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THE CHEMISTRY OF 2',3'-SECONUCLEOSIDES III. SYNTHESIS AND REACTIONS OF PURINE-2',3'-SECORIBONUCLEOSIDES

GRAHAM BEATON, A. STANLEY JONES and RICHARD T. WALKER*

Chemistry Department, University of Birmingham, Birmingham B15 2TT

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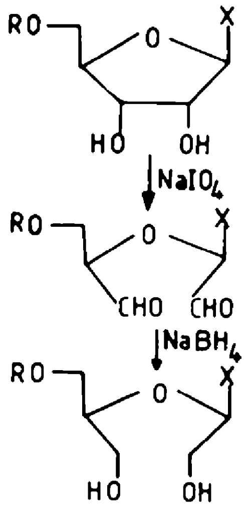
Abstract - 5'-O-Protected purine-ribonucleosides were oxidised with periodate to give dialdehydes which upon reduction with sodium borohydride gave 5'-O-protected purine-2',3'-secoribonucleosides, which were converted into their 2',3'-di-O-mesyl derivatives. These were converted into 2',3'-disubstituted-2',3'-dideoxy derivatives and because the 2'-O-mesyl group was significantly less reactive than the 3'-O-mesyl group, selective substitution at either the 2' or 3'-positions was achieved. As an example of the latter procedure, syntheses of 3'-amino-3'-deoxy-2',3'-secoadenosine and of 3'-deoxy-2',3'-secoinosine are described. The former compound was used as the starting material for the synthesis of a secopuromycin analogue but this analogue was not capable of inhibiting protein synthesis in a reticulocyte system using globin mRNA.

The 2',3'-secoribonucleosides (compounds which can be considered as ribonucleosides with the C-2'-C-3' bond missing) contain three primary hydroxyl groups. In order to synthesise derivatives which might show useful properties, it is desirable to obtain methods for selectively functionalising these groups. In the case of the pyrimidine-2',3'-secoribonucleosides this has been achieved by suitably blocking the 5'-hydroxyl group of the parent ribonucleoside and then obtaining the 2',3'-seco-derivative by periodate oxidation followed by sodium borohydride reduction. The previous two papers of this series have described how to substitute selectively at either the 2'- or 3'-positions.[1,2] The present paper describes procedures by which similar selectivity can be achieved with purine-2',3'-secoribonucleosides.

To block the 5'-hydroxyl group of the purine ribonucleosides the 4,4'-dimethoxytrityl group (DMT) was first chosen (the trityl group used previously for the pyrimidine ribonucleosides being too acid stable). Although this was fairly successful, great care had to be taken to avoid its premature removal during subsequent reaction sequences. In later work, therefore, the t-butyldiphenylsilyl group (TBDPS) was used. This was more stable and could be easily and specifically removed with tetrabutylammonium fluoride although recently we have found that this group can be partially hydrolysed under mild aqueous alkaline conditions. Thus by the sequence of reactions shown in Scheme 1, 5'-O-protected-2',3'-secoinosines (9,10) and 5'-O-protected-2',3'-secoadenosines (11,12) were obtained.

The reactions shown in Scheme 1 were initially carried out in two steps and the dialdehydes (5-8) isolated, but later it was found to be possible to proceed without isolating these intermediates. When isolated and dried, these dialdehydes often contain half a molecule of water[3] and in solution have been shown to be a complex mixture of cyclic acetals.[4] However they have the chemical reactions of the free dialdehydes which are used to represent them here. It was not necessary to block the adenine amino group.



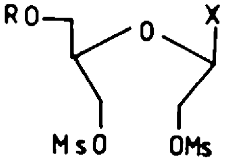
1 R = DMT; X = hypoxanthin-9-yl
2 R = DMT; X = adenin-9-yl
3 R = TBDPS; X = hypoxanthin-9-yl
4 R = TBDPS; X = adenin-9-yl

5 R = DMT; X = hypoxanthin-9-yl
6 R = DMT; X = adenin-9-yl
7 R = TBDPS; X = hypoxanthin-9-yl
8 R = TBDPS; X = adenin-9-yl

9 R = DMT; X = hypoxanthin-9-yl
10 R = DMT; X = adenin-9-yl
11 R = TBDPS; X = hypoxanthin-9-yl
12 R = TBDPS; X = adenin-9-yl

Scheme 1.

Treatment of compounds (9-12) with an excess of mesyl chloride gave the corresponding 2',3'-di-O-mesyl compounds (13-16). Compounds (13) and (14) were treated with lithium chloride in dimethylformamide (DMF) to give the 2',3'-dichloro compounds, (17) and (18), this showing the ready displacement of the 2', and 3'-O-mesyl groups. The structures of all these compounds were established by u.v. and n.m.r. spectroscopy, mass spectrometry and elemental analysis.

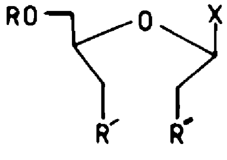


13 R = DMT; X = hypoxanthin-9-yl
14 R = DMT; X = adenin-9-yl
15 R = TBDPS; X = hypoxanthin-9-yl
16 R = TBDPS; X = adenin-9-yl

However the main objective of this investigation was to obtain selective reaction at either the 2'- or the 3'-positions. This has been already achieved in the pyrimidine series by treating 5'-O-trityl-2',3'-di-O-mesyl-2',3'-secouridine with 1,8-diazabicyclo 5,4,0 -undec-7-ene (DBU). Under these conditions the 2'-O-mesyl group was displaced to form an O^{2},2'-anhydro-3'-O-mesyl compound. It was then possible selectively to react the 3'-O-mesyl group.[1] In the present case however, the analogous compounds (13 and 14) were resistant to treatment with DBU and no 3,2'- or 3,3'-anhydroderivatives were formed. This is not too surprising because the purine ribonucleosides do not form stable anhydrocompounds at these positions.[5,6]

The first indication that selectivity between the 2'- and 3'-positions could be achieved was when compound (12) was treated with methyltriphenylphosphonium iodide (Rydon Reagent) (1.1 equiv).[7] 5'-O-TBDPS-2',3'-dideoxy-2',3'-diiodo-2',3'-secoadenosine (19) was formed as a minor product (11% yield), but the major product (43% yield) was 5'-O-TBDPS-3'-deoxy-3'-iodo-2',3'-secoadenosine 2'-(phenyl methylphosphonate) (20) which was a mixture of diastereoisomers. The structures of (19) and (20) were established by the usual methods. In the case of the ^{1}H n.m.r. spectrum of (20), in addition to the low field signal of the H-1' anomeric proton, a second triplet integrating to two protons could be observed at δ 4.60 indicating the presence of an electron withdrawing group at either C-2' or C-3'. On decoupling the anomeric signal, this triplet collapsed to a doublet indicating this group to be C-2'-bound. This and the rest of the spectral data established the structure allocated.

The formation of (20) could be rationalised on the assumption that there is first formed a diphosphonium intermediate (21). Nucleophilic attack by iodide occurred readily at C-3', to give a product which upon work-up gave (20). Much slower attack by iodide at C-2' gave (19). It appears, therefore, that there may be steric hinderance at C-2'. If this is so it should be possible preferentially to displace the 3'-O-mesyl group in compounds (13-16). This proved to be so. Thus mild treatment of (15) with NaI gave 5'-O-TBDPS-3'-deoxy-3'-iodo-2',3'-secoinosine (22). More drastic treatment gave 5'-O-TBDPS-2',3'-dideoxy-2',3'-diiodo-2',3'-secoinosine (23) as the major product. Similar products (24) and (19) were obtained from the corresponding 2',3'-secoadenosine derivative (16), although here the mesyl groups appeared to be somewhat less reactive.

