $[\alpha]_D$ +86 (*c* 1.0, water)}; δ_H(200 MHz; CD_3OD) 1.6–1.8 (2 H, m, 4-H_2), 3.36 (3 H, s, OMe), 3.55 (2 H, m, 6-H_2), 3.64 (1 H, dd, 2-H), 3.75 (1 H, m, 5-H), 3.90 (1 H, m, 3-H) and 4.68 (1 H, br s, 1-H).

Methyl 2,3,6-*Tri*-O-*acetyl*-4-*deoxy*-α-D-lyxo-*hexopyranoside* **10**.—A solution of triol **9** (0.3 g) in pyridine (2 cm^3) and acetic anhydride (1 cm^3) was kept for 14 h. The residue, obtained after evaporation, was chromatographed on silica with light petroleum–diethyl ether (3:1) as eluent to give the tri-*O*-acetyl compound **10**[2] (0.47 g, 92%) as an oil; δ_H(360 MHz) 1.75 (1 H, q, J ~ 11, 4-H^{ax}), 1.79 (1 H, ddd, J_{gem} 12.0, $J_{4eq,3}$ 5.5, $J_{4eq,5}$ 3.4, 4-H^{eq}), 1.99, 2.08 and 2.11 (each 3 H, s, OAc), 3.36 (3 H, s, OMe), 4.05 (1 H, m, 5-H), 4.11 (1 H, dd, J 11.6 and 3.7, 6-H^a), 4.16 (1 H, dd, J 11.6 and 6.5, 6-H^b), 4.71 (1 H, d, J 1.8, 1-H), 5.06 (1 H, dd, $J_{2,3}$ 3.2, 2-H) and 5.24 (1 H, ddd, $J_{3,4ax}$ 11.2, $J_{3,4eq}$ 5.7, $J_{3,2}$ 3.2, 3-H); *m/z* 304 (M^+).

1,2,3-*Tri*-O-*acetyl*-6-O-*benzoyl*-4-*deoxy*-α-D-lyxo-*hexopyranose* **11**.—A solution of the acetal **7**[4] (2.57 g) in glacial acetic acid (45 cm^3)–acetic anhydride (15 cm^3) was cooled to 0 °C. Acetic acid (4.6 cm^3) and conc. sulfuric acid (0.4 cm^3) were added in one batch. The reaction mixture was stirred at room temperature for 18 h, poured into a mixture of aq. sodium hydrogen carbonate and ice, stirred for 30 min, and extracted with diethyl ether. The extracts were dried, filtered, and evaporated to give an oil, which was chromatographed on silica, with light petroleum–diethyl ether (3:1) as eluent, to give the *tri*-O-*acetyl derivative* (1.83 g, 62%) as crystals, m.p. 82–83 °C; $[\alpha]_D$ +45 (*c* 0.8, MeOH); δ_H(200 MHz) 2.03, 2.12 and 2.14 (each 3 H, s, OAc), 2.0–2.2 (2 H, m, 4-H_2), 4.25 (1 H, m, 5-H), 4.38 (2 H, m, 6-H_2), 5.10 (1 H, m, 2-H), 5.32 (1 H, ddd, $J_{3,4ax}$ 11.8, $J_{3,4eq}$ 5.4, $J_{3,2}$ 3.2, 3-H), 6.12 (1 H, d, $J_{1,2}$ 2.0, 1-H), 7.35–7.6 (3 H, m, Ph) and 8.0–8.1 (2 H, m, Ph); *m/z* 335 (M − OAc)$^+$ (Found: C, 58.0; H, 5.5. $C_{19}H_{22}O_9$ requires C, 57.8; H, 5.5%).

Methyl (*Methyl* 4-*Deoxy*-2,3-O-*isopropylidene*-α-D-lyxo-*hexopyranosid*)*uronate* **12**.—The alcohol **8**[4] (5.8 g), tetrachloromethane (53 cm^3), acetonitrile (53 cm^3), water (80 cm^3) and sodium periodate (22.8 g) were stirred at room temperature. To this biphasic mixture was added ruthenium trichloride hydrate (0.156 g, 2.2 mol-%) and the mixture was stirred for 1 h, by which time the colour of the mixture had changed from brown to pale yellow and TLC analysis (developer: diethyl ether) showed only baseline material. The reaction mixture was extracted with dichloromethane and the combined organic extracts were passed through a Celite filter, prior to evaporation. The resultant black oil was dissolved in diethyl ether and added to ethereal diazomethane. After 1 h, the excess of diazomethane was destroyed with glacial acetic acid and the residue, obtained after evaporation, was chromatographed on silica gel, with light petroleum–diethyl ether (1:1) as eluent, to give the *uronic ester* **12** (4.8 g, 72%) as an oil, $[\alpha]_D$ +40.4 (*c* 0.96, MeOH); δ_H(360 MHz) 1.30 and 1.45 (each 3 H, s, CMe_2), 2.11 (1 H, dt, J_{gem} 14.0, $J_{4ax,3}$ ~ $J_{4ax,5}$ ~ 7, 4-H^{ax}), 2.29 (1 H, dt, J_{gem} 13.9, $J_{4eq,3}$ ~ $J_{4eq,5}$ ~ 5, 4-H^{eq}), 3.42 (3 H, s, OMe), 3.78 (3 H, s, CO_2Me), 3.96 (1 H, dd, $J_{2,3}$ 6.2, $J_{2,1}$ 1.4, 2-H), 4.30 (1 H, dd, $J_{5,4ax}$ 7.5, $J_{5,4eq}$ 5.0, 5-H), 4.37 (1 H, m, 3-H) and 4.92 (1 H, d, J 1.3, 1-H); *m/z* 231 (M − Me)$^+$, 215 (M − OMe)$^+$, 187 (M − CO_2Me)$^+$ and 171 (231 − AcOH)$^+$ (Found: C, 53.6; H, 7.3. $C_{11}H_{18}O_6$ requires C, 53.6; H, 7.6%).

