Pergamon

Tetrahedron 55 (1999) 14649–14664

TETRAHEDRON

Synthesis of 3,6-Anhydro Sugars from Cyclic Sulfites and Sulfates and their Applications in the Preparation of Bicyclonucleoside Analogues of ddC and ddA

M. Pineda Molas, M. Isabel Matheu, Sergio Castillón*
Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili. Pl. Imperial Tarraco 1, 43005 Tarragona. Spain

Joaquín Isac-García, Fernando Hernández-Mateo, Francisco G. Calvo-Flores, Francisco Santoyo-González*
Departamento de Química Orgánica, Universidad de Granada. 18071 Granada. Spain

Received 11 June 1999; revised 24 September 1999; accepted 7 October 1999

Abstract: Cyclic sulfates **21-23** and sulfite **27** derived from glucofuranose lead to the 3,6-anhydrosugar **28** in excellent yields when treated with sodium sulfite or in basic media. When treated with sodium sulfite, the 3-deoxy derivative **24** fails to give the intramolecular cyclization which leads to the anhydrosugars. Instead it gives the disulfonate derivative **26**. **28** was used as starting material to prepare bicyclonucleosides **43** and **46**, which are analogues of the anti-HIV agents ddC and ddA.

INTRODUCTION

2',3'-Dideoxynucleosides **1-4** are some of the most active agents against HIV and other viruses.[1] Bicyclic analogues of nucleosides are conformationally restricted, so they have been widely used to synthesize antisense oligonucleotides. They facilitate the interaction with the complementary DNA or RNA, by stabilizing the pairing process, duplex formation.[2] In fact, oligonucleotides containing bicyclic nucleosides have a greater affinity for complementary RNA or DNA. It has also been suggested that a C-3' *exo* conformation is predictive of anti-HIV activity.[3] Thus, it has been shown that a cyclopropane-fused dideoxycarbocyclic nucleoside, designed by V. E. Marquez *et al.* and structurally related to neplanocin-C, is forced to adopt a typical N-geometry.[4] Bicyclic nucleoside analogues incorporating a fused methylene group (**5**),[5] oxirane (**6**)[6] or oxetane (**7**)[7] have been shown to inhibit HIV replication. Similar analogues of nucleosides containing a cyclopentyl (**8-9**)[8] were not active, and other related nucleosides (**10-11**)[9] have been prepared but no biological data reported. All these nucleosides have a hydroxymethyl group which is usually considered to be a requirement for antiviral activity.[10] However, some nucleosides which have a secondary hydroxyl group, such as the bicyclic derivatives **12**[11] and **16**,[12] which incorporate a hydroxylamino group, have shown antiviral activity. A related nucleoside designed by E. Kaes and co-workers,[13] with the base appended at the C-5' hydroxyl group of the hexitol by a methylene linker, have also shown antiviral activity. Nucleoside **15** is an isonucleoside with a similar bicyclic backbone.[14]

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00911-4

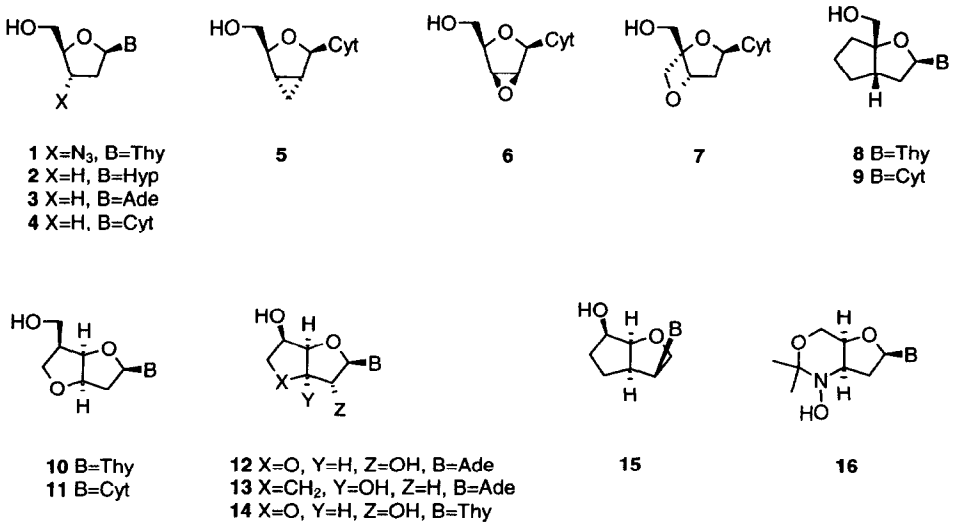
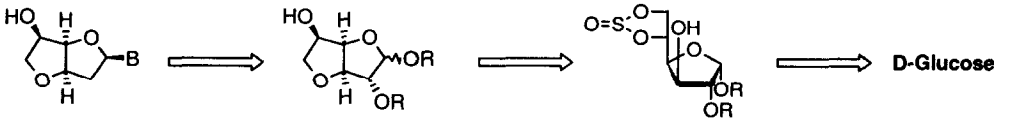


Figure 1

Several authors have used similar nucleosides such as **13**[2a-c] and **14**[15] to prepare oligonucleotides.

The bicyclic framework in compounds **10-15** has been synthesised from isosorbide (compounds **10**, **11**, **15**), by internal rearrangement of 3,5,6-*O*-orthoester glucose derivatives (compound **14**), from a 3-*O*-mesyl glucofuranose derivative (compound **12**), or from cyclopentylderivatives (compound **13**).

Cyclic sulfites and sufates of vicinal diols have recently been shown to be useful intermediates in carbohydrate synthesis.[16] Continuing our studies in cyclic sulfites and sulfates we describe in this paper a new easy route for the synthesis of 3,6-anhydro-1,2-*O*-isopropilidene-α-D-glucofuranose starting from a sulfite and its transformation into 2',3'-dehydroxy bicyclic nucleosides (See Scheme 1) that can be considered as analogues of ddA and ddC with restricted conformational mobility.