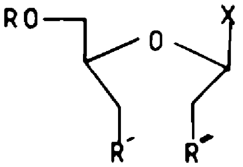


17 R = DMT; R',R" = Cl; X = hypoxanthin-9-yl
18 R = DMT; R',R" = Cl; X = adenin-9-yl
19 R = TBDPS; R',R" = I; X = adenin-9-yl
20 R = TBDPS; R' = I; R" = -O-P(O)(OPh)Me; X = adenin-9-yl
21 R = TBDPS; R,R" = $-O-\overset{+}{P}(OPh)_2Me$; X = adenin-9-yl
22 R = TBDPS; R' = I; R" = OMs; X = hypoxanthin-9-yl
23 R = TBDPS; R',R" = I; X = hypoxanthin-9-yl
24 R = TBDPS; R' = I; R" = OMs; X = adenin-9-yl

The fact that the 3'-O-mesyl group could be displaced more rapidly than the 2'-O-mesyl group made it possible to obtain selective substitution at the 2' and 3'-positions. This is illustrated by the following reaction series:

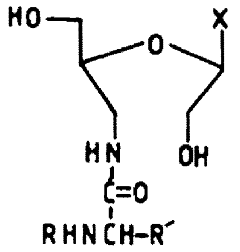
Compound (16) was treated with NaN_3 in DMF to give 5'-O-TBDPS-3'-azido-3'-deoxy-2'-O-mesyl-2',3'-secoadenosine (25). Treatment of this with NaI under drastic conditions gave 5'-O-TBDPS-3'-azido-2',3'-dideoxy-2'-iodo-2',3'-secoadenosine (26) but in poor yield. Treatment of (25) with potassium acetate readily gave the 2'-O-acetate, (27), which upon mild alkaline hydrolysis gave the 2'-hydroxy compound, (28). Removal of the TBDPS group with tetrabutylammonium fluoride gave 3'-azido-3'-deoxy-2',3'-secoadenosine (29), which upon reduction with H_2/Pd gave 3'-amino-3'-deoxy-2',3'-secoadenosine (30).

Reduction of compound (22) with H_2/Pd gave 5'-O-TBDPS-3'-deoxy-2'-O-mesyl-2',3'-secoinosine (31). The 2'-O-mesyl group was converted into the 2'-O-acetate, (32), which upon hydrolysis gave the 2'-hydroxy compound, (33). Removal of the TBDPS group in the usual way gave 3'-deoxy-2',3'-secoinosine (34).



25 R = TBDPS; R' = $-N_3$; R" = -OMs; X = adenin-9-yl
26 R = TBDPS; R' = $-N_3$; R" = -I; X = adenin-9-yl
27 R = TBDPS; R' = $-N_3$; R" = -OAc; X = adenin-9-yl
28 R = TBDPS; R' = $-N_3$; R" = -OH; X = adenin-9-yl
29 R = H; R' = $-N_3$; R" = -OH; X = adenin-9-yl
30 R = H; R' = $-NH_2$; R" = -OH; X = adenin-9-yl
31 R = TBDPS; R' = H; R" = -OMs; X = hypoxanthin-9-yl
32 R = TBDPS; R' = H; R" = -OAc; X = hypoxanthin-9-yl
33 R = TBDPS; R' = H; R" = -OH; X = hypoxanthin-9-yl
34 R,R' = H; R" = OH; X = hypoxanthin-9-yl

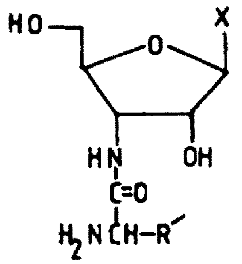
We have subsequently used 3'-amino-3'-deoxy-2',3'-secoadenosine (30) as the starting material for one of a number of derivatives which might potentially have interesting biological activity. We will here focus our attention on the synthesis of a seconucleoside of puromycin (36). Puromycin (37) can bind to both eukaryotic and prokaryotic ribosomes and prevents elongation of the growing peptide chain. Many analogues of puromycin have been synthesised and various acyclic analogues which are resistant to phosphorylases have also been made. These compounds have shown little or no biological activity and this is thought to arise from an inability of the acyclic species to adopt the specific conformation required for ribosome binding. The L-phenylalanyl derivative of the 2',3'-secopuromycin analogue (36) was chosen for synthesis as it is known that an aromatic side chain in the amino acid of puromycin is required.



X = adenin-9-yl

35 R = $PhCH_2OCO$-; R' = $PhCH_2$-

36 R = H; R' = $PhCH_2$-



X = 6-dimethylaminopurin-9-yl

37 R' = $-CH_2Ph(pOCH_3)$

The coupling reaction of compound (30) with N-benzyloxycarbonyl-L-phenylalanine, N-hydroxysuccinimide and dicyclohexylcarbodiimide in DMF was achieved using the procedure of Daluge and Vince.[8] Compound (35) was isolated in 50% yield and was fully characterised. The benzyloxycarbonyl protecting group was removed by hydrogenolysis to give the puromycin analogue (36). This analogue was tested for its ability to inhibit protein synthesis in a reticulocyte system using globin mRNA. Under conditions (50 μg/ml) where puromycin inhibited completely protein synthesis, the analogue showed no significant inhibition and thus it joins the growing list of acyclic puromycin analogues which do not possess demonstrable biological activity.

It can be seen that, provided the 5'-hydroxyl group of the parent ribonucleoside is suitably blocked before the formation of the purine-2',3'-seconucleoside, then selective substitution at the 2'- or 3'-positions can be readily achieved. We have since shown that no similar selectivity can be achieved if the base is a pyrimidine and therefore in that series one still has to use anhydronucleoside formation for this purpose (A. Kumar, unpublished results).

EXPERIMENTAL

N.m.r. spectra were recorded on one of the following instruments: Varian XL100, Jeol FX90Q or Jeol GX270 with $(CD_3)_2SO$ as the solvent unless otherwise stated. U.v. spectra were measured in ethanol on a Perkin Elmer 552 spectrophotometer. Mass spectra were recorded on a Kratos MS 80 RF instrument using the fast atom bombardment technique, sodium chloride was added as required. Column chromatography was carried out on silica gel either Kieselgel 60 type 7734, 0.063-0.200 mm, 70-230 mesh ASTM or Kieselgel 60 type 9385, 0.04-0.063 mm, 230-400 mesh ASTM (E. Merck A.G. Darmstadt, W. Germany). The latter was used under flash chromatography conditions under pressure. In the purification of 4,4'-dimethoxytrityl-containing compounds, 0.1% triethylyamine was added to all eluents. Small samples of compounds (∼ 100 mg) were often purified using a Chromatotron (Harrison Research Ltd.). The plates were eluted under a nitrogen atmosphere. All experiments were carried out under scrupulously dry conditions unless otherwise stated and all evaporations of solvents were carried out under reduced pressure.

5'-O-(4,4'-Dimethoxytrityl)inosine (1). Inosine (20.4 g, 75.9 mmol) was dried by co-evaporation with dry pyridine (2 x 200 ml). To the resulting white solid suspended in dry pyridine (600 ml), was added dropwise a solution of 4,4'-dimethoxytrityl chloride (33.5 g, 98.7 mmol in pyridine (230 ml) over a 5 h period with stirring. The resulting suspension was stirred at room temperature (15°) for 4 d, after which time all starting material had disappeared. Ethanol (5 ml) was added and after stirring for a further 15 min, the orange solution was evaporated to dryness, dissolved in chloroform, extracted with sodium bicarbonate solution, washed with water, taken to dryness and co-evaporated with toluene and acetone to yield an orange foam. Impurities were removed by treatment of the foam with hot ethyl acetate. Filtration of the suspension so formed afford the product as a chromatographically pure white solid (25.7 g, 59% yield). This could be recrystallised from ethanol. (Found: C, 65.2; H, 5.5; N, 10.1. Calc. for $C_{21}H_{30}N_4O_7$ C, 65.25; H, 5.30; N, 9.82%); u.v. λ_{max} 265 and 236 nm (ε, 5,900 sh and 20,500); n.m.r. δ 8.21 (1H,s,H-8), 8.01 (1H,s,H-2), 6.7-7.5 (13H,m,DMT-), 5.96 (1H,d,H-1'), 4.7-5.8 (2H,bd,m,OH-3',OH-5'), 4.62 (1H,m,H-2'), 4.0-4.4 (2H,m,H-3',H-4'), 3.77 (6H,s,OCH_3), 32.6 (2H,m,H-5'); mass spec. m/z 593 $(M+Na)^+$, 615 $(M+2Na-H)^+$.