Methyl 1,2,3-*Tri*-O-*acetyl*-4-*deoxy*-α-D-lyxo-*hexopyranuronate* **14**.—A stirred solution of the uronic ester **12** (1.97 g) in glacial acetic acid (45.7 cm^3)–acetic anhydride (15 cm^3) was cooled to 0 °C, whereupon glacial acetic acid (4.6 cm^3) and conc. sulfuric acid (0.44 cm^3) were added in one batch. After 18 h

the reaction mixture was poured into a mixture of aq. sodium hydrogen carbonate and ice, stirred for 30 min, and extracted with diethyl ether. The dried extracts were filtered and evaporated to give a yellow oil, which was chromatographed on silica, with light petroleum–diethyl ether (3:1) as eluent, to give the *tri*-O-*acetyl compound* **14** (0.89 g, 35%) as an oil, $[\alpha]_D$ 0 (*c* 0.31, MeOH); δ_H(200 MHz) 2.05, 2.12 and 2.13 (each 3 H, s, OAc), 2.1–2.2 (2 H, m, 4-H_2), 3.81 (3 H, s, CO_2Me), 4.52 (1 H, dd, $J_{5,4ax}$ 10.7, $J_{5,4eq}$ 4.1, 5-H), 5.08 (1 H, m, 2-H), 5.30 (1 H, ddd, $J_{3,4ax}$ 10.8, $J_{3,4eq}$ 5.7, $J_{3,2}$ 3.2, 3-H) and 6.22 (1 H, d, $J_{1,2}$ 2.3, 1-H); δ_C(50 MHz) 20.76 (3 × CO*Me*), 28.42 (C-4), 52.52 (CO_2*Me*), 65.81, 66.43 and 69.32 (C-2, -3 and -5), 91.28 (C-1), 167.91 (*C*O_2Me) and 169.55, 169.71 and 169.77 (3 × *C*OMe) [Found: $(M - OAc)^+$, 259.082. $C_{11}H_{15}O_7$ requires *m/z*, 259.082. Found: C, 48.8; H, 5.8. $C_{13}H_{18}O_9$ requires C, 49.0; H, 5.6%].

2,3-*Di*-O-*acetyl*-6-O-*benzoyl*-4-*deoxy*-α-D-lyxo-*hexopyranosyl Bromide* **13**.—To a solution of the triacetyl derivative **11** (0.21 g) in 1,2-dichloroethane (0.6 cm^3) was added hydrogen bromide–acetic acid solution (30%; 0.5 cm^3), and the reaction mixture was kept for 2 h. Toluene (10 cm^3) was added to the reaction mixture, which was then evaporated. This procedure was repeated and gave the bromide **13** (0.22 g, ~100%) as a brown oil. TLC showed the bromide to decompose rapidly and, as a result, only NMR data were recorded for the compound; δ_H(200 MHz) 2.0 and 2.10 (each 3 H, s, OAc), 1.95–2.21 (2 H, m, 4-H_2), 4.42 (3 H, m, 5-H and 6-H_2), 5.30 (1 H, m, 2-H), 5.69 (1 H, m, 3-H), 6.39 (1 H, d, *J* 1.5, 1-H), 7.35–7.64 (3 H, m, Ph) and 8.0–8.12 (2 H, d, Ph); δ_C(50 MHz) 20.51 (CO*Me*), 20.62 (CO*Me*), 27.53 (C-4), 64.94 (C-5), 65.03 (C-6), 69.80 and 70.86 (C-2 and -3), 85.03 (C-1), 128.21, 129.46 and 133.04 (Ph), 165.79 (*C*OPh), 169.32 (*C*OMe) and 169.43 (*C*OMe).

Methyl 2,3-*Di*-O-*acetyl*-1-*bromo*-1,4-*dideoxy*-α-D-lyxo-*hexopyranuronate* **15**.—The glycosyl acetate **14** (0.16 g) was treated as in the preparation of benzoate **13** (above) to give the bromide **15** (0.17 g, ~100%) as a yellow oil which decomposed on storage; δ_H(200 MHz) 2.05 and 2.12 (each 3 H, s, OAc), 2.1–2.2 (2 H, m, 4-H_2), 3.81 (3 H, s, CO_2Me), 4.65 (1 H, dd, *J* 12.2 and 2.6, 5-H), 5.25 (1 H, m, 2-H), 5.65 (1 H, ddd, $J_{3,4ax}$ 12.0, $J_{3,4eq}$ 4.9, $J_{3,2}$ 3.1, 3-H) and 6.40 (1 H, d, *J* 1.5, 1-H); δ_C(50 MHz) 20.34 (2 × OCO*Me*), 27.86 (C-4), 52.38 (OMe), 64.57 (C-5), 69.29 and 70.55 (C-2 and -3), 83.73 (C-1), 168.34 (*C*O_2Me) and 169.36 (2 × *C*OMe).

Reaction of Compound **13** *with* 3-(*Cyanomethyl*)*indole* **20**.—3-(Cyanomethyl)indole **20** (0.085 g) was heated under reflux in dry benzene (30 cm^3) under nitrogen, in the presence of silver(I) oxide (0.13 g) and 4 Å molecular sieves. After 30 min, the reflux apparatus was rearranged and benzene (20 cm^3) was distilled over, in order to azeotrope any water present. The apparatus was then returned to its original reflux position and the bromide **13** [prepared from the triacetyl derivative **11** (0.21 g)], dissolved in dry benzene (4 cm^3), was added dropwise over a period of 20 min. The reaction mixture was heated under reflux for a further 4 h and monitored by TLC [light petroleum–diethyl ether (4:1)]. Analysis showed the presence of unchanged starting indole, a UV-active product at lower R_f, and a number of lower intensity spots which were thought to be decomposition products from the bromide. The reaction mixture was cooled and filtered. The insoluble material was washed with two portions of dry benzene. The filtrate and washings were combined and evaporated. The resultant brown syrup was chromatographed on silica gel, with light petroleum–diethyl ether (2:1) as eluent, to give the unchanged indole **20** followed by the UV-active product which, on evaporation of the collected fractions, gave compound **19** as a yellow, amorphous foam (0.08 g, 31%); δ_H(200 MHz) 1.98 and 2.15 (each 3 H, s, OAc), 2.0–2.2 (2 H, m, 4′-H_2), 3.79 (2 H, d, *J* 0.9, CH_2CN), 4.03 (1 H, m, 5′-H), 4.33 (1 H, apparent t, $J_{2',3'} \sim J_{2',1'} \sim$ 3.0, 2′-H), 4.47 (2 H, d, $J_{6',5'}$ 4.9, 6′-H_2), 5.20 (1 H, m, 3′-H), 5.54 (1 H, d, $J_{1',2'}$ 3.0, 1′-H) and 7.15–8.13 (10 H, m, ArH); *m/z* 490 (M^+), 335 $(M - C_{10}H_7N_2)^+$, 275 $(335 - AcOH)^+$ and 156 $(C_{10}H_8N_2)^+$.