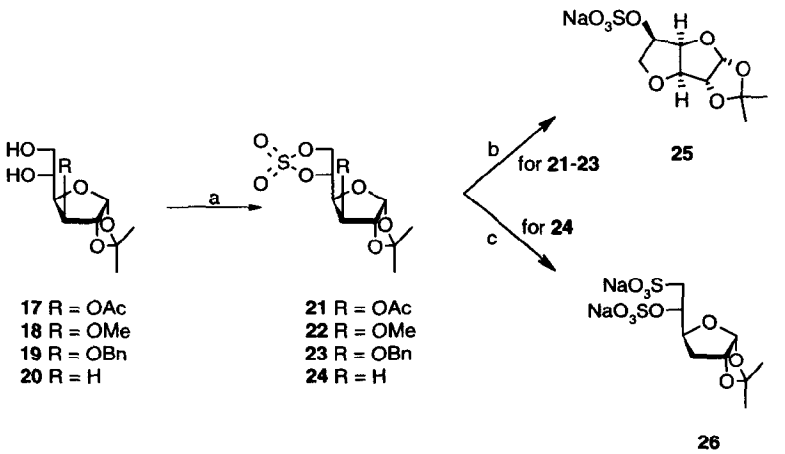


Scheme 1

RESULTS AND DISCUSSION

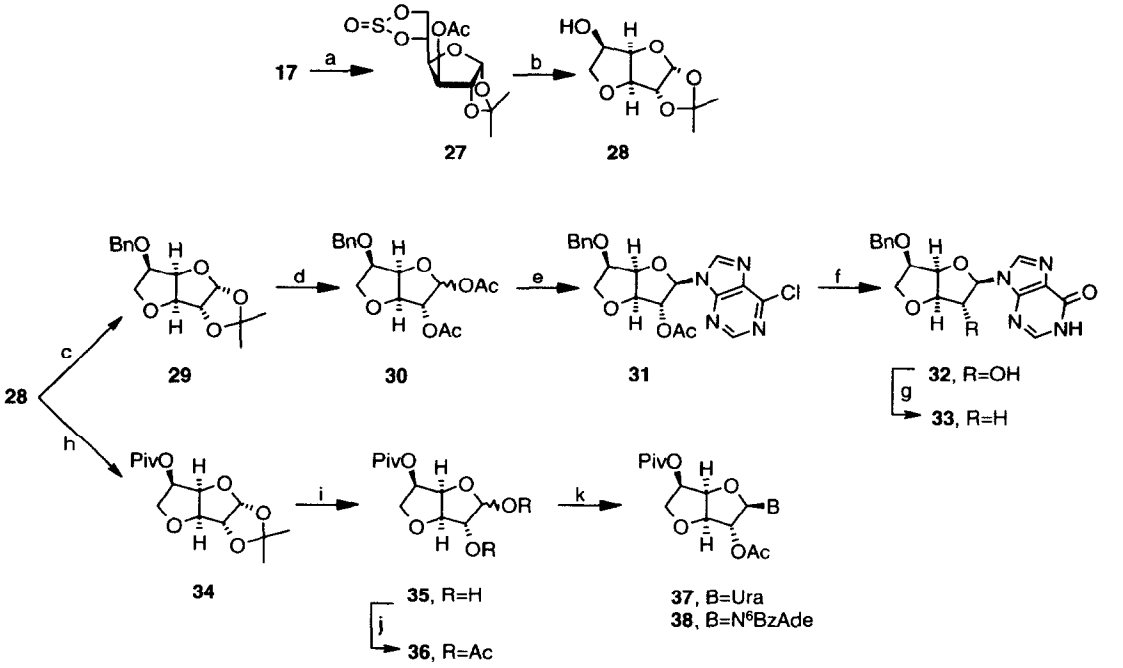
The reaction of 5,6-cyclic sulfate sugar derivatives with sulfur,[16a,b,d] selenium,[16a] nitrogen,[17] fluorine[17] and carbon[16c,18] nucleophiles allow a regiospecific ring opening which

generates a secondary *O*-sulfate salt or alcohol function on workup with dilute acid. Considering this behaviour and continuing our studies on the reactivity of cyclic sulfate sugars, it was expected that treating the 5,6-cyclic sulfates **21-24** with sodium sulfite would lead to the corresponding 6-sulfonic acid derivatives. However, this only happened in the case of the 3-deoxy derivative **24** when compound **26** was isolated in an 85% yield. For cyclic sulfates **21-23** the reaction product was characterised as the 3,6-anhydro sugar **25** which was isolated in a 75-80% yield. Several anhydro sugars have been obtained by internal sugar ortho ester rearrangements in polar aprotic solvents under acid catalysis.[19] A review of the literature showed that K.S. Kim *et al.* obtained a similar result[20] in the reaction of cyclic sulfate sugars with phosphines. These 3,6-anhydro sugars form because of the remote participation of the oxygen atom present at C-3 *via* an oxonium ion intermediate. Similar cyclizations have been described in a variety of different substrates which have a leaving group present in the δ-position with respect to an oxygen atom of an ether or ester function.[21] In order to demonstrate that this process is generalized, $NaHCO_3$ was used as a weak base and the reactions of **21-23** were performed in aqueous THF. Compound **25** was again the only reaction product isolated in similar yields (Scheme 2).



Scheme 2. a) Ref. 16a; b) Na_2SO_3-Me_2CO-H_2O, 16h at r.t. and 4h under reflux or $NaHCO_3$-THF-H_2O, reflux, 4h (75-80%); c) Na_2SO_3-Me_2CO-H_2O, 16h at r.t. and 4h at reflux (85%).

Because the bicyclic structure **25** just described forms so easily, it was thought that this could be synthetically exploited to give access to bicyclonucleoside analogues of ddC and ddA. In this respect, the derivative **28** is the pivotal compound for the synthesis. Although it can be obtained by treating **25** with acid, its synthesis could be improved by using the cyclic sulfite **27** as the starting material and by reaction with NaOMe in methanol. In this way compound **28** was obtained in an overall yield of 80% from **17**. This result shows that the synthetic strategy described is a straightforward and high yielding route for the synthesis of 3,6-anhydro sugars using inexpensive reagents (Scheme 3).