5'-O-(4,4'-Dimethoxytrityl)adenosine (2). Adenosine (2.67 g, 10.1 mmol) dried as previously described was suspended in pyridine (100 ml) to which a solution of 4,4'-dimethoxytrityl chloride (4.42 g, 13.0 mmol) in pyridine (50 ml) was added with stirring over a period of 1 h at room temperature. After 3 d, reaction was still incomplete and a further portion of tritylating agent (2.27 g, 6.7 mmol) was added which resulted in the disappearance of all starting material after one further day at room temperature. The reaction mixture was worked up as previously described to give an orange foam. This was then dissolved in chloroform and fractionated on a silica column. Elution of the column with chloroform-ethanol (9:1) gave the product as a chromatographically pure white foam contaminated with triethylamine salts. These could be removed by dissolving the material in ethyl acetate and repeatedly washing the solution with water. The organic layer when dried and evaporated to dryness, gave the product (3.08 g, 54% yield). U.v. λ_{max} 260 and 236 nm (ϵ, 15,700 sh and 22,400); n.m.r. δ 8.25 (1H,s,H-8), 8.10 (1H,s,H-2), 6.7-7.5 (15H,m,2H lost on D_2O shake, NH_2,DMT-), 5.95 (1H,d,H-1'), 5.51 (1H,d,OH-2'), 5.18 (1H,d,OH-3'), 4.71 (1H,m, H-2'), 4.32 (1H,m,H-3'), 4.08 (1H,m,H-4'), 3.72 (6H,s,OCH_3), 3.24 (2H,m,H-5'); mass spec. m/z 570 $(M+H)^+$.

5'-O-(4,4'-Dimethoxytrityl)nucleoside dialdehydes (5,6). To a solution of the 5'-O-(4,4'-dimethoxytrityl)nucleoside (10.6 mmol) in acetone (350 ml) and water (50 ml), was added a solution of sodium periodate (11.7 mmol) in water (100 ml) and left for 24 h at room temperature with the exclusion of light. The solvent was then removed and the white solid so obtained extracted with water (2 x 100 ml), dissolved in acetone, filtered and evaporated to dryness to give a white foam which was purified on a silica column. The products were eluted with chloroform-ethanol (9:1) and triethylamine salts were removed as previously described.

5'-O-(4,4'-Dimethoxytrityl)inosine dialdehyde (5). (5.5 g, 91% yield). U.v. λ_{max} 265 and 236 nm (ϵ, 5,600 sh and 22,500); n.m.r. δ 8.0-8.4 (2H,bd,H-8,H-2), 6.5-7.5 (13H,bd,DMT-), 5.4-6.2 (bd,H-1', H-2',H-3',H-5'), 2.8-4.4 (bd,H-4',H-5',OCH_3). As previously reported, the dialdehydes so prepared are in solution a complex mixture of diasterioisomeric cyclic acetals and give typical broad n.m.r. resonances. Mass spec. m/z 591 $(M+Na)^+$.

5'-O-(4,4'-Dimethoxytrityl)adenosine dialdehyde (6). (5.5 g, 91% yield). (Found: C, 65.3; H, 5.4; N, 12.0. $C_{31}H_{29}N_5O_6$ requires C, 65.59; H, 5.15; N, 12.34%); u.v. λ_{max} 260 and 236 (ϵ, 14,800 and 19,400); n.m.r. δ 8.1-8.5 (2H,bd,H-8,H-2), 6.5-7.5 (15H,bd,DMT-,NH_2), 4.8-6.5 (bd,H-1',H-2',H-3', H-4'), 2.8-4.4 (bd,H-4',H-5',OCH_3). See the comment above on n.m.r. spectra of nucleoside dialdehydes. Mass spec. m/z 586 $(M+H_3O)^+$.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-seconucleosides (9,10). To a solution of the 5'-O-(4,4'-dimethoxytrityl)nucleoside dialdehyde (7.9 mmol) in ethanol-water (7:3, 400 ml), was added sodium borohydride (79 mmol) and allowed to stand overnight at room temperature. The vigorously stirred solution was carefully adjusted to pH 7 by the dropwise addition of 1M HCl and the solvent removed. The white solid so obtained was extracted with water (2 x 10 ml), dissolved in acetone (200 ml), filtered and taken to dryness to give a white foam which was purified on a silica column. The adenosine seconucleoside was eluted with chloroform-ethanol (9:1) and inosine seconucleoside was eluted with chloroform-ethanol (3:1). Triethylamine salts were removed from the products as previously described and the inosine derivative could be crystallised from chloroform-ethanol.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-secoinosine (9). (2.96 g, 66% yield). (Found: C, 64.75; H, 5.9; N, 9.1. $C_{31}H_{33}N_4O_7$ requires C, 65.02; H, 5.63; N, 9.7%); u.v. λ_{max} 265 and 236 nm (ϵ, 5,500 sh and 21,900); n.m.r. δ 8.28 (1H,s,H-8), 8.08 (1H,s,H-2), 6.6-7.4 (14H,m,DMT-,NH), 5.86 (1H,t,H-2'), 4.2-5.4 (2H,bd,OH-2',OH-3'), 4.0 (2H,d,H-2'), 3.72 (7H,s,H-4',OCH_3), 3.46 (2H,m,H-3'), 2.80 (2H,m, H-5'); mass spec. m/z 595 $(M+Na)^+$, 573 $(M+H)^+$.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-secoadenosine (10). (3.6 g, 79% yield). (Found: C, 65.2; H, 6.1; N, 12.0. $C_{31}H_{33}N_5O_6$ requires C, 65.13; H, 5.82; N, 12.25%); u.v. λ_{max} 260 and 236 nm (ϵ, 13,800 and 20,700); n.m.r. δ 8.38 (1H,s,H-8), 8.22 (1H,s,H-2), 6.6-7.5 (15H,DMT-,NH_2), 5.92 (1H,t, H-1'), 5.22 (1H,bd,OH-2'), 4.80 (1H,bd,OH-3'), 4.06 (2H,m,H-2'), 3.76 (7H,s,H-4',OCH_3), 3.48 (2H,m, H-3'), 2.80 (2H,m,H-5'); mass spec. m/z 594 $(M+Na)^+$, 572 $(M+H)^+$.

One-pot synthesis of 5'-O-(4,4'-dimethoxytrityl)-2',3'-seconucleosides of inosine and adenosine (9,10). To a solution of the 5'-O-(4,4'-dimethoxytrityl)-inosine or -adenosine (6 mmol) in ethanol-water (3:1, 400 ml) was added a solution of sodium periodate (6.6 mmol) in water (100 ml) and the solution was allowed to stand in the dark at room temperature (15°) for 24 h. Sodium borohydride (61 mmol) was then added and the reaction left overnight at room temperature. The vigorously stirred solution was carefully adjusted to pH 7 by the dropwise addition of 1M HCl, the solution evaporated to dryness, extracted with water (2 x 100 ml) and dissolved in acetone (200 ml). After filtration and evaporation to dryness, a foam was obtained which could be purified on a silica column, eluting first with chloroform-ethanol (9:1) to remove impurities and then with chloroform-ethanol (3:1) to yield the products (50-86% yield) which had spectral data identical to those already described for the fully characterized compounds.

5'-O-t-Butyldiphenylsilylinosine (3). Inosine (20.35 g, 75.86 mmol) was dried by azeotroping the nucleoside with benzene for 16 h. Removal of the solvent gave a white solid which was dissolved in dry DMF (350 ml) and to the solution was added triethylamine (22 ml, 157.8 mmol) and t-butylchlorodiphenylsilane (43 ml, 165.4 mmol). A white precipitate formed and the mixture was stirred at room temperature for 16 h and then water (15 ml) added. After 15 min the solvent was removed and the residue allowed to stand with water (200 ml) for 24 h, the precipitate so formed was filtered off and dissolved in chloroform (600 ml). The organic solution was washed with water (2 x 300 ml), evaporated to dryness to give an off-white solid which could be crystallised from ethanol to give the product (28.72 g, 74.7%) (Found: C, 61.7; H, 5.7; N, 11.0. $C_{26}H_{30}N_4O_5Si$ requires C, 61.63; H, 5.97; N, 11.06%); u.v. λ_{max} (249 nm (ϵ, 11,300); n.m.r. δ 8.25 (1H,s,H-8), 8.02 (1H,s,H-2), 7.2-7.8 (10H,m,Ph_2Si), 5.96 (1H,d,H-1'), 5.0-5.8 (2H,bd,OH-2',OH-3'), 4.58 (1-H,t, H-2'), 4.34 (1H,t,H-3'), 3.98-4.2 (1H,m,H-4'), 3.8-3.98 (2H,m,H-5'), 1.02 (9H,s,t-butyl); mass spec. m/z 551 $(M+2Na-H)^+$.