Reaction of Compound **15** *with* 3-(*Cyanomethyl*)*indole* **20**.—3-(Cyanomethyl)indole **20** (0.1 g), silver oxide (0.16 g) and bromide **15** [prepared from triacetate **14** (0.22 g)] were treated as described above but with a reaction time of 6 h to give compound **21** (20 mg, 8%) as an amorphous foam; δ_H(200 MHz) 1.94 and 2.18 (each 3 H, s, OAc), 2.30 (2 H, m, 4′-H_2), 3.80 (3 H, s, CO_2Me), 3.85 (2 H, s, CH_2CN), 4.70 (1 H, dd, *J* 11.4 and 3.5, 5′-H), 5.05–5.2 (2 H, m, 2′- and 3′-H), 5.61 (1 H, d, *J* 4.0, 1′-H) and 7.15–7.75 (5 H, m, indole); *m/z* 414 (M^+) and 259 ($M^+ - C_{10}H_7N_2$).

4-*Methoxyindole* **22**.—To a stirred solution of 2-methoxy-6-nitrotoluene[24] (0.34 g) in *N*,*N*-dimethylformamide (DMF) (3.5 cm^3) were added DMF dimethyl acetal (0.3 cm^3) and pyrrolidine (0.2 cm^3). The reaction mixture was stirred under nitrogen at 125°C for 3 h, then was evaporated at 70–80 °C to give the intermediate β-aminostyrene as a dark red, oily residue. This was taken up in a minimum volume of acetone and added to a mixture of 20% aq. titanium(III) chloride (9.3 cm^3) and ammonium acetate buffer (4 mol dm^{-3}; 18 cm^3). The mixture was shaken for 10 min, then was extracted with several portions of diethyl ether. The combined ether layers were dried, filtered, and evaporated to give a dark green syrup, which was chromatographed on silica gel, with light petroleum–diethyl ether (3:1) as eluent, to give 4-methoxyindole **22** (0.18 g, 61%) as a pale yellow, amorphous solid, m.p. 68 °C (lit.,[25] 69.5 °C); δ_H(200 MHz) 4.05 (3 H, s, Me), 6.5–6.75 (2 H, m, ArH), 7.0–7.24 (3 H, m, ArH) and 8.1 (1 H, br s, exchangeable, NH).

Reaction of Compound **13** *with* 3-*Cyanomethyl*-4-*methoxyindole* **23**.—The indole **23** (0.07 g), silver oxide (0.09 g) and bromide **13** [from compound **11** (0.28 g)] were treated as described in the earlier similar reactions above, but with a reaction time of 20 h, and with toluene–diethyl ether (9:1) as chromatographic eluent, to give compound **24** (0.03 g, 18%) as a glass; δ_H(200 MHz) 1.97 and 2.16 (each 3 H, s, OAc), 2.0–2.2 (2 H, m, 4-H_2), 3.92 (3 H, s, OMe), 4.02 (2 H, d, *J* 0.8, CH_2CN), 4.04 (1 H, m, 5′-H), 4.33 (1 H, t, *J* ~ 3.0, 2′-H), 4.49 (2 H, d, *J* 4.8, 6′-H_2), 5.20 (1 H, m, 3′-H), 5.53 (1 H, d, *J* 3.0, 1′-H), 6.52 (1 H, m, 5-H) and 7.15–8.15 (8 H, m, ArH).

Methyl 6-O-*Benzoyl*-4-*deoxy*-α-D-lyxo-*hexopyranoside* **25**.—The acetal **7**[4] (3 g) was stirred in 90% TFA (60 cm^3) for 10 min, by which time all the starting material had undergone reaction as monitored by TLC (diethyl ether). The reaction mixture was evaporated to give a pale yellow oil, which was taken up in dichloromethane and washed with aq. sodium hydrogen carbonate. The organic layer was dried and evaporated, and the residue was chromatographed on silica with diethyl ether as eluent, to afford the *diol* **25** (1.4 g, 54%) as an amorphous solid, m.p. 75–80 °C; $[\alpha]_D$ +65.7 (*c* 1.14, MeOH); δ_H(200 MHz) 1.75–1.95 (2 H, m, 4-H_2), 2.05 (2 H, br s, exchangeable, OH), 3.38 (3 H, s, OMe), 3.79 (1 H, m, 2-H), 4.08 (2 H, m, 3- and 5-H), 4.39 (2 H, m, 6-H_2), 4.81 (1 H, br s, 1-H), 7.32–7.62 (3 H, m, Ph) and 8.01–8.15 (2 H, dd, Ph) [Found: $(M - OMe)^+$, 251.089. $C_{13}H_{15}O_5$ requires *m/z*, 251.092. Found: C, 59.1; H, 6.5. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4%].

Methyl 6-O-*Benzoyl*-4-*deoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranoside* **26**.—To a solution of diol **25** (1.1 g) in dry pyridine (5 cm^3) was added freshly distilled pivaloyl chloride