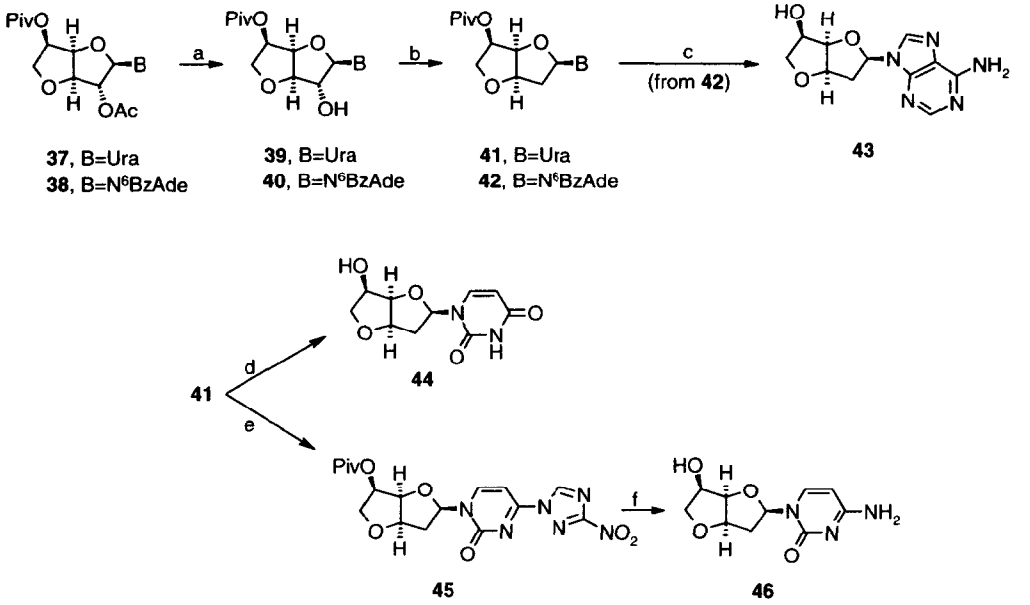


Scheme 3. a) Ref. 16a; b) NaOMe, MeOH, 0°C→r.t., 30 min (97%); c) NaH, BnBr, THF, r.t., 5 h (84%); d) AcOH, H_2SO_4, Ac_2O, r.t., 5 h (74%); e) BSA, TMSOTf, $Cl_2C_2H_4$, 6-chloropurine, reflux, 40 min (64%); f) $HSCH_2CH_2OH$, MeOH, NaOMe, reflux, 4 h (87%); g) CH_3CN, DMAP, PhOCSCl, r.t., 3 h, then toluene, AIBN, *n*-Bu_3SnH, reflux, 3.5 h (42%); h) PivCl, pyridine, DMAP, r.t., 24 h (98%); i) 80% aq. AcOH, 120-125°C, 4 h (83%); j) Ac_2O, pyridine, r.t., overnight (93%); k) BSA, TMSOTf, $Cl_2C_2H_4$, uracil or N^6-benzoyladenine, reflux, 40-45 min (80%).

Compound **28** was transformed into compounds **30** and **36** which were considered to be appropriate starting materials for N-glycosylation. Initially we chose to protect the free hydroxyl group in **28** by reaction with benzyl bromide, since benzyl ether is stable in the basic conditions required for selective deprotection of 2-OAc and for substituting chlorine in **31**. 6-Chloropurine was considered to be an appropiate base because it enables various substituents to be easily introduced at position 6. Thus, compound **28** was initially treated with benzyl bromide to give compound **29** which was hydrolyzed and subsequently reacted with acetic anhydride to obtain compound **30**. 6-Chloropurine was glycosylated by reaction with **30** in the presence of BSA and with trimethylsilyl triflate as a promoter, to obtain nucleoside **31** in a 64% yield. Initially we attempted to transform **31** into the hypoxantine derivative by treating it with mercapto ethanol. This led to compound **32** in an 87% yield. **32** was deoxygenated with the Barton procedure (i. e. treatment with phenoxythiocarbonyl chloride and subsequently with tributyltin hydride) to obtain **33** with a moderate yield. However, all attempts to deprotect the benzyl group in **32** or in **33** under hydrogenolytic conditions (Pd-C, $Pd(OH)_2$-C, Ni-Raney) [22] were unsuccessful even at 70 bar of pressure. In all cases, the starting material was recovered. Treatment with oxidants such as DDQ[23] or with Lewis acids[24] such as BCl_3 led to the

deglycosylated compound. So, this approach was abandoned and the pivaloyl group was used as the protective group.

Following a similar scheme of synthesis, compound **28** was treated with pivaloyl chloride to give compound **34**, which by subsequent hydrolysis and acetylation gave compound **36**. Using a similar glycosylation procedure, Uracil and N^6-Bz-Adenine were glycosylated with **36** to afford compounds **37** and **38**, respectively, in an 80% yield in both cases.



Scheme 4. a) MeOH/NH_3(10-20%), r.t., 50 min-3 h (85-99%); b) i: CH_3CN or $Cl_2C_2H_4$, DMAP, PhOCSCl, r.t., 40 min-4 h. ii: Toluene, AIBN, *n*-Bu_3SnH, reflux, 50 min-1.5 h (63-80%); c) Conc. aq. NH_3 soln., 55-60 °C, 8 h (67%); d) Basic resin Amberlite IRA- 402, MeOH, r.t., 16 h (quantitative); e) Pyridine, MSNT, diphenylphosphate, r.t., 8 h (66%); f) MeOH/NH_4OH conc., r.t., 3 days, (91%).

When the reaction was performed with cytosine under the same conditions, yields were very low. The use of acetylcytosine improved the yield, but various attempts to selectively deprotect the acetyl group were unsuccessful, because in all cases the acetamido group was also deprotected. Due to these negative results, we decided to synthesise the deoxycytidine from the uracil derivative **37**.

Position 2 of **37** and **38** was deacetylated using a dilute solution of ammonia in methanol (Scheme 4). In these conditions, the acetoxy group reacts much faster than pivaloy and benzoyl groups. Compounds **39** and **40** were deoxygenated with the Barton procedure to lead to compounds **41** and **42** in good yields.[25] Treatment of **41** in basic media led to the uridine nucleoside **44**. The uracil derivative **41** was transformed into the cytosine derivative **46** with a well established protocol. It was treated with 1-mesyl-3-nitro-1,2,4-triazole (MSNT) in the presence of diphenylphosphate to give compound **45**, which by reaction with ammonia in

methanol leads to the cytosine derivative **46**.[26] In the same way, compound **42** was deprotected by reaction with ammonia to give adenine derivative **43**.

As has been mentioned, the presence of a second ring fused to the furanoid decreases the conformational mobility of nucleosides. Bicyclonucleosides are usually found in a low-energy conformation, but there may be a lower proportion of other conformers. To find out whether **43** and **46** had a single conformation or whether there is a mixture of conformers in solution we decided to record an NMR ^{1}H spectrum at different temperatures of 1-(3',6'-anhydro-D-glucofuranosyl)-cytosine. Throughout the experiment, which started at 40°C and was cooled to −78°C, the appearance of the spectrum did not change. The signals were seen to broaden, perhaps because the viscosity of the solvent increased.