5'-O-t-Butyldiphenylsilyladenosine (4). Adenosine (20.39 g, 76.3 mmol) was dried as previously described, dissolved in DMF (340 ml) to which was added dimethylaminopyridine (2.33 g, 19.1 mmol), triethylamine (19 ml, 83.1 mmol) and t-butylchlorodiphenylsilane (21.6 ml, 83.1 mmol) and the reaction stirred at room temperature for 60 h. Water (20 ml) was then added and the mixture stirred for a further 30 min. Solvent was removed and water (200 ml) added to the residue which was allowed to stand for 16 h after which time the precipitate which had formed was filtered, washed with water (2 x 100 ml), ether (2 x 100 ml) and dissolved in acetone. The solution was filtered, evaporated to dryness to give a solid which could be crystallised from ethanol to give the product (21.7 g, 56% yield). Silica column chromatography of the residues from the mother liquor and ether washings gave further product (7.6 g, 20% yield) (Found: C: 61.8; H, 6.0; N, 14.0. Calc. for $C_{26}H_{31}N_5O_4Si$ C, 61.75; H, 6.18; N, 13.85%); u.v. λ_{max} 259.5 nm (ε, 13,900); n.m.r. δ 8.27 (1H,s,H-8), 8.11 (1H,s,H-2), 7.1-7.8 (12H,m,NH_2 and Ph_2Si, 5.99 (1H,d,H-1'), 5.56 (1H,d,OH-2'), 5.26 (1H,d,OH-3'), 4.69 (1H,m,H-2'), 4.40 (1H,d,H-3'), 4.0-4.2 (1H,m,H-4'), 3.7-4.0 (2H,m,H-5'), 1.01 (1H,s,t-butyl); mass spec. m/z 528 $(M+Na)^+$, 506 $(M+H)^+$.

5'-O-t-Butyldiphenylsilylnucleoside dialdehydes (7,8). To a solution of the 5'-protected nucleoside (4.02 mmol) in acetone-water (3:1, 300 ml) was added a solution of sodium periodate (4.39 mmol) in water (50 ml) and the solution allowed to stand at room temperature (15°) in the dark overnight. Evaporation of the solvent yielded a white solid which was extracted with water (2 x 100 ml), and the residue dissolved in acetone (200 ml). The solution was filtered, evaporated to give a white foam which could be purified on a silica column using chloroform-ethanol (9:1) as eluant.

5'-O-t-Butyldiphenylsilylinosine dialdehyde (7). (1.92 g, 95% yield) (Found: C, 60.1; H, 5.8; N, 10.4. $C_{26}H_{28}N_4O_5Si$. H_2O requires C, 59.75; H, 5.79; N, 10.72%); u.v. λ_{max} 249 (ε, 11,300); n.m.r. (see previous comment on nucleoside aldehyde n.m.r. spectra) δ 12.2-12.4 (1H,m,NH), 8.0-8.4 (2H,bd,H-8,H-2), 7.0-7.8 (10H,m,Ph_2Si), 4.8-6.2 (bd,H-1',H-2',H-3',H-5'), 3.2-4.4 (bd,H-4', H-5'), 0.7-1.4 (9H,bd,t-butyl).

5'-O-t-Butyldiphenylsilyladenosine dialdehyde (8). (1.80 g, 89% yield) (Found: C, 60.6; H, 6.1; N, 13.1. $C_{26}H_{29}N_5O_4Si.0.75\,H_2O$ requires C, 60.38; H, 5.94; N, 13.5%); u.v. λ_{max} 260.5 nm (ε, 14,500); n.m.r. (see previous comment on nucleoside dialdehyde n.m.r. spectra) δ 8.0-8.5 (2H,bd,H-8,H-2), 6.9-7.8 (12H,bd,NH_2,Ph_2Si), 4.8-6.4 (bd,H-1',H-2',H-3',H-5'), 3.2-4.8 (bd,H-4', H-5'), 0.4-1.4 (bd,t-butyl); mass spec. m/z 504 $(M+H)^+$, 522 $(M+H_3O)^+$.

5'-O-t-Butyldiphenylsilyl-2',3'-seconucleosides (11,12). To a solution of the 5'-O-t-butyldiphenylsilylnucleoside dialdehyde (11.6 mmol) in ethanol-water (3:1, 400 ml) was added sodium borohydride (116 mmol) and the resulting solution left in the dark overnight at room temperature. The solution was then neutralized with 2M HCl and evaporated to dryness, extracted with water (2 x 100 ml) and dissolved in acetone (200 ml). After filtration and evaporation of the solution, the residue could be purified by silica chromatography using chloroform-ethanol (9:1) to remove impurities and chloroform-ethanol (3:1) to give the products.

5'-O-t-Butyldiphenylsilyl-2',3'-secoinosine (11). Recrystallized from aqueous ethanol (4.94 g, 84% yield) (Found: C, 61.6; H, 6.1; N, 10.8. $C_{26}H_{32}N_4O_5Si$ requires C, 61.39; H, 6.34; N, 11.02%); u.v. λ_{max} 249 nm (ε, 10,600); n.m.r. δ 12.1-12.5 (1H,bd,N-H), 8.19 (1H,s,H-8), 8.04 (1H,s,H-2), 7.43 (10H,s,Ph_2Si), 5.88 (1H,t,H-1'), 5.20 (1H,t,OH-2'), 4.80 (1H,t,OH-3'), 3.95 (2H,t,H-2'), 3.25-3.8 (5H,m,H-3',H-4',H-5'), 1.04 (9H,s,t-butyl), mass spec. m/z 553 $(M+2Na-H)^+$, 531 $(M+Na)^+$ 509 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-2',3'-secoadenosine (12). Recrystallized from chloroform-ether (4.88g, 83% yield) (Found: C, 61.3; H, 6.4; N, 13.5. $C_{26}H_{33}N_5O_4Si$ requires C, 61.51; H, 6.55; N, 13.80%); u.v. λ_{max} 260 nm (ε, 13,200); n.m.r. δ 8.24 (1H,s,H-8), 8.18 (1H,s,H-2), 7.1-7.6 (12H,m,NH_2,Ph_2Si), 5.94 (1H,t,H-1'), 5.2 (1H,t,OH-2'), 4.82 (1H,t,OH-3'), 3.99 (2H,t,H-2'), 3.3-3.86 (5H,m,H-3',H-4', H-5'), 0.83 (9H,s,t-butyl); mass spec. m/z 508 $(M+H)^+$.

One-pot synthesis of 5'-O-t-butyldiphenylsilyl-2',3'-seconucleosides of inosine and adenosine (11,12). To a solution of the 5'-O-t-butyldiphenylsilylnucleoside (6.1 mmol) in ethanol-water (3:1, 300 ml) was added sodium periodate (6.7 mmol) in water (50 ml) and the resulting solution was left in the dark at room temperature overnight. Sodium borohydride (60.8 mmol) was then added and the mixture again left at room temperature overnight. The resulting solution was adjusted to pH 7 with 2M HCl, evaporated to dryness, extracted with water (2 x 200 ml), the residue dissolved in acetone (200 ml), filtered, evaporated to dryness and purified on a silica column, eluting impurities with chloroform-ethanol (9:1) and the desired products with chloroform-ethanol (3:1) which had spectral data identical to those already described for the fully characterized compounds (1.92-2.32 g, 63-75% yield).