($3\ cm^3$) and the reaction mixture was heated at 50 °C for 24 h. A few drops of water were added, while homogeneity of the solution was maintained, and the mixture was stirred for 1 h. After this time, the mixture was taken up in chloroform and washed successively with aq. sodium hydrogen carbonate, dil. hydrochloric acid (1 mol dm^{-3}) and water. The dried organic layer was evaporated to give a yellow oil, which was chromatographed on silica with light petroleum–diethyl ether (3:1) as eluent. Crystallisation from pentane gave the *dipivaloate* **26** (1.3 g, 76%), m.p. 72–73 °C; $[\alpha]_D$ +29.1 (*c* 1.03, MeOH); δ_H(200 MHz) 1.16 and 1.25 (each 9 H, s, OPv), 1.9 (2 H, m, 4-H_2), 3.41 (3 H, s, OMe), 4.23 (1 H, m, 5-H), 4.39 (2 H, m, 6-H_2), 4.73 (1 H, d, $J_{1,2}$ 1.8, 1-H), 5.06 (1 H, m, 2-H), 5.28 (1 H, ddd, $J_{3,4ax}$ 11.4, $J_{3,4eq}$ 5.6, $J_{3,2}$ 3.0, 3-H), 7.35–7.63 (3 H, m, Ph) and 8.0–8.15 (2 H, m, Ph); *m/z* 419 $(M - OMe)^+$, 348 $(M - PvOH)^+$, 328 $(M - BzOH)^+$ and 315 $(M - CH_2OBz)^+$; *m/z* (ammonia CI) 451 $(M + H)^+$ and 468 $(M + NH_4)^+$ (Found: C, 64.1; H, 7.7. $C_{24}H_{34}O_8$ requires C, 64.0; H, 7.6%).

1-O-*Acetyl*-6-O-*benzoyl*-4-*deoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranose* **27**.—To a stirred solution of the dipivaloyl derivative **26** (1.3 g) in glacial acetic acid (18 cm^3)–acetic anhydride (3 cm^3) was added at 0 °C a mixture of glacial acetic acid (2 cm^3) and conc. sulfuric acid (0.2 cm^3). The reaction mixture was stirred at room temperature for 24 h, then was poured into an ice–water mixture and stirred for 10 min. The mixture was extracted with diethyl ether and the combined extracts were washed successively with water and aq. sodium hydrogen carbonate. The dried organic layer was evaporated and the residue was chromatographed on silica, with light petroleum–diethyl ether (3:1) as eluent, to give the *glycosyl acetate* **27** (1.2 g, 87%) as a syrup, $[\alpha]_D$ +15.6 (*c* 0.64, MeOH); δ_H(200 MHz) 1.15 and 1.25 (each 9 H, s, OPv), 2.10 (2 H, m, 4-H_2), 2.14 (3 H, s, OAc), 4.29 (1 H, m, 5-H), 4.40 (2 H, m, 6-H_2), 5.09 (1 H, m, 2-H), 5.32 (1 H, ddd, $J_{3,4ax}$ 11.8, $J_{3,4eq}$ 5.0, $J_{3,2}$ 3.0, 3-H), 6.08 (1 H, d, $J_{1,2}$ 2.0, 1-H), 7.35–7.64 (3 H, m, Ph) and 7.98–8.0 (2 H, dd, Ph); δ_C 20.83 (CO*Me*), 27.02 and 27.11 (CMe_3), 27.96 (C-4), 38.71 and 38.93 (CMe_3), 66.00 (C-6), 66.27, 66.30 and 68.60 (C-2, -3 and -5), 91.76 (C-1), 128.36, 129.70, 129.81 and 133.14 (Ph), 166.19 (Ph*C*O), 168.34 (Me*C*O) and 176.78 and 177.45 (Bu^t*C*O) [Found: $(M^+ - OAc)$, 419.205. $C_{23}H_{31}O_7$ requires *m/z*, 419.206. Found: C, 63.0; H, 7.6. $C_{25}H_{34}O_9$ requires C, 62.8; H, 7.1%].

6-O-*Benzoyl*-4-*deoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranosyl Bromide* **28**.—To a solution of glycosyl acetate **27** (0.49 g) in 1,2-dichloroethane (1.2 cm^3) was added hydrogen bromide–acetic acid solution (30%; 1.0 cm^3) and the reaction mixture was stirred at room temperature for 1 h. After this time, the mixture was evaporated twice with dry toluene (2 × 10 cm^3) to leave bromide **28** (0.51 g, ~100%) as a yellow oil. TLC analysis showed the bromide to decompose rapidly and, as a result, only NMR data were obtained for this compound; δ_H(200 MHz) 1.16 and 1.24 (each 9 H, s, OPv), 2.10 (2 H, m, 4-H_2), 4.44 (3 H, m, 5-H and 6-H_2), 5.27 (1 H, m, 2-H), 5.69 (1 H, ddd, $J_{3,4ax}$ 11.0, $J_{3,4eq}$ 5.8, $J_{3,2}$ 3.0, 3-H), 6.35 (1 H, d, $J_{1,2}$ 1.6, 1-H), 7.36–7.65 (3 H, m, Ph) and 8.0–8.12 (2 H, dd, Ph); δ_C(50 MHz) 27.03 (2 × $COCMe_3$), 27.91 (C-4), 38.68 and 38.93 ($COCMe_3$), 65.35 (C-5), 65.44 (C-6), 69.83 and 71.02 (C-2 and -3), 85.37 (C-1), 128.38, 129.71 and 133.20 (Ph), 166.06 (*C*OPh) and 176.68 and 177.15 ($COCMe_3$).