NOE experiments were done to obtain information about the furanose ring. Due to the similarities between the coupling constants of products **43** and **46** the experiments were done with compound **46**. After H-6 had been irradiated it was found that the nitrogenated base was in a *syn/anti* equilibrium. NOE effects obtained after the irradiation of H-1', H-3' and H-5' were consistent with a C-4'-*exo* conformation, possibly due to a gauche effect between the two endocyclic oxygens.

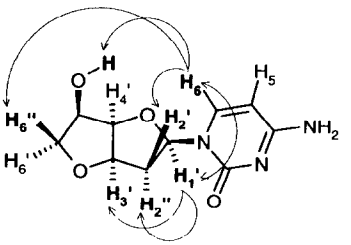


Figure 2. NOE experiments

The PSEUROT program was used to corroborate the information obtained with NOE experiments about the conformation of the sugar ring.[27] Two N-conformers were found to be in equilibrium: P_1= -70.5, ν_1 = 34.9 and X_1 = 0.53 values were found for the first one that are in agreement with a $^1T_4$ conformation. P_2 = 62.6 and ν_2 = 85.9 values for the second one are consistent with a $_4T^0$ conformation.

In conclusion, a new family of bicyclonucleosides analogues of ddC and ddA have been prepared from D-glucose using an intramolecular sulfate substitution as key step. The nucleoside analogues **43** and **46** were tested for their *in vitro* inhibitory effects on the replication of HIV-1 in CEM-SS and MT-4 cell systems. None of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (100 μM). When evaluated in anti-HBV assays in HepG2 cells, none of the tested compounds showed any antiviral effect (up to a concentration of 100 μM) nor cytotoxicity (up to a concentration of 200 μM).

EXPERIMENTAL

General methods. All solvents were distilled before use. Thin layer chromatography (TLC) was performed using Alugram Sil G/UV$_{254}$ Düren, and charring with H_2SO_4/EtOH 20:300. Column chromatography (CC) was performed on silica gel (Matrix Silica 60A, 40-60 μm

SDS). Radial chromatography (RC) was performed on a 7924T Chromatotron Harrison Research apparatus, with silica 60 PF_{254} Merck. Organic phases were dried over anhydrous magnesium sulfate or sodium sulfate. Concentrations were performed under reduced pressure. Melting points were recorded on a Tottoli Buchi 510 apparatus and are uncorrected. NMR spectra were recorded on a Varian Gemini-300 pulse Fourier transform spectrometer, with tetramethylsilane as internal standard when using $CDCl_3$ as solvent. Ultraviolet absorption spectra were recorded on a Diode Array HP 8452A spectrophotometer. Infrared spectra were recorded on a Hidac Prospect-IR Fourier transform spectrophotometer, with samples as neat liquids or nujol null between potassium bromide plates. Elemental analyses were performed with a Carlo Erba EA microanalyzer. Specific rotations were recorded on a Perkin-Elmer 241 MC apparatus, d=10 cm, and concentrations are given in mg/mL. Compounds **21-24** and **27** were synthesised according to the procedure described in the literature.[16a]

3,6-Anhydro-1,2-*O*-isopropylidene-5-*O*-sulfo-α-D-glucofuranose sodium salt (25). Procedure A: Sodium sulfite (1.1 mmol) was added to a solution of the cyclic sulfate **21-23** (1 mmol) in acetone-water (20 mL, 1:1). The solution was kept at rt for 16 h and then heated under reflux for 4 h. The solvent was evaporated to give a crude product that was purified by column chromatography ($CHCl_3$-MeOH 5:1) giving **25** (75-80%) as a solid. Procedure B: $NaHCO_3$ (1.1 mmol) was added to a solution of the cyclic sulfate **21-23** (1 mmol) in THF-water (25 mL, 4:1). The solution was heated under reflux for 4 h. The solvent was evaporated to give a crude product that was purified as described above giving **25** (75-80%) as white crystals: Mp 184-186 °C; $[\alpha]_D$ +52 (*c* 1, $CHCl_3$); IR 1382, 1244, 1165, 1067, 1039 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ in ppm): 5.89 (d, 1 H, $J_{1,2}$=3.7 Hz, H-1), 4.69 (t, 1 H, $J_{4,5}$=3.7 Hz, H-4), 4.55 (ddd, 1 H, $J_{5,6'}$=9.2, $J_{5,6}$=7.2 Hz, H-5), 4.49 (d, 1 H, H-2), 4.39 (d, 1 H, $J_{3,2}$=3.7 Hz, H-3), 3.85 (t, 1 H, H-6), 3.44 (dd, 1 H, $J_{6',6}$=9.0 Hz, H-6'), 1.46, 1.23 (2s, 6 H, Me_2C); ^{13}C NMR (DMSO-d_6, δ in ppm): 111.4 (Me_2C), 106.4 (C-1), 84.5, 84.1, 81.2, 74.5 (C-2,3,4,5), 68.4 (C-6), 27.1, 26.7 (Me_2C). RSMS (FAB) calc. for $C_9H_{13}O_8SNa$ [M + Na]$^+$ 327.0126, found 327.0119.

3,6-Dideoxy-1,2-*O*-isopropylidene-5-*O*-sulfo-6-*O*-sulfo-α-D-ribohexofuranoside disodium salt (26). Sodium sulfite (139 mg, 1.1 mmol) was added to a solution of the cyclic sulfate **24** (250 mg, 1 mmol) in acetone-water (20 mL, 1:1). The solution was kept at rt for 16 h and then heated under reflux for 4 h. The solvent was evaporated to give a crude that was purified by column chromatography ($CHCl_3$-MeOH 3:1) giving **26** (366 mg, 85%) as a white solid: Mp 230 °C (dec); $[\alpha]_D$ -18 (*c* 1, water); IR (KBr) 1225, 1062, 1036 and 971 cm^{-1}; ^1H NMR (D_2O, δ in ppm): 5.99 (d, 1 H, $J_{1,2}$=3.6 Hz, H-1), 5.02-4.95 (m, 3 H, H-2, H-4, H-5), 3.46 (dd, 1 H, $J_{6,6'}$=14.7, $J_{6,5}$=4.7 Hz, H-6), 3.25 (dd, 1 H, $J_{6',5}$=7.8 Hz, H-6'), 2.25 (dd, 1 H, $J_{3,3'}$=13.8, $J_{3,4}$=5.0 Hz, H-3), 2.06 (ddd, 1 H, $J_{3',2}$=10.6, $J_{3',4}$=4.8 Hz, H-3'), 1.58, 1.43 (2s, 6 H, Me_2C); ^{13}C NMR (D_2O, δ in ppm): 113.7 (Me_2C), 106.7 (C-1), 81.8, 79.8, 76.0 (C-2,4,5), 53.0 (C-6), 32.9 (C-3), 27.4, 26.8 (Me_2C); RSMS (FAB) calc. for $C_9H_{14}O_{10}S_2Na_3$ [M + Na]$^+$ 414.9721, found 414.9713.