5'-O-(4,4'-Dimethoxytrityl)-2',3'-di-O-methanesulphonyl-2',3'-seconucleosides (13,14). 5'-O-(4,4'-Dimethoxytrityl)-2',3'-seconucleoside (2.7 mmol) was dried by co-evaporation with dry pyridine (2 x 100 ml) and to a stirred solution of the seconucleoside in dry pyridine (200 ml) at 0° was added dropwise a solution of methanesulphonyl chloride (0.6 ml, 7.8 mmol) in pyridine (50 ml) with exclusion of moisture. The reaction was left at 0° overnight and further mesylating agent then added if necessary (t.l.c.). To the final solution was added ethanol (2 ml) and the solvent removed after stirring for 15 min. The residue obtained was dissolved in chloroform (200 ml), extracted with saturated sodium bicarbonate solution (2 x 100 ml) and washed with water

(2 x 100 ml). The dried organic layer was taken to dryness, co-evaporated with toluene and acetone and the resulting syrup fractionated by flash chromatography on a silica column using chloroform-ethanol (9:1) as eluant. Triethylamine salts were removed in the usual way to yield the products.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-di-O-mesyl-2',3'-secoinosine (13). (2.17 g, 85% yield) (Found: C, 54.1; H, 5.1; N, 7.8. $C_{33}H_{36}N_4O_{11}S_2$ requires C, 54.38; H, 4.98; N, 7.69%); u.v. λ_{max} 265 and 236 nm (ε, 6,900 sh and 24,800); n.m.r. δ 12.46 (1H,bd,N-H), 8.39 (1H,s,H-8), 8.10 (1H,s,H-2), 6.6-7.4 (13H,m,DMT), 6.2 (1H,t,H-1'), 4.88 (2H,d,H-2'), 4.38 (2H,m,H-3'), 4.1 (1H,m,H-4'), 3.72 (6H,s,OCH_3), 3.22 (3H,s,CH_3SO_2-2'), 3.18 (3H,s,CH_3SO_2-3'), 2.7-3.1 (2H,m, H-5'); mass spec. m/z 751 $(M+Na)^+$.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-di-O-mesyl-2',3'-secoadenosine (14). (2.28 g, 90% yield). U.v. λ_{max}260 and 236 nm (ε, 13,800 sh and 21,000); n.m.r. δ 8.45 (1H,s,H-8), 8.20 (1H,s,H-2), 7.42 (2H,s,NH_2), 6.6-7.4 (13H,m,DMT), 6.22 (1H,t,H-1'), 4.92 (2H,d,H-2'), 4.38 (2H,m,H-3'), 3.9-4.25 (1H,m,H-4'), 3.74 (6H,s,OCH_3), 3.23 (3H,s,CH_3SO_2-2'), 3.18 (3H,s,CH_3SO_2-3'), 2.6-3.1 (2H,m,H-5'); mass spec. m/z 751 $(M+Na)^+$.

5'-O-t-Butyldiphenylsilyl-2',3'-di-O-mesyl-2',3'-secoinosine (15). Compound (11) (1.78 g, 3.5 mmol) was dried by co-evaporation with dry pyridine (2 x 75 ml) and then dissolved in dry pyridine (30 ml). The solution was cooled to 0° and mesyl chloride (0.6 ml, 7.8 mmol) in pyridine (5 ml) was added dropwise. On standing overnight, all the starting material had disappeared (t.l.c.) and ethanol (10 ml) was added, the solution allowed to stand for 15 min, evaporated to dryness and triturated with water (50 ml) to give a yellow precipitate which was removed by filtration. This was co-evaporated with acetone to give a gum which was purified by flash chromatography on silica gel using chloroform-ethanol (9:1) as eluent. The product was obtained as a white foam and could be crystallized from ethanol (1.78 g, 77% yield) (Found: C, 50.2; H, 5.2; N, 8.2 $C_{28}H_{36}N_4O_9S_2Si$ requires C, 50.58; H, 5.46; N, 8.43%); u.v. λ_{max} 248 nm (ε, 9,500); n.m.r. δ 12.3 (1H,s,N-H), 8.31 (1H,s,H-8), 8.06 (1H,s,H-2), 7.45 (10H,s,Ph_2Si), 6.21 (1H,t,H-1'), 4.82 (2H,d, H-2'), 4.50 (2H,m,H-3'), 4.06 (1H,m,H-4'), 3.48 (2H,m,H-5'), 3.26 (3H,s,CH_3SO_2-2'), 3.22 (3H,s, CH_3SO_2-3'), 0.87 (9H,s,t-butyl); mass spec. m/z 665 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-2',3'-di-O-mesyl-2',3'-secoadenosine (16). Compound (12) (11.94 g, 23.6 mmol) was dried by co-evaporation with dry pyridine (2 x 150 ml) and dissolved in dry pyridine (120 ml). To the solution cooled to 0° was added dropwise a solution of mesyl chloride (5.47 ml, 70.7 mmol) in pyridine (20 ml). After standing at 0° overnight, all the starting material had been consumed and two new products were present (t.l.c.). Ethanol (20 ml) was added to the solution and after 30 min the solvent was evaporated and the residue triturated with water (200 ml). The precipitate which formed was filtered, co-evaporated with acetone and the resulting mixture purified on a silica column using chloroform-ethanol (9:1) as eluant and then separated into the two pure compounds on a second silica column using chloroform-ethanol (20:1) as eluant. The title product was obtained as the major species (12.52 g, 80% yield) while the minor product was identified as 5'-O-t-butyldiphenylsilyl-3'-chloro-3'-deoxy-2'-O-mesyl-2',3'-secoadenosine (1.0 g, 7% yield).

5'-O-t-Butylphenylsilyl-2',3'-di-O-mesyl-2',3'-secoadenosine (16). U.v. λ_{max} 260 nm (ε, 14,000), n.m.r. δ 8.35 (1H,s,H-8), 8.17 (1H,s,H-2), 7.53 (12H,s,NH_2,Ph_2Si), 6.23 (1H,t,H-1'), 4.85 (2H,d, H-2'), 4.51 (2H,m,H-3'), 4.09 (1H,m,H-4'), 3.45 (2H,m,H-5'), 3.27 (3H,s,CH_3SO_2-2'), 3.23 (3H,s, CH_3SO_2-3'), 0.85 (9H,s,t-butyl); mass spec. m/z 664 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-3'-chloro-3'-deoxy-2'-O-mesyl-2',3'-secoadenosine. (Found: C, 53.8; H, 5.9; N, 12.0. $C_{27}H_{34}N_5O_5$ ClSSi requires C, 53.66; H, 5.67; N, 11.59%) u.v. λ_{max} 260 nm (ε, 12,900); n.m.r. δ 8.38 (1H,s,H-8), 8.16 (1H,s,H-2), 7.37 (12H,m,NH_2,Ph_2Si-), 6.23 (1H,t,H-1'), 4.85 (2H,d,H-2'), 3.94 (3H,m,H-3',H-4'), 3.43 (2H,m,H-5'), 3.24 (3H,s,CH_3SO_2-2'), 0.80 (9H,s,t-butyl); mass spec. m/z 603 $(M+H)^+$.

2',3'-Dichloro-2',3'-dideoxy-5'-O-(4,4'-dimethoxytrityl)-2',3'-seconucleosides (17,18). Separately, dry samples of compounds (13) and (14) (0.9 mmol) were dissolved in dry DMF (30 ml) and the solutions heated to 100°. To the stirred solutions was added lithium chloride (4.5 mmol) and the temperature maintained at 100° for 3 h. The solvent was removed, the syrup so obtained co-evaporated with water to give a gum which was purified by silica chromatography using flash chromatography with chloroform-ethanol (9:1) as eluant to give the pure products after removal of triethylamine salts in the usual way.

2',3'-Dichloro-2',3'-dideoxy-5-O-(4,4'-dimethoxytrityl)-2',3'-secoinosine (17). (0.52 g, 97% yield) (Found: C, 61.2; H, 5.1; N, 9.1. $C_{31}H_{30}N_4O_5Cl_2$ requires C, 61.08; H, 4.96; N, 9.19%); u.v. λ_{max} 265 and 236 nm (ε 7,900 sh and 26,400); n.m.r. δ 12.45 (1H,bd,NH), 8.42 (1H,s,H-8), 8.10 (1H,s,H-2), 6.7-7.5 (13H,m,DMT), 6.10 (1H,t,H-1'), 4.38 (2H,m,H-2'), 3.6-4.1 (3H,m,H-3',H-4'), 3.74 (6H,s,-OCH_3), 2.90 (2H,m,H-5'); mass spec. m/z 631 $(M+Na)^+$, 609 $(M+H)^+$.