1-(6-O-*Benzoyl*-4-*deoxy*-2,3-*di*-O-*pivaloyl*-α-D-*hexopyranosyl*)-3-(*cyanomethyl*)*indole* **29**.—3-(Cyanomethyl)indole **20** (0.11 g) was heated under reflux in dry benzene (40 cm^3) under nitrogen, in the presence of silver(I) oxide (0.16 g) and 4 Å molecular sieves. After 30 min, the reflux apparatus was rearranged and benzene (30 cm^3) was distilled over, in order to azeotrope any water present. The apparatus was returned to its original reflux position. The bromide **28** [prepared from compound **27** (0.49 g)], dissolved in dry benzene (4 cm^3), was added dropwise over a period of 20 min and the reaction mixture was heated under reflux for 3 h. The reaction was monitored by TLC [eluent: light petroleum–diethyl ether (3:2)] and showed the presence of the unchanged indole **20**, a UV-active product at lower R_f, and a number of lower intensity spots, which were thought to be decomposition products from the bromide. The reaction mixture was cooled and filtered. The insoluble material was washed with two portions of dry benzene, and the combined filtrate and washings were evaporated. The resultant brown syrup was chromatographed on silica gel, with light petroleum–diethyl ether (2:1) as eluent to give the unchanged indole **20** followed by the UV-active N-*glycosylindole* **29** (0.05 g, 12%) as an amorphous solid, $[\alpha]_D$ +7.7 (*c* 1.2, MeOH); δ_H(360 MHz) 1.12 and 1.27 (each 9 H, s, OPv), 2.06 (1 H, dt, J_{gem} 13.2, $J_{4'eq,3'} \sim J_{4'eq,5'} \sim$ 4.1, 4'-H^{eq}), 2.18 (1 H, dt, $J_{4'ax,3'} \sim J_{4'ax,5'} \sim$ 9.0, 4'-H^{ax}), 3.81 (2 H, s, CH_2CN), 4.11 (1 H, m, 5'-H), 4.30 (1 H, dd, *J* 11.9 and 3.4, 6'-H^a), 4.76 (1 H, dd, *J* 11.9 and 7.6, 6'-H^b), 5.56 (1 H, ddd, $J_{3',2'}$ 2.9, 3'-H), 5.74 (1 H, t, $J_{2',3'} \sim J_{2',1'} \sim$ 3.5, 2'-H), 6.00 (1 H, d, $J_{1',2'}$ 4.1, 1'-H) and 7.1–8.0 (10 H, m, ArH); *m/z* 575 $(M + 1)^+$, 574 $(M)^+$, 419 $(M - C_{10}H_7N_2)^+$ and 317 $(419 - PvOH)^+$ (Found: M^+, 574.264. $C_{33}H_{38}N_2O_7$ requires M, 574.267).

Methyl (*Methyl* 4-*Deoxy*-α-D-lyxo-*hexopyranosid*)*uronate* **30**.—The uronic ester **12** (0.44 g) was stirred in 90% TFA (8 cm^3) for 15 min at room temperature, by which time TLC (diethyl ether) showed that the reaction was complete. The reaction mixture was evaporated. The resultant syrup was dissolved in ethyl acetate, and the solution was dried, filtered and evaporated to give a pale brown oil, which was chromatographed on silica, with ethyl acetate as eluent, to give the *diol* **30** (0.33 g, 89%) as an amorphous, hygroscopic solid, $[\alpha]_D$ +48.2 (*c* 0.83, MeOH); δ_H(200 MHz) 1.89–2.02 (2 H, m, 4-H_2), 3.32 (3 H, s, OMe), 3.68 (1 H, m, 2-H), 3.71 (3 H, s, CO_2Me), 3.92 (1 H, m, 3-H), 4.28 (2 H, br s, exchangeable, 2- and 3-OH), 4.35 (1 H, dd, $J_{5,4ax}$ 11.3, $J_{5,4eq}$ 3.2, 5-H) and 4.80 (1 H, d, $J_{1,2}$ 2.1, 1-H); *m/z* 205 $(M - H)^+$, 188 $(M - H_2O)^+$, 175 $(M - OMe)^+$, 147 $(M - CO_2Me)^+$ and 129 $(147 - H_2O)^+$ [Found: $(M - OMe)^+$, 175.063. $C_7H_{11}O_5$ requires *m/z*, 175.0611].

Methyl (*Methyl* 4-*Deoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranosid*)*uronate* **31**.—To a stirred solution of diol **30** (2.4 g) in dry pyridine (13 cm^3) was added freshly distilled pivaloyl chloride (7.9 cm^3) and the reaction mixture was stirred for 26 h. A few drops of water were added, while homogeniety of the solution was maintained, and the mixture was stirred for 3 h before being extracted with chloroform, and the extracts were washed successively with aq. sodium hydrogen carbonate, dil. hydrochloric acid (1 mol dm^{-3}) and water. The organic layer was dried, filtered, and evaporated to give a yellow oil, which was chromatographed on silica, with light petroleum–ether (3:1) as eluent, to give the *di-O-pivaloyl derivative* **31** (3.5 g, 81%) as a syrup, $[\alpha]_D$ +33.7 (*c* 1.75, MeOH); δ_H(360 MHz) 1.13 and 1.23 (each 9 H, s, OPv), 2.00 (1 H, q, *J* ~ 12.0, 4-H^{ax}), 2.17 (1 H, m, 4-H^{eq}), 3.41 (3 H, s, OMe), 3.78 (3 H, s, CO_2Me), 4.45 (1 H, dd, $J_{5,4ax}$ 12.0, $J_{5,4eq}$ 2.8, 5-H), 4.82 (1 H, d, $J_{1,2}$ 2.0, 1-H), 5.02 (1 H, m, 2-H) and 5.26 (1 H, ddd, $J_{3,4ax}$ 11.7, $J_{3,4eq}$ 4.8, $J_{3,2}$ 3.2, 3-H); *m/z* 375 $(M + 1)^+$, 343 $(M - OMe)^+$, 315 $(M - CO_2Me)^+$, 241 $(343 - PvOH)^+$ and 213 $(315 - PvOH)^+$ [Found: $(M - OMe)^+$, 343.174. $C_{17}H_{27}O_7$ requires *m/z*, 343.175. Found: C, 58.0; H, 7.8. $C_{18}H_{30}O_8$ requires C, 57.7; H, 8.0%].

Methyl 1-O-*Acetyl*-4-*deoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranuronate* **32**.—The methyl glycoside **31** (3.5 g) was stirred

with glacial acetic acid (62 cm^3)–acetic anhydride (10.4 cm^3). The mixture was cooled to 0 °C, when a mixture of glacial acetic acid (5.3 cm^3) and conc. sulfuric acid (0.5 cm^3) was added. After 24 h at room temperature, the reaction mixture was poured onto ice, and extracted with diethyl ether. The extracts were washed successively with water and aq. sodium hydrogen carbonate, dried, filtered and evaporated. The resultant syrup was chromatographed on silica with light petroleum–diethyl ether (4:1) as eluent. Crystallization from pentane gave the *glycosyl acetate* **32** (3.4 g, 89%), m.p. 104–105 °C; $[\alpha]_D$ +37.8 (*c* 0.18, MeOH); δ_H(200 MHz) 1.16 and 1.24 (each 9 H, s, OPv), 2.13 (3 H, s, OAc), 2.18 (2 H, m, 4-H_2), 3.79 (3 H, s, CO_2Me), 4.54 (1 H, dd, $J_{5,4ax}$ 11.4, $J_{5,4eq}$ 3.4, 5-H), 5.08 (1 H, m, 2-H), 5.32 (1 H, ddd, $J_{3,4ax}$ 11.3, $J_{3,4eq}$ 4.9, $J_{3,2}$ 3.2, 3-H) and 6.19 (1 H, d, $J_{1,2}$ 2.5, 1-H) [Found: $(M - OAc)^+$, 343.173. $C_{17}H_{27}O_7$ requires *m/z*, 343.175. Found: C, 56.4; H, 7.2. $C_{19}H_{30}O_9$ requires C, 56.7; H, 7.4%].