3,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (28). A sodium methoxide solution (freshly prepared from 0.79 g of Na in 50 mL of methanol) was added under stirring to a cold (0 °C) solution of **27** (4.68 g, 15.2 mmol) in methanol (20 mL). The reaction mixture was left at rt until TLC (ether) showed complete disappearance of the starting material (30 min). The reaction mixture was evaporated under vacuum giving a crude product that was purified by

column chromatography (ether) to give compound **28** (3.0 g, 97%) isolated as a syrup: $[\alpha]_D$ +15 (*c* 1, $CHCl_3$); +30 (*c* 1, H_2O); IR 1266, 1214, 1164, 1083, 1051, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, δ in ppm): 5.90 (d, 1H, $J_{1,2}$=3.5 Hz, H-1), 4.73 (t, 1H, $J_{4,5}$=4.2 Hz, H-4), 4.58 (d, 1H, H-2), 4.46 (d, $J_{3,4}$ = 3.8 Hz, H-3), 4.23 (m, 1 H, H-5), 3.89 (dd, 1 H, $J_{6,6'}$=8.8, $J_{6,5}$=6.5 Hz, H-6), 3.45 (dd, 1 H, $J_{6',5}$= 7.7 Hz, H-6'), 2.70 (bs, 1H, OH), 1.45 (s, 3H, Me_2C), 1.30 (s, 3H, Me_2C); ^{13}C NMR ($CDCl_3$, δ in ppm): 112.9 (*C*Me_2), 106.9 (C-1), 85.4, 85.1, 82.5, 72.4 (C-2,3,4,5), 72.3 (C-6), 27.4, 26.6 (C*Me*$_2$); Anal. Cald. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.42; H, 6.95.

3,6-Anhydro-1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-glucofuranose (34). Pivaloyl chloride (2.5 mL, 20.3 mmol) and a catalytic amount of 4-dimethylaminopyridine (10 mg) were added to a solution of **28** (2.88 g, 14.3 mmol) in dry pyridine (15 mL). The mixture was kept at rt for 24 h, poured into ice-water (100 mL), and extracted with CH_2Cl_2 (150 mL). The organic phase was washed with 5% HCl (2 x 150 mL), aq. $NaHCO_3$ (150 mL), and water (100 mL), and then dried and concentrated. The crude product was purified by column chromatography (ether:hexane 1:1) to give **34** (4.0 g, 98%) as a solid: Mp 57-58 °C; $[\alpha]_D$ +58 (*c* 2, $CHCl_3$); IR 1731, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, δ in ppm): 5.94 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.04 (ddd, 1 H, $J_{5,6}$=6.8, $J_{5,6'}$=7.3, $J_{5,4}$=4.5 Hz, H-5), 4.97 (dd, 1 H, $J_{4,3}$=3.5 Hz, H-4), 4.61 (d, 1H, H-2), 4.52 (d, 1 H, H-3), 4.02 (dd, 1 H, $J_{6,6'}$= 8.8Hz, H-6), 3.73 (dd, 1 H, H-6'), 1.49 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.22 (s, 9 H, Me_3C); ^{13}C NMR ($CDCl_3$, δ in ppm): 178.1 (CO), 112.7(*C*Me_2), 107.2(C-1), 85.6, 85.0 (C-3,4), 81.0 (C-2), 73.2 (C-5), 69.4 (C-6), 38.8 (*C*Me_3), 27.5, 27.2, 26.9 (C*Me*$_2$ and C*Me*$_3$); Anal. Cald. for $C_{14}H_{22}O_6$: C, 58.72; H, 7.74. Found: C, 58.59; H, 7.76.

3,6-Anhydro-5-*O*-pivaloyl-α,β-D-glucofuranose (35). A solution of **34** (3.9 g, 13.6 mmol) in 80% aq. AcOH (10 mL) was heated at 120-125 °C for 4 h. After this time, the starting material had completely disappeared from tlc. After cooling, the reaction mixture was concentrated and coevaporated with toluene and the crude product was purified by column chromatography (ether) giving **35** (2.75 g, 83%) of an α/β mixture of anomers (80:20) as a syrup: $[\alpha]_D$+90 (*c* 1, $CHCl_3$); IR (film): 3422, 1726, 1163, 1081, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ in ppm: 5.40 (d, $J_{1,2}$= 3.6 Hz, H-1α), 5.30 (s, H-1β), 5.04 (m, H-5β), 4.99 (m, H-5α), 4.93 (t, 1H, $J_{4,3}$ = 5.0 Hz, H-4α), 4.44 (dd, $J_{3,2}$=1.8 Hz, H-3α), 4.38 (d, $J_{3,4}$ = 4.3 Hz, H-3β), 4.26 (s, H-2β), 4.11(dd, H-2α), 4.07 (dd, $J_{6,6'}$=9.9, $J_{6,5}$=4.9 Hz, H-6β), 3.95 (d, $J_{6,6'}$= 9.8Hz, $J_{6,5}$=5.8 Hz, H-6α), 3.80 (dd, $J_{6',5}$=5.3 Hz, H-6'α), 1.24 (s, 3H, CH_3), 1.22 (s, 3H, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm: 178.4 (CO), 105.1, 99.3 (C-1), 88.0, 87.0 (C-4), 82.1, 79.3, 78.4, 75.8 (C-3,5), 73.5, 73.1 (C-2), 71.1, 70.2 (C-6), 38.9 (*Me*$_3$*C*), 27.3, 27.2 (*Me*$_3$C); Anal. Cald. for $C_{11}H_{18}O_6$: C, 53.65; H, 7.32. Found: C, 53.61; H, 7.34.