2',3'-Dichloro-2',3'-dideoxy-5'-O-(4,4'-dimethyoxytrityl)-2',3'-secoadenosine (18). (0.52 g, 97% yield) (Found: C, 61.2; H, 5.3; N, 11.8. $C_{31}H_{33}N_5O_4Cl_2$ requires C, 61.18; H, 5.14; N, 11.51%); u.v. λ_{max} 260 and 236 nm (ε, 17,800 and 25,000); n.m.r. δ 8.47 (1H,s,H-8), 8.19 (1H,s,H-2), 6.6-7.6 (15H,m,NH_2,DMT), 6.16 (1H,t,-H-1'), 3.4-4.6 (11H,m,OCH_3,H-2',H-3',H-4'), 2.7-3.36 (2H,m, H-5'); mass spec. m/z 608, 610, 612 (ratio 9:6:1, $(M+H)^+$).

Reaction of 5'-O-t-butyldiphenylsilyl-2',3'-secoadenosine (12) with Rydon reagent. Compound (12) (2.2 g, 4.3 mmol) was dissolved in dry DMF (20 ml) and the Rydon reagent (methyltriphenylphosphonium iodide) (2.55 g, 5.6 mmol) added to the solution under a stream of dry nitrogen. After 5 min when starting material has disappeared to be replaced by two new products (t.l.c.), methanol (3 ml) was added to the solution and after 15 min, the solvent was removed and the syrup obtained fractionated on a silica column using chloroform-ethanol (20:1) as eluant. The major species was identified as 5'-O-t-butyldiphenylsilyl-3'-deoxy-3'-iodo-2',3'-secoadenosine 2'-(phenyl methylphosphonate (20)). The minor, less polar product was isolated in crystalline form and characterised as 5'-O-t-butyldiphenylsilyl-2',3'-dideoxy-2',3'-diiodo-2',3'-secoadenosine (19). A Chromatotron was used to obtain analytically pure samples of both products using chloroform-ethanol (20:1) as the eluant.

5'-O-t-Butyldiphenylsilyl-2',3'-dideoxy-2',3'-diiodo-2',3'-secoadenosine (19). (0.35 g, 11% yield) (Found: C, 43.05; H, 4.1; N, 9.3. $C_{26}H_{31}N_5O_2I_2Si$ requires C, 42.93; H, 4.30; N, 9.63%); u.v. λ_{max} 260 nm (ε, 14,900); n.m.r. δ 8.37 (1H,s,H-8), 8.14 (1H,s,H-2), 7.4 (12H,m,NH_2,Ph_2Si), 6.04 (1H,t,H-1'), 3.97 (2H,m,H-2'), 3.58 (3H,m,H-3',H-4'), 3.4 (2H,m,H-5'), 0.38 (9H,s,t-butyl); mass spec. m/z 728 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-3'-deoxy-3'-iodo-2',3'-secoadenosine 2'-(phenyl methylphosphonate) (20). (1.5 g, 43% yield) (Found: C, 51.4; H, 5.0; N, 9.4. $C_{32}H_{38}N_5O_5IPSi$ requires C, 51.36; H, 5.09; N, 9.08%); u.v. λ_{max} 260 nm (ε, 14,400); n.m.r. δ 8.31 (1H,s,H-8), 8.14 (1H,s,H-2), 6.9-7.6 (17H, m,NH_2,Ph_2Si,Ph), 6.12 (1H,t,H-1'), 4.66 (2H,t,H-2'), 3.2-3.7 (5H,m,H-3',H-4',H-5'), 1.63 (3H,dd, CH_3-P-), 0.83 (9H,s,t-butyl); ^{31}P n.m.r. δ $(CD_3)_2SO$ + 4.40 (phosphonate); mass spec. m/z 772 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-2',3'-dideoxy-2',3'-diiodo-2',3'-seconucleosides (19,23). To a solution of the 5'-O-t-butyldiphenylsilyl-2',3'-di-O-mesyl-2',3'-seconucleoside (1.4 mmol) in dry DMF (30 ml) at 100° was added sodium iodide (1.05 g, 6.6 mmol) and a further portion of sodium iodide (1.05 g) was added after 6 h. After one further hour, all starting material had been consumed (t.l.c.), the mixture was allowed to cool, the solvent removed and the residue purified by flash chromatography on silica gel using chloroform-ethanol (20:1) as eluant. The product from the inosine nucleoside was isolated as a white foam (0.61 g, 60% yield). The adenosine nucleoside gave two products which could be further purified and separated using a Chromatotron with chloroform-ethanol (20:1) as eluant. The minor product (0.2 g, 20% yield) was identified as 5'-O-t-butyldiphenylsilyl-2',3'-dideoxy-2',3'-diiodo-2',3'-secoadenosine (19) which had been previously characterised. The major product was identified as 5'-O-t-butyldiphenyl-3'-iodo-2'-O-mesyl-2',3'-secoadenosine (0.63 g, 65% yield).

5'-O-t-Butyldiphenylsilyl-2',3'-dideoxy-2',3'-diiodo-2',3'-secoinosine (23). (Found: C, 43.2; H, 4.3; N, 7.5. $C_{26}H_{30}N_4O_2I_2Si$ requires C, 42.87; H, 4.15; N, 7.69%); u.v. λ_{max} 248 nm (ε, 10,100); n.m.r. δ 12.43 (1H,bd,NH), 8.34 (1H,s,H-8), 8.06 (1H,s,H-2), 7.44 (10H,m,Ph_2Si), 6.04 (1H,t,H-1'), 3.97 (2H,m,H-2'), 3.6 (3H,m,H-3',H-4'), 3.41 (2H,m,H-5'), 0.86 (9H,s,t-butyl); mass spec. m/z 729 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-3'-deoxy-3'-iodo-2'-O-mesyl-2',3'-secoadenosine (24). (Found: C, 46.6; H, 4.6; N, 9.8. $C_{27}H_{34}N_5O_5ISSi$ requires C, 46.61; H, 4.93; N, 10.07%); u.v. λ_{max} 260 nm (ε, 13,800); n.m.r. δ 8.37 (1H,s,H-8), 8.16 (1H,s,H-2), 7.43 (12H,s,NH_2,Ph_2Si), 6.2 (1H,t,H-1'), 4.85 (2H,d,H-2'), 3.25-3.7 (5H,m,H-3',H-4',H-5'), 3.23 (3H,s,CH_3SO_2-2'), 0.84 (9H,s,t-butyl); mass spec. m/z 696 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-3'-deoxy-3'-iodo-2'-O-mesyl-2',3'-seconucleosides (22,24). A stirred solution of the 5'-O-t-butyldiphenylsilyl-2',3'-di-O-mesyl-2',3'-seconucleoside (5.5 mmol) in dry DMF (100 ml) was warmed to 75° and sodium iodide (1.88 g, 11.8 mmol) added. After 2 d, the mixture was allowed to cool, the solvent removed and the residue dissolved in chloroform (150 ml) and washed with water (2 x 100 ml). The dried organic layer was taken to dryness and the residue applied to a silica column and eluted with chloroform-ethanol (9:1). The title products were obtained in good yield and in the case of the adenosine derivative 5'-O-t-butyldiphenylsilyl-2',3'-dideoxy-2',3'-diiodo-2',3'-secoadenosine (0.8 g, 19% yield) was also obtained.

5'-O-t-Butyldiphenylsilyl-3'-deoxy-3'-iodo-2'-O-mesyl-2',3'-secoadenosine (24). (3.02 g, 78% yield). This was identical to the compound previously characterized.

5'-O-t-Butyldiphenylsilyl-3'-iodo-2'-O-mesyl-2',3'-secoinosine (22). (2.83 g, 74% yield) (Found: C, 46.7; H, 4.6; N, 8.2. $C_{27}H_{33}N_4O_6ISSi$ requires C, 46.55; H, 4.78; N, 8.04%); u.v. λ_{max} 248 nm (ε, 10,100); n.m.r. δ 12.48 (1H,bd,NH), 8.33 (1H,s,H-8), 8.09 (1H,s,H-2), 7.43 (10H,s,Ph_2Si), 6.19 (1H,s,H-1'), 4.80 (2H,d,H-2'), 3.25-3.75 (5H,m,H-3',H-4',H-5'), 3.24 (3H,s,CH_3SO_2-2'), 0.80 (9H,s,t-butyl); mass spec. m/z 697 $(M+H)^+$.