Methyl 1-*Chloro*-1,4-*dideoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranuronate* **33**.—To a stirred solution of acetate **32** (1.6 g) in dry dichloromethane (32 cm^3) was added dichloromethyl methyl ether (3.6 cm^3) and a catalytic quantity of anhydrous zinc chloride. The reaction mixture was stirred under nitrogen for 5 h, filtered and evaporated to give a pink solid. The solid was chromatographed on silica, with light petroleum–diethyl ether (3:1) as eluent. Recrystallisation from diethyl ether–light petroleum gave the *glycosyl chloride* **33** (1.5 g, 96%), m.p. 137–138 °C; $[\alpha]_D$ +76.7 (*c* 1.09, MeOH); δ_H(360 MHz) 1.16 and 1.24 (each 9 H, s, OPv), 2.07 (1 H, q, *J* ~ 12.3, 4-H^{ax}), 2.33 (1 H, m, 4-H^{eq}), 3.80 (3 H, s, CO_2Me), 4.73 (1 H, dd, $J_{5,4ax}$ 12.3, $J_{5,4eq}$ 2.7, 5-H), 5.21 (1 H, m, 2-H), 5.55 (1 H, ddd, $J_{3,4ax}$ 11.9, $J_{3,4eq}$ 4.8, $J_{3,2}$ 3.1, 3-H) and 6.07 (1 H, d, $J_{1,2}$ 1.9, 1-H) [Found: $(M - Cl)^+$, 343.173. $C_{17}H_{27}O_7$ requires *m/z*, 343.175. Found: C, 53.6; H, 7.2. $C_{17}H_{27}ClO_7$ requires C, 53.9; H, 7.1%].

Methyl 1-[3-(*Cyanomethyl*)*indol*-1-*yl*]-1,4-*dideoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranuronate* **34**.—(*a*) 3-(Cyanomethyl)-indole **20** (0.42 g), glycosyl chloride **33** (0.5 g), freshly distilled 2,6-lutidine (0.46 cm^3), and molecular sieves (4 Å; ~1 g) were placed in dry dichloromethane (10 cm^3). The mixture, stirred under nitrogen and protected from light, was cooled to 0 °C, silver(I) triflate (0.75 g) was added, and the mixture was maintained at room temp. for 24 h, when TLC (diethyl ether) indicated the absence of starting chloride **33** and the presence of a new UV-active material in addition to residual substrate **20**. The mixture was filtered, and the filtrate was washed with aq. citric acid (1 mol dm^{-3}). The residue obtained after evaporation was chromatographed twice on silica, with light petroleum–diethyl ether (6:5) as eluent. The residue obtained on evaporation of product-containing fractions was subjected to preparative TLC [developer: light petroleum–diethyl ether (3:5)] to give the *nucleoside* **34** (0.24 g, 36%) as an amorphous foam, $[\alpha]_D$ +18.7 (*c* 0.48, MeOH); δ_H(360 MHz) 0.79 and 1.25 (each 9 H, s, C*Me*$_3$), 3.76 (2 H, d, *J* 1.0, CH_2CN), 3.86 (3 H, s, CO_2Me), 7.22 (1 H, t, 5/6-H), 7.24 (1 H, s, 2-H), 7.33 (1 H, t, 6/5-H), 7.54 and 7.69 (each 1 H, d, 4- and 7-H); other signals as in Table 1; *m/z* 498 (M^+) and 343 ($M^+ - C_{10}H_7N_2$) (Found: M^+, 498.240; C, 64.7; H, 6.8; N, 5.6%. $C_{27}H_{34}N_2O_7$ requires M, 498.237; C, 65.1; H, 6.8; N, 5.6%).

(*b*) To a stirred solution of 3-(cyanomethyl)indole **20** (0.234 g) in dry acetonitrile (3 cm^3) was added sodium hydride (50% dispersion in mineral oil; 0.076 g) at room temperature under nitrogen. The mixture was stirred for 30 min and was then cooled to 0 °C. A solution of the glycosyl chloride **33** (0.6 g) in dry acetonitrile (3 cm^3) was added dropwise to the reaction mixture, which was maintained at 0 °C for 24 h. The solution was filtered and the filtrate was evaporated to give a brown oil, which was chromatographed on silica, with light petroleum–diethyl ether (2:1) as eluent, to give the UV-active product (0.32 g, 44%) as an amorphous foam. Analysis of this product by ^1H NMR spectroscopy showed it to be an isomeric mixture (ratio 6:1), the major component of which was identical with the product **34** prepared by method (*a*). For the β-isomer, δ_H(200 MHz) 0.75 and 1.32 (each 9 H, s, OPv), 2.31 (2 H, m, 4′-H_2), 3.79 (5 H, 2 × s, CO_2Me and CH_2CN), 4.71 (1 H, dd, $J_{5',4'ax}$ 10.8, $J_{5',4eq}$ 4.7, 5′-H), 5.29 (1 H, dd, $J_{1',2'}$ 9.5, $J_{2',3'}$ 2.9, 2′-H), 5.65 (1 H, m, 3′-H), 5.94 (1 H, d, $J_{1',2'}$ 9.5, 1′-H) and 7.15–7.75 (5 H, m, indole).