1,2-Di-*O*-acetyl-3,6-anhydro-5-*O*-pivaloyl-α,β-D-glucofuranose (36). Compound **35** (2.7 g, 11 mmol) was acetylated overnight at rt with acetic anhydride (10 mL, 106 mmol) and pyridine (6 mL). The mixture was treated with an excess of methanol and evaporated with several portions of added methanol followed by toluene. The crude product obtained was purified by CC (ether-hexane 1:1) giving **36** (3.35 g, 93 %) as an α/β mixture (10:1) as a syrup: IR (film): 1749, 1282, 1216, 1158, 1080, 1058, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ in ppm: 6.46 (d, $J_{1,2}$= 4.4 Hz, H-1α), 6.18 (s, H-1β), 5.18 (s, H-2β), 5.14 (t, $J_{2,3}$= 4.3 Hz, H-2α), 5.03-4.94 (m, H-4α, H-5α, H-4β, H-5β), 4.78 (dd, $J_{3,4}$= 5.7Hz, H-3α), 4.62 (d, $J_{3,4}$= 4.9

Hz, H-3β), 4.17 (dd, $J_{6,5}$= 8.1 Hz, $J_{6,6'}$= 9.8Hz, H-6β), 4.09 (dd, $J_{6,6'}$= 9.6, $J_{6,5}$=5.8 Hz, H-6α), 3.97 (t, $J_{6',5}$= 8.8 Hz, H-6'α), 3.85 (dd, $J_{6',5}$=6.2 Hz, H-6'β), 2.12, 2.10, 2.09, 2.07 (4s, 6H, 2 Ac), 1.23 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm: 177.8, 169.7, 169.0 (CO), 104.1 (C-1β), 96.3 (C-1α), 85.1 (C-4β), 84.0 (C-4α), 82.8, 81.4, 72.7, 69.1 (C-2β,3β,5β,6β), 78.9, 77.2, 71.6, 69.5 (C-2α,3α,5α,6α), 38.8 (Me_3C), 27.05 (Me_3C), 20.9, 20.7, 20.4, 20.1 (MeCO); Anal. Cald. for $C_{15}H_{22}O_8$: C, 54.54; H, 6.67. Found: C, 54.68; H, 6.66.

3,6-Anhydro-5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (29). A suspension of 4.0 g of NaH (60% dispersed in mineral oil) in 39 mL of THF was added to a solution of 2.37 g (11.7 mmol) of **28** in 47 mL of anhydrous THF. After stirring for 30 min at 0 °C, 4 mL (33.6 mmol) of BnBr was slowly added under argon. The reaction was controlled by TLC (EtOAc/Hexane 1:3) and quenched by adding methanol after stirring for 5 h at rt. The reaction crude was purified by CC (EtOAc/Hexane 1:3) to give **25** (2.9 g, 84%) as a white solid, Mp. 86.6-90.8 °C. TLC (EtOAc/Hexane 1:3): Rf=0.40. $[\alpha]_D^{20}$+84 (*c* 5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ in ppm): 7.45 (m, 5H, H-Ar), 6.01 (d, 1H, $J_{1,2}$=3.5Hz, H-1), 4.94 (t, 1H, $J_{4,3}$=$J_{4,5}$=3.7Hz, H-4), 4.75, 4.56 (q, 2H, AB system, J=11.8 Hz, PhCH_2), 4.58, 4.47 (2d, 2H, H-2,3), 4.08-4.02 (ddd, 1H, $J_{5,6}$=7.0Hz, $J_{5,6'}$=8.5Hz, H-5), 3.92-3.88 (dd, 1H, $J_{6,6'}$=8.2Hz, H-6), 3.71-3.66 (m, 1H, H-6'), 1.50, 1.33 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, δ in ppm: 137.3, 128.4, 127.9 (C_6H_5), 112.3 (Me_2C) 107.1 (C-1), 85.5, 85.0, 80.6, 78.5, 72.4, 69.4 (C-2,3,4,5,6 and CH_2Ph), 27.3, 26.6 (Me_2C); Anal. Cald. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.85. Found: C, 65.77; H, 6.83.

1,2-Di-*O*-acetyl-3,6-anhydro-5-*O*-benzyl-α,β-D-glucofuranose (30). Ac_2O (3 mL) and H_2SO_4 (0.3 mL) were added to a solution of 2.85 g (9.79 mmol) of **29** in 30 mL of HOAc. The reaction mixture was stirred at rt until starting material disappeared from the TLC. After 5h it was quenched by adding a mixture of ice and $NaHCO_3$ 5%. After repeated extractions with $CHCl_3$ the resulting mixture of α and β anomers was purified by CC using Hexane/EtOAc 1:3 as eluent. This led to **30** (2.42g, 74%) as a foam; ^{1}H NMR ($CDCl_3$, δ in ppm): 7.27-7.38 (m, 5H, H-Ar), 6.57 (d, 1H, $J_{1,2}$=4.5Hz, H-1α), 6.23 (s, 1H, H-1β), 5.16 (s, 1H, H-2β), 5.14 (dd, 1H, $J_{2,3}$=3.4Hz, H-2α), 4.91 (t, 1H, $J_{4,3}$=$J_{4,5}$=3.4Hz, H-4α), 4.78-4.71 (m, 2H, H-3α, PhCH_2), 4.57-4.55 (t, 1H, H-3β), 4.48 (d, 1H, J_{AB}=11.5 Hz, PhCH_2), 4.12-4.05 (ddd, 1H, $J_{5,6}$=7.3Hz, $J_{5,6'}$=9.0Hz, H-5), 4.01-3.89 (m, 2H, H-6, H-6'), 2.10-2.00 (OAc); ^{13}C NMR ($CDCl_3$, δ in ppm): 169.2 (CO), 137.3 (C-Ar), 128.3, 127.9 (CH-Ar), 100.5, 96.0 (C-1α, 1β), 85.0, 84.3, 83.0, 81.1, 78.7, 77.7, 77.6, 77.1, 72.5, 72.1, 69.9, 68.6 (C-2α,3α,4α,5α,6α, C-2β,3β,4β,5β,6β and CH_2Ph), 20.9, 20.3 (*Me*CO); Anal. Cald. for $C_{17}H_{20}O_7$: C, 60.70; H, 5.94. Found: C, 60.77; H, 5.93.