3'-Azido-5'-O-t-butyldiphenylsilyl-3'-deoxy-2'-O-mesyl-2',3'-secoadenosine (25). To a solution of compound (16) (0.8 mmol, 0.53 g) in dry DMF (30 ml) at 55-60° was added lithium azide (1.5 mmol, 0.074 g) and the reaction mixture stirred for 2 d. The mixture was allowed to cool, the solvent removed, the residue dissolved in chloroform (50 ml), washed with water (2 x 50 ml) and evaporation of the dried organic layer left a solid which could be purified by flash silica chromatography using chloroform-ehtanol (9:1) as eluant. The title product was isolated as a white foam (0.33 g, 66% yield) (Found: C, 53.1; H, 5.7; N, 18.5. $C_{27}H_{34}N_8O_5SSi$ requires C, 53.09; H, 5.61; N, 18.35%); u.v. λ_{max} 260 nm (ε, 12,800); n.m.r. δ 8.35 (1H,s,H-8), 8.15 (1H,s,H-2), 7.38 (12H,m,NH_2Ph_2Si-), 6.22 (1H,t,H-1'), 4.83 (2H,d,H-2'), 3.5-4.1 (3H,m,H-3',H-4'), 3.4 (2H,m,H-5'), 3.23 (3H,s,CH_3-SO_2-2'), 0.82 (9H,s,t-butyl); mass spec. m/z 611 $(M+H)^+$. Other nucleophiles used under similar conditions which gave products with the same regioselectivity were potassium acetate and potassium phthalimide.

3'-Azido-5'-O-t-butyldiphenylsilyl-2',3'-dideoxy-2'-iodo-2',3'-secoadenosine (26). Compound (25) (1.12 g, 1.8 mmol) was dissolved in dry DMF (35 ml) and the solution heated to 100°. To the solution was added sodium iodide (0.58 g, 3.6 mmol) and the mixture stirred for 24 h. A further portion of sodium iodide (0.72 g, 4.5 mmol) was then added and after 5 d at 100°, a further portion (0.68 g, 4.3 mmol) was added. After a further 24 h, all starting material had disappeared (t.l.c.), the mixture was allowed to cool and the solvent removed to give a brown syrup. This was dissolved in chloroform (50 ml), washed with water (2 x 50 ml) and when dried, the organic solution was evaporated to dryness to give a brown syrup which could be purified on a silica column using chloroform-ethanol (20:1) as eluant. The product was obtained as a clear syrup which could be crystallised from ethanol (0.82 g, 70% yield) (Found: C, 48.9; H, 4.9; N, 17.1. $C_{26}H_{31}N_8O_2ISi$ requires C, 48.59; H, 4.86; N, 17.44%); u.v. λ_{max} 259.5 nm (ε, 15,600); n.m.r. δ 8.35 (1H,s,H-8), 8.15 (1H,s,H-2), 7.39 (12H,m,NH_2,Ph_2Si), 6.07 (1H,t,H-1'), 3.15-4.15 (7H,m, H-2',H-3',H-4',H-5'), 0.84 (9H,s,t-butyl); mass spec. m/z 643 $(M+H)^+$.

2'-O-Acetyl-3'-azido-5'-O-t-butyldiphenylsilyl-3'-deoxy-2',3'-secoadenosine (27). Compound (25) (2.07 g, 3.4 mmol) was dissolved in dry DMF (60 ml) and the solution heated to 95°. To this solution was added potassium acetate (0.4 g, 4.1 mmol) and the mixture stirred for 2 d. The mixture was allowed to cool and the solvent removed to give a brown residue which was dissolved in chloroform (50 ml), washed with water (2 x 50 ml) and when dried, the organic layer was evaporated to dryness to give a brown solid which could be purified by flash chromatography using chloroform-ethanol (20:1) as eluant. The product was obtained as a white solid (1.87 g, 96% yield) (Found: C, 58.8; H, 6.3; N, 19.2. $C_{28}H_{34}N_8O_4Si$ requires C, 58.51; H, 5.96; N, 19.5%); u.v. λ_{max} 260 nm (ε, 13,500); n.m.r. δ 8.32 (1H,s,H-8), 8.13 (1H,s,H-2), 7.41 (12H,m,NH_2,Ph_2Si), 6.14 (1H,t,H-1'), 4.61 (2H,m,H-2'), 3.15-4.0 (5H,m,H-3',H-4',H-5'), 1.95 (3H,s,CH_3CO-2'), 0.80 (9H,s,t-butyl); mass spec. m/z 575 $(M+H)^+$.

3'-Azido-5'-O-t-butyldiphenylsilysl-3'-deoxy-2',3'-secoadenosine (28). To a solution of compound (27) (0.4 g, 0.7 mmol) in methanol (30 ml) was added potassium carbonate (0.11 g, 0.8 mmol) and the reaction mixture was stirred overnight at room temperature. Water (1 ml) was added, the solvent removed after 15 min, and the resulting white solid dissolved in chloroform (30 ml), washed with water (2 x 15 ml), the aqueous layer back-extracted with chloroform (30 ml), the organic layers combined, dried and evaporated to dryness. The resulting white solid was purified on a silica column using chloroform-ethanol (9:1) as eluant to give the title compound which could be crystallized from ethanol (0.35 g, 94% yield) (Found: C, 58.6; H, 6.1; N, 21.0. $C_{26}H_{32}N_8O_3Si$ requires C, 58.62; H, 6.06; N, 21.04%); u.v. λ_{max} 260 nm (ε, 13,800); n.m.r. δ 8.25 (1H,s,H-8), 8.14 (1H,s,H-2), 7.4 (10H,m,Ph_2Si), 7.29 (2H,s,NH_2), 5.89 (1H,t,H-1'), 5.22 (1H,t, OH-2'), 3.45-4.15 (5H,m,H-2',H-3',H-5'), 3.33 (2H,m,H-5'), 0.83 (9H,s,t-butyl); mass spec. m/z 533 $(M+H)^+$

3'-Azido-3'-deoxy-2',3'-secoadenosine (29). To a solution of compound (28) (0.27 g, 0.5 mmol) in tetrahydrofuran (30 ml) at room temperature, was added tetrabutylammonium fluoride (0.17 g, 0.65 mmol) and the reaction allowed to proceed for 2 h. The solvent was removed and the resulting brown residue purified on a silica column using chloroform-ethanol (3:1) as eluant. The title compound was obtained as a white solid (0.11 g, 87% yield) (Found: C, 41.1; H, 4.8; N, 38.0. $C_{10}H_{14}N_8O_3$ requires C, 40.81; H, 4.80; N, 38.08%); u.v. λ_{max} 259.7 nm (ε, 13,900); n.m.r. δ 8.32 (1H,s,H-8), 8.23 (1H,s,H-2), 7.36 (2H,s,NH_2), 5.92 (1H,t,H-1'), 5.24 (1H,t,OH-2'), 4.73 (1H,t, OH-5'), 3.95 (2H,d,H-2'), 3.53 (3H,m,H-3',H-4'), 3.18 (2H,d,H-5'); mass spec. m/z 317 $(M+Na)^+$, 295 $(M+H)^+$.