Methyl 1-(3-*Cyanomethyl*-4-*methoxyindol*-1-*yl*)-1,4-*dideoxy*-2,3-*di*-O-*pivaloyl*-α-D-lyxo-*hexopyranuronate* **35**.—To a stirred solution of 3-cyanomethyl-4-methoxyindole **23** (0.28 g) in dry acetonitrile (3 cm^3) was added, under nitrogen, sodium hydride (50% dispersion in mineral oil; 0.072 g). The mixture was stirred for 20 min, then was cooled in an ice-bath. A solution of the glycosyl chloride **33** (0.56 g) in dry acetonitrile (3 cm^3) was added dropwise to the reaction mixture. After 24 h at 0 °C, TLC analysis (diethyl ether) showed the presence of a UV-active product at lower R_f than that for substrate **23**. The mixture was filtered and the filtrate was evaporated to give an orange syrup, which was chromatographed on silica gel, with light petroleum–diethyl ether (2:1) as eluent, to give the UV-active product (0.40 g, 51%) as a solid. Traces of an isomeric impurity were removed by crystallisation from diethyl ether–light petroleum to give *nucleoside* **35** (0.24 g, 31%), m.p. 170 °C; $[\alpha]_D$ +20.9 (*c* 0.95, $CHCl_3$); δ_H(360 MHz) 0.82 and 1.24 (each 9 H, s, OPv), 3.85 (3 H, s, CO_2Me), 3.89 (3 H, s, OMe), 3.95 (2 H, AB of ABX, J_{gem} 15, $J_{AX/BX}$ 1.5, CH_2CN), 6.53 (1 H, d, *J* 7.3, 5-H), 7.05 (1 H, s, 2-H), 7.19 (1 H, t, *J* 8.0, 6-H), 7.27 (1 H, d, *J* 8.0, 7-H); other signals as in Table 1; *m/z* 528 (M^+), 343 ($M^+ - C_{11}H_9N_2O$), 241 (343 – PvOH)$^+$ and 186 $(C_{11}H_{10}N_2O)^+$ [Found: M^+, 528.244; C, 63.4; H, 6.8; N, 5.2%. $C_{28}H_{36}N_2O_8$ requires M, 528.247; C, 63.6; H, 6.8; N, 5.3%].

Methyl 1-(3-*Cyanomethyl*-4-*methoxyindol*-1-*yl*)-1,4-*dideoxy*-α-D-lyxo-*hexopyranuronate* (*SF-2140*) **3**.—To a vigorously stirred solution of the glycosylindole **35** (0.188 g) in dry methanol (3 cm^3) was added lithium hydroxide monohydrate (0.06 g). After 6 days, Amberlite resin (IRC 50, H^+-form) was added and the mixture was stirred for 1 h prior to filtration. The filtrate was added to ethereal diazomethane and the solution was kept for 1 h. The excess of diazomethane was destroyed with glacial acetic acid and the solution was evaporated to give a semi-solid mass, which was chromatographed on silica, with light petroleum–ethyl acetate (1:1) as eluent, to give SF-2140 **3** (0.097 g, 76%) as a glass; δ_H[200 MHz; $(CD_3)_2CO$] 2.28 (1 H, ddd, *J* 14.3, $J_{4'ax,5'}$ 7.0, $J_{4'ax,3'}$ 2.4, 4′-H^{ax}), 2.50 (1 H, ddd, $J_{4'eq,3'}$ 1.3, 4′-H^{eq}), 3.75 (3 H, s, CO_2Me), 3.90 (3 H, s, OMe), 4.02 (2 H, s, CH_2CN), 4.12 (1 H, dd, $J_{2',1'}$ 9.4, $J_{2',3'}$ 2.8, 2′-H), 4.26 (1 H, m, 3′-H), 4.42 (1 H, br d, 5′-H), 6.29 (1 H, d, $J_{1',2'}$ 9.4, 1′-H), 6.57 (1 H, d, *J* 7.5, 5-H), 7.11 (1 H, t, *J* 8.0, 6-H), 7.36 (1 H, s, 2-H) and 7.42 (1 H, d, *J* 8.0, 7-H) (Found: M^+, 360.132. Calc. for $C_{18}H_{20}N_2O_6$: M, 360.132).

2′,3′-*Di*-O-*acetyl*-*SF-2140* **4**.—(*a*) The synthetic material **3** above (0.09 g) was dissolved in pyridine (3.3 cm^3)–acetic anhydride (0.9 cm^3). After 24 h the mixture was evaporated and the residue was chromatographed on silica, with light petroleum–diethyl ether (1:1) as eluent, to give a solid, which was crystallised from diethyl ether to give the di-*O*-acetyl compound **4** (0.059 g, 53%), m.p. 104 °C (lit.,[2] 114 °C); $[\alpha]_D$ +23.0 (*c* 0.56, MeOH); δ_H(360 MHz) 1.81 and 2.11 (each 3 H, s, OAc), 2.40 (1 H, ddd, J_{gem} 15.0, $J_{4'ax,5'}$ 7.1, $J_{4'ax,3'}$ 2.5, 4′-H^{ax}), 2.60 (1 H, ddd,

$J_{4'eq,3'}$ 4.1, $J_{4'eq,5'}$ 1.6, 4'-H^{eq}), 3.85 (3 H, s, CO_2Me), 3.90 (3 H, s, OMe), 3.98 (2 H, d, *J* 0.7, CH_2CN), 4.57 (1 H, dd, 5'-H), 5.39 (1 H, dd, $J_{2',1'}$ 9.5, $J_{2',3'}$ 2.9, 2'-H), 5.57 (1 H, m, 3'-H), 6.43 (1 H, d, *J* 9.5, 1'-H), 6.55 (1 H, d, *J* 7.5, 5-H), 7.11 (1 H, s, 2-H), 7.21 (1 H, t, *J* 8.1, 6-H) and 7.33 (1 H, d, *J* 8.1, 7-H) (Found: M^+, 444.153; C, 59.2; H, 5.5; N, 6.3%. Calc. for $C_{22}H_{24}N_2O_8$: M, 444.153; C, 59.4; H, 5.4; N, 6.3%).

(*b*) Natural SF-2140[2] (7 mg) was treated as above to give the di-*O*-acetyl compound **4** (5 mg, 58%), m.p. 105 °C (lit.,[2] 114 °C); mixed m.p. with product from (*a*), 104 °C; the ^1H NMR spectrum of this material (360 MHz) was identical with that of material produced in (*a*).