Glycosylation reaction. General procedure.

The dry solvent dichloroethane or CH_3CN (100 mL of solvent/10 mmol of base) was added under argon to a mixture of the glycosyl donor **30** or **36** and nitrogenated base (1.15 eq/mol) which had been previously activated (by being placed under vacuum for 24 h at 80 °C) BSA (N,O-Bis(trimethylsilyl)acetamide) (1.30 eq/mol of sugar) was added to the stirred suspension and warmed to 70-80 °C. The catalyst $SnCl_4$ or TMSOTf, (1.30 eq/mol of sugar) was added slowly and the solution was stirred for 20-45 minutes approximately and controlled by TLC. The reaction was quenched with a $NaHCO_3$ saturated solution and CH_2Cl_2, and then washed with $NaHCO_3$. For **38** it was quenched with a $NaHCO_3$ saturated solution and EtOAc and

extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and evaporated. The residue was purified by CC or RC.

6-Chloro-9-(2'-*O*-acetyl-3',6'-anhydro-5'-*O*-benzyl-β-D-glucofuranosyl)-purine (31). When the general procedure was applied to carbohydrate **30** (260 mg, 0.77 mmol), 6-chloropurine (137 mg), $Cl_2C_2H_4$ (8.9 mL), BSA (0.25 mL), TMSOTf (0.18 mL), the reaction finished in 40 min. CC and RC (EtOAc/Hexane 1:1, 3:2 and 2:1) gave **31** (219mg, 64%) as a white foam. When using $SnCl_4$, a 1:1 mixture of N-7 and N-9 isomers was obtained. TLC (EtOAc/Hexane 3:2): Rf=0.25. $[\alpha]_D$+56 (*c* 9, $CHCl_3$). UV(MeOH): λ_{max}=264nm; ^{1}H NMR ($CDCl_3$, δ in ppm): 8.75 (s, 1H, H-2), 8.59 (s, 1H, H-8), 7.28 - 7.10 (m, 5H, H-Ar), 6.43 (d, 1H, $J_{1',2'}$=1.7 Hz, H-1'), 5.72 (bd, 1H, H-2'), 5.02 (t, 1H, $J_{4',3'}$=$J_{4',5'}$=4.4 Hz, H-4'), 4.60 (dd, 1H, $J_{3',2'}$=0.9 Hz, H-3'), 4.56 and 4.46 (2d, 2H, AB system, J=11.5Hz, PhCH_2), 4.28-4.22 (m, 1H, H-5'), 3.99 - 3.90 (m, 2H, H-6',6''), 2.15 (s, 3H, MeCO); ^{13}C NMR ($CDCl_3$, δ in ppm): 169.0 (CO), 152.0 (C-2), 144.2 (C-8), 137.8, 128.3, 128.0, 127.6 (CH-Ar), 89.7 (C-1'), 85.6, 84.2, 80.1, 78.1 (C-2', 3', 4', 5'), 72.5, 71.9 (C-6', PhCH_2), 20.6 (*Me*CO). Anal. calcd. for $C_{20}H_{19}N_4ClO_5$: C, 55.76; H, 4.43; N, 13.04. Found: C, 55.73; H, 4.44; N, 13.00.

1-(2'-*O*-Acetyl-3',6'-anhydro-5'-*O*-pivaloyl-β-D-glucofuranosyl)-uracil (37). When the general procedure was applied to carbohydrate **36** (170 mg, 0.51 mmol), uracil (66 mg, 0.58 mmol), CH_3CN (6 mL), BSA (0.17 mL) and TMSOTf (0.12 mL), the reaction finished in 40 min. CC and RC (mixtures of CH_2Cl_2/MeOH) gave **37** (158 mg, 80%) as white crystals, Mp 204-208 °C. TLC(CH_2Cl_2/MeOH 50:1): Rf=0.37. $[\alpha]_D$= 160 (c 0.85, MeOH), $[\alpha]_D^{20}$+ 251 (*c* 8, $CHCl_3$). UV(MeOH): λ_{max}=260nm;IR, 3490, 2976, 2870, 1701, 1698, 1689,1680, 1465, 1409, 1360,1280, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ in ppm): 9.38 (s, 1H, H-3), 7.56 (d, 1H, $J_{6,5}$=8.1 Hz, H-6), 6.17 (d, 1H, $J_{1',2'}$=3.0 Hz, H-1'), 5.80 (d, 1H, H-5), 5.23 (d, 1H, H-2'), 5.21-5.16 (m, 1H, H-5'), 4.92 (dd, 1H, $J_{4',3'}$=3.7, $J_{4',5'}$=5.0 Hz, H-4'), 4.47 (d, 1H, H-3'), 4.15 (dd, 1H, $J_{6',5'}$=7.1, $J_{6',6''}$=10.0 Hz, H-6'), 4.00 (dd, 1H, $J_{6'',5'}$=5.4 Hz, H-6''), 2.14 (s, 3H, MeCO), 1.20 (s, 9H, Me_3C); ^{13}C NMR ($CDCl_3$, δ in ppm): 179.4, 164.7, 161.4, 150.0 (CO), 139.8 (C-6), 103.2 (C-1'), 90.9 (C-5), 85.9, 81.4, 79.6, 73.5 (C-2',3',4',5'), 70.9 (C-6'), 39.5 (Me_3C), 27.0 (Me_3C), 20.6 (*Me*CO). Anal. calcd. for $C_{17}H_{22}N_2O_8$: C, 53.41; H, 5.80; N, 7.33; Found: C, 53.56; H, 5.82; N, 7.31.