3'-Amino-3'-deoxy-2',3'-secoadenosine (30). A solution of compound (29) (0.6 g, 2.0 mmol) was prepared in ethanol-water (3:1, 120 ml) using an ultrasound water bath. To the solution was added palladium (10% on charcoal, 0.2 g) and the mixture was shaken for 3 days in an atmosphere of hydrogen. The solution was then filtered through celite and evaporated to yield a colourless glass which was dissolved in water, washed with chloroform and the aqueous layer evaporated to dryness. The resulting glass was co-evaporated with acetone and the title product was isolated by precipitating it from a solution of ethanol with ether (0.51 g, 93% yield) (Found: C, 41.8; H, 6.5. $C_{10}H_{16}N_6O_3 \cdot H_2O$ requires C, 41.95; H, 6.34%) u.v. λ_{max} 259.7 (ε, 16,400); n.m.r. δ 8.35 (1H,s,H-8), 8.22 (1H,s,H-2), 7.31 (2H,s,NH_2), 5.91 (1H,t,H-1), 3.98 (2H,m,H-2'), 3.44 (1H,m,H-4'), 3.26 (2H, m,H-5'), 2.84 (2H,m,H-3'), 3.0-4.0 (2H,bd,H_2O); mass spec. m/z 269 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-3'-deoxy-2'-O-mesyl-2',3'-secoinosine (31). Compound (22) (3.0 g, 4.3 mmol) was dissolved in ethanol-water (5:1, 180 ml) using an ultrasonic bath. Sodium acetate (0.52 g, 6.3 mmol) and palladium (10% on charcoal, 0.5 g) were added and the mixture shaken under an atmosphere of hydrogen for 16 h. The mixture was then filtered through celite, the solvent removed, the resulting yellow solid was dissolved in methanol (30 ml), neutralised with concentrated ammonia solution and the solvent evaporated to leave a yellow residue which could be purified on a silica column using chloroform-ethanol (9:1) to give the title compound (1.93 g, 79% yield) (Found: C 56.5; H, 5.8; N, 9.5. $C_{27}H_{34}N_4O_6SSi$ requires C, 56.82; H, 6.00; N, 9.82%); u.v. λ_{max} 248 nm (ε, 10,000); n.m.r. δ 12.42 (1H,s,NH), 8.31 (1H,s,H-8), 8.07 (1H,s,H-2), 7.43 (10H,m,Ph_2Si-), 6.08 (1H,t,H-1'), 4.75 (2H,d,H-2'), 3.7 (1H,m,H-4'), 3.39 (2H,d,H-5'), 3.24 (3H,s,CH_3SO_2-2'), 1.19 (3H,d,H-3'), 0.87 (9H,s,t-butyl); mass spec. m/z 571 $(M+H)^+$.

2'-O-Acetyl-5'-O-t-butyldiphenylsilyl-3'-deoxy-2',3'-secoinosine (32). This compound was prepared in an exactly analogous way to that previously described for the adenosine derivative (27). The title compound was obtained in 84% yield. (Found: C, 62.6; H, 6.6; N, 10.5. $C_{28}H_{34}N_4O_5Si$ requires C, 62.89; H, 6.41; N, 10.48%); u.v. λ_{max} 248 nm (ε, 10,100); n.m.r. δ 8.29 (1H,s,H-8), 8.09 (1H,s,H-2), 7.45 (10H,m,Ph_2Si), 6.01 (1H,t,H-1'), 4.6 (2H,m,H-2'), 3.65 (1H,m,H-4'), 3.32 (2H,m,H-5'), 1.98 (3H,s,CH_3CO-2'), 1.16 (3H,d,H-3'), 0.84 (9H,s,t-butyl); mass spec. m/z 5.35 $(M+H)^+$.

5'-O-t-Butyldiphenylsilyl-3'-deoxy-2',3'-secoinosine (33). This compound was made as described for the adenine derivative (28). The *title compound* was obtained in 84% yield. (Found: C, 63.3; H, 6.6; N, 11.1. $C_{26}H_{32}N_4O_4Si$ requires C, 63.38; H, 6.55; N, 11.38%); u.v. λ_{max} 249 nm (ε, 10,000); n.m.r. δ 11.7-12.8 (1H,bd,NH), 8.18 (1H,s,H-8), 8.04 (1H,s,H-2), 7.45 (10H,m,Ph_2Si), 5.74 (1H,t, H-1'), 4.0-5.5 (1H,bd,OH-2'), 3.89 (2H,d,H-2'), 3.61 (1H,m,H-4'), 3.37 (2H,d,H-5'), 1.17 (3H,d, H-3'), 0.86 (9H,s,t-butyl); mass spec. m/z 493 $(M+H)^+$.

3'-Deoxy-2',3'-secoinosine (34). This compound was prepared in an exactly analogous way to that previously described for the adenosine derivative (29). The *title compound* was obtained in 74% yield. (Found: C, 47.3; H, 5.3; N, 22.2. $C_{10}H_{14}N_4O_4$ requires C, 47.24; H, 5.55; N, 22.04%); u.v. λ_{max} 248 nm (ε, 10,800); n.m.r. δ 8.25 (1H,s,H-8), 8.09 (1H,s,H-2), 5.73 (1H,t,H-1'), 5.22 (1H,bd,OH-2'), 4.53 (1H,bd,OH-5'), 3.82 (2H,d,H-2'), 3.33 (3H,m,H-4',H-5'), 1.12 (3H,d,H-3'); mass spec. m/z 255 $(M+H)^+$.

3'-N-(N'-Benzyloxycarbonyl-L-phenylalanyl)-3'-deoxy-2'-3'-secoadenosine (35). To a solution of 3'-amino-3'-deoxy-2',3'-secoadenosine (30) (127 mg, 0.47 mmol) in dry DMF (7 ml) was added *N*-hydroxysuccinimide (61 mg, 0.53 mmol) and *N*-benzyloxycarbonyl-*L*-phenylalanine (160 mg, 0.53 mmol) and the resulting solution was cooled to 5°. 1,3-*N*,*N*-Dicyclohexylcarbodiimide (110 mg, 0.53 mmol) was added to the stirred solution, the mixture kept at this temperature for 30 min before being allowed to stand overnight with stirring at room temperature. When no free amine remained, the precipitate was filtered off, washed with ethanol and the combined organic solutions evaporated to dryness. The residue obtained was applied as a slurry in chloroform-ethanol (3:1) to a silica column and eluted with the same solvent to give the *product* (131 mg, 50% yield) (Found: C, 58.7; H, 5.5; N, 17.95. $C_{27}H_{31}N_7O_6$ requires C, 59.00; H, 5.69; N, 17.84%); u.v. λ_{max} 260 nm (ε, 14,100); n.m.r. δ 8.29 (1H,s,H-8), 8.17 (1H,s,H-2), 7.30 (12H,m,NH_2+2xPh), 5.82 (1H,t,H-1'), 5.19 (1H,m, OH-2'), 4.95 (2H,s,-COO-CH_2-Ph), 4.55 (1H,m,OH-5'), 4.27 (1H,m,*α*-CH), 3.88 (2H,m,H-2'), 3.42 (1H, m,H-4'), 3.14 (4H,m,H-3',H-5'), 2.10 (2H,s,CH_2-Ph); mass spec. *m*/z 550 $(M+H)^+$.

3'-Deoxy-3'-N-L-phenylalanyl-2',3'-secoadenosine (36). To a solution of compound (35) (227 mg, 0.41 mmol) in glacial acetic acid (30 ml), was added palladium (10% on charcoal, 120 mg) and the mixture was shaken in an atmosphere of hydrogen for 3.5 h at room temperature. The mixture was then filtered through celite and the resulting solution evaporated to dryness to give a syrup which was dissolved in methanol and passed slowly down a column of IRA 400 resin (OH^- form, 10 ml) packed in methanol. The resulting solution was evaporated to dryness to yield the *product* (150 g, 87% yield) as a hygroscopic white foam. This could be further purified by precipitation from ethanol with ether. (Found: C, 53.0; H, 5.96; N, 22.6. $C_{19}H_{25}N_7O_4.0.75H_2O$ requires C, 53.20; H, 6.23; N, 22.85%); u.v. λ_{max} 259.7 nm (ε, 12,900); n.m.r. δ 8.25 (1H,s,H-8), 8.15 (1H,s,H-2), 8.00 (1H,m,NH-3'), 7.24 (7H,m,NH_2-6+Ph), 5.83 (1H,t,H-1'), 5.21 (1H,m,OH-2'), 4.57 (1H,m,OH-5'), 3.87 (2H,d,H-2'), 2.60-3.70 (m,H-3',H-4',H-5',*α*-CH,CH_2-Ph,H_2O), 1.64 (2H,m,NH_2 of amino acid); mass spec. m/z 416 $(M+H)^+$.

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