Methyl 1-[3-(*Carbamoylmethyl*)*indol*-1-*yl*]-1,4-*dideoxy*-2,3-*di*-O-pivaloyl-α-D-lyxo-*hexopyranuronate* **36** *and the* β-*Isomer*.—To a solution of the nitrile **34** and its β-anomer (ratio 6:1) [0.3 g, prepared by method (*b*)] in glacial acetic acid (30 cm^3) was added $Ni(OAc)_2 \cdot 4H_2O$ (0.96 g) and the mixture was heated under reflux for 24 h, by which time TLC analysis (ethyl acetate) showed complete reaction. The mixture was cooled and poured into chloroform, which was then washed with aq. sodium hydrogen carbonate. The organic layer was dried, filtered and evaporated to give an orange oil, which was chromatographed on silica with ethyl acetate as eluent to give a UV-active product (0.21 g, 67%) as an amorphous foam. Analysis by ^1H NMR spectroscopy showed that this product was an isomeric mixture (ratio 6:1), the major component of which was the *amide* **36**, δ_H(360 MHz) 0.70 and 1.27 (each 9 H, s, OPv), 3.69 (2 H, s, CH_2CONH_2), 3.87 (3 H, s, CO_2Me), 5.42 and 5.63 (each 1 H, br s, exchangeable, NH), 7.1–7.3 (3 H, m, indole-H), 7.5–7.6 (2 H, m, indole-H); for other signals see Table 1; signals for β-anomer, 0.63 and 1.36 (each 9 H, s, OPv), 2.32 (2 H, m, 4-H_2), 4.72 (1 H, dd, $J_{5',4'ax}$ 11.8, $J_{5',4'eq}$ 2.8, 5'-H), 5.26 (1 H, dd, $J_{2',1'}$ 9.2, $J_{2',3'}$ 2.9, 2'-H), 5.59 (1 H, m, 3'-H) and 5.92 (1 H, d, 1'-H); *m/z* 516 (M^+), 498 ($M^+ - H_2O$) and 343 ($M^+ - C_{10}H_9N_2O$) (Found: M^+, 516.243; C, 62.1; H, 7.0; N, 5.1%. $C_{27}H_{36}N_2O_8$ requires M, 516.246; C, 62.8; H, 7.0, N, 5.4%).

Methyl 1-[3-(*Carbamoylmethyl*)*indol*-1-*yl*]-1,4-*dideoxy*-α-D-lyxo-*hexopyranuronate* (*Neosidomycin*, **5**).—To a stirred solution of compound **36** and the β-anomer (ratio 6:1) (0.08 g) in dry methanol (1 cm^3) was added lithium hydroxide monohydrate (0.03 g) at room temperature. After 4 days, Amberlite resin (IRC 50, H^+) was added and the mixture was stirred for 1 h prior to filtration. The filtrate was added to ethereal diazomethane and the solution was kept in an ice-bath for 5 h. The excess of diazomethane was destroyed with glacial acetic acid and the solution was evaporated to give a semi-solid mass. This was chromatographed on silica, with ethyl acetate–acetonitrile (9:1) as eluent, to give a UV-active product (0.04 g, 72%) as a glass. Analysis (^1H NMR) showed that this product was an isomeric mixture (ratio 6:1), the major component of which was neosidomycin **5**; δ_H[200 MHz; $(CD_3)_2SO$] 2.2 (2 H, m, 4'-H_2), 3.46 (2 H, s, 3-CH_2), 3.69 (3 H, s, CO_2Me), 4.05 (2 H, m, 2'- and 3'-H) 4.1 (1 H, br s, exchangeable, OH), 4.46 (1 H, m, 5'-H), 5.1 (1 H, br s, exchangeable, OH), 6.21 (1 H, d, $J_{1',2'}$ 9, 1'-H), 6.9 (1 H, br s, exchangeable, NH), 7.34 (1 H, br s, exchangeable, NH) and 7.0–7.9 (5 H, m, indole). It was not possible to assign signals to the minor isomer with any certainty.

Methyl 2,3-*Di*-O-*acetyl*-1-[3-(*carbamoylmethyl*)-*indol*-1-*yl*]-1,4-*dideoxy*-α-D-lyxo-*hexopyranuronate* (*Di*-O-*acetylneosidomycin*, **6**).—A solution of neosidomycin **5** (and β-anomer) in dry pyridine (1.8 cm^3)–acetic anhydride (0.45 cm^3) was stirred for 24 h. The excesses of reagents were removed under reduced pressure and the yellow residue was chromatographed on silica, with ethyl acetate as eluent, to give a UV-active product (0.045 g, 87%) as a glass. Analysis (^1H NMR) showed that this was an isomeric mixture (6:1), the major component of which was di-*O*-acetylneosidomycin **6**; δ_H(200 MHz) 1.68 and 2.07 (each 3 H, s, OAc), 2.40 (1 H, ddd, J_{gem} 15.0, $J_{4'ax,5'}$ 6.9, $J_{4'ax,3'}$ 2.4, 4'-H^{ax}), 2.63 (1 H, ddd, $J_{4'ax,3'}$ 4.0, $J_{4'eq,5'}$ 1.6, 4'-H^{eq}), 3.76 (2 H, s, CH_2CONH_2), 3.85 (3 H, s, CO_2Me), 4.62 (1 H, br d, 5'-H), 5.36 (1 H, dd, $J_{2',1'}$ 9.4, $J_{2',3'}$ 3.0, 2'-H), 5.3 (1 H, br s, exchangeable, NH), 5.52 (1 H, m, 3'-H), 5.74 (1 H, br s, exchangeable, NH), 6.48 (1 H, d, $J_{1',2'}$ 9.4, 1'-H) and 7.1–7.8 (5 H, m, indole). For the β-epimer, δ_H(200 MHz) 1.52 and 2.26 (each 3 H, s, OAc), 2.3 (2 H, m, 4'-H_2), 4.74 (1 H, dd, $J_{5',4'ax}$ 12.0, $J_{5',4'eq}$ 3.0, 5'-H) 5.24 (1 H, dd, $J_{2',1'}$ 9.3, $J_{2',3'}$ 3.1, 2'-H) and 5.88 (1 H, d, *J* 9.3, 1'-H) (Found: M^+, 432.155. $C_{21}H_{24}N_2O_8$ requires M, 432.153).

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