N^6-Benzoyl-9-(2'-*O*-acetyl-3',6'-anhydro-5'-*O*-pivaloyl-β-D-glucofuranosyl)-adenine (38). When the general procedure was applied to **36** (524 mg, 1.59 mmol), N^6-benzoyladenine (437 mg, 1.8 mmol), $Cl_2C_2H_4$ (18 mL), BSA (0.5 mL), TMSOTf (0.4 mL), the reaction finished in 45 min. CC (CH_2Cl_2/MeOH 250:1, 100:1 and 50:1) gave **38** (710 mg, 80%) as a white foam. TLC (CH_2Cl_2/MeOH 50:1): Rf=0.29. $[\alpha]_D$+84.2 (*c* 16.8, $CHCl_3$). UV($CHCl_3$): λ_{max}=282nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ in ppm, 9.28 (s, 1H, H-6), 8.78 (s, 1H, H-2), 8.43 (s, 1H, H-8), 8.04 (d, 1H, J_{orto}=7.2 Hz, H-Ar), 7.64-7.49 (m, 3H, H-Ar), 6.44 (d, 1H, $J_{1',2'}$=1.5 Hz, H-1'), 5.71 (bs, 1H, H-2'), 5.21 (ddd, 1H, $J_{5',4'}$=3.7 Hz, $J_{5',6'}$=6.9 Hz, $J_{5',6''}$=5.4 Hz, H-5'), 5.12 (dd, 1H, $J_{4',3'}$=5.1 Hz, H-4'), 4.62 (d, 1H, H-3'), 4.17 (dd, 1H, $J_{6',6''}$=10.2 Hz, H-6'), 4.03 (dd, 1H, H-6''), 2.06 (s, 3H, *Me*CO), 1.01 (s, 9H, Me_3C); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm, 178.0, 169.3, 164.8 (CO), 152.9 (C-2), 141.5 (C-8), 133.4-127.9 (CH-Ar), 89.3 (C-1'), 85.7, 83.0, 80.9, 73.3, 70.6 (C-2',3',4',5',6'), 38.4 (Me_3C), 26.6 (Me_3C), 20.5 (*Me*CO). Anal. calcd. for $C_{25}H_{27}N_5O_7$: C, 58.94; H, 5.30; N, 13.75. Found: C, 58.78; H, 5.29; N, 13.77.

9-(5'-O-Benzyl-3',6'-anhydro-β–D-glucofuranosyl)-inosine (32). To a solution of 195 mg, (0.43 mmol) of **31** in MeOH (23 mL) were added 0.11 mL (1.90 mmol) of mercaptoethanol and 1.65 mL of MeONa (1N in MeOH) freshly prepared. After stirring for 4 h at 65 °C, TLC showed complete disappearance of the starting material. The reaction mixture was neutralized with HOAc and then concentrated. The crude product was purified by CC (CH_2Cl_2/MeOH 20:1) to give **32** (141 mg, 87%) as a white solid: Mp 119.2-120.4 °C (from MeOH/CH_2Cl_2). TLC (CH_2Cl_2/MeOH 20:1): Rf=0.20. $[\alpha]_D$ +160 (*c* 5.6, MeOH). UV (MeOH): λ_{max}=246 nm; IR, 3258, 3130, 2950, 1687, 1586, 1546, 1204, 1074 cm^{-1}; ^1H NMR (CD_3OD, δ in ppm): 8.36 (s, 1H, H-2), 8.03 (s, 1H, H-8), 7.25-7.23 (m, 5H, H-Ar), 6.20 (d, 1H, $J_{1',2'}$=1.2 Hz, H-1'), 5.05 (t, 1H, $J_{3',4'}=J_{4',5'}$=4.5 Hz, H-4'), 4.80 (d, 1H, H-2'), 4.64 (d, 1H, J_{AB}=11.4 Hz, H-7'), 4.49 (d, 1H, H-7''), 4.49 (dd, 1H, $J_{2',3'}$=1.2 Hz, H-3'), 4.34-4.28 (m, 1H, H-5'), 3.93 (dd, 1H, $J_{5',6'}$=6.6 Hz, $J_{6',6''}$=9.6 Hz, H-6'), 3.78 (dd, 1H, $J_{5',6''}$=4.8 Hz, H-6''); ^{13}C NMR (CD_3OD/$CDCl_3$ 1:1, δ in ppm): 146.2 (C-2), 140.1 (C-8), 129.0-128.6 (CH-Ar), 93.5 (C-1'), 89.1, 85.2, 82.3, 79.6 (C-2', C-3', C-4', C-5'), 73.2, 72.1 (C-6', C-7'). Anal. Calcd. for $C_{18}H_{18}N_4O_5$: C, 58.38%; H, 4.86%; N, 15.12%. Found: C, 58.21%; H, 4.87%; N, 15.10%.

Selective deprotection of O-acetyl groups of compounds 37 and 38. General method. The acetylated compound **37** or **38** was dissolved in MeOH/NH_3 (10-20% in NH_3) and stirred at room temperature for 50 min - 3 h. The reaction was controlled by TLC. After quenching the reaction by evaporation under reduced pressure, the residue was purified by CC or RC.

1-(3',6'-Anhydro-5'-*O*-pivaloyl-β–D-glucofuranosyl)-uracil (39). When the general method was applied to compound **37** (745 mg, 1.95 mmol), 25mL of MeOH/NH_3 (20% in NH_3), RC (CH_2Cl_2/MeOH 20:1) gave **39** (659 mg, 99%) as white crystals, Mp 210-212. TLC (CH_2Cl_2/MeOH 20:1): Rf=0.27. $[\alpha]_D$ +177 (*c* 4, $CHCl_3$). UV(MeOH): λ_{max}=270nm; IR, 3466, 3130, 2980, 2885, 1700, 1693, 1622, 1468, 1413, 1393, 1260, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, δ in ppm): 10.28 (s, 1H, H-3), 7.77 (d, 1H, $J_{6,5}$=8.1 Hz, H-6), 5.86 (s, 1H, H-1'), 5.71 (d, 1H, H-5), 5.32-5.25 (m, 1H, H-5'), 5.13 (dd, 1H, $J_{4',3'}$=3.0, $J_{4',5'}$=5.1 Hz, H-4'), 4.51 (s,1H, H-2'), 4.41 (d,1H, H-3'), 4.10 (dd, 1H, $J_{6',5'}$=7.5 Hz, $J_{6',6''}$=10.5 Hz, H-6'), 3.90 (dd, 1H, $J_{6'',5'}$=3.9 Hz, H-6''), 1.23 (s, 9H, Me_3C); ^{13}C NMR ($CDCl_3$, δ in ppm): 179.5, 162.0, 150.5 (CO), 139.7 (C-6), 101.7 (C-1'), 95.8 (C-5), 87.6, 84.1, 79.3, 74.5 (C-2', 3', 4', 5'), 71.7 (C-6'), 38.5 (Me_3C), 27.0 (Me_3C). Anal. calcd. from $C_{15}H_{20}N_2O_7$: 52.94; H, 5.88; N, 8.23. Found: C, 53.04; H, 5.90; N, 8.20.

N^6-Benzoyl-9-(3',6'-anhydro-5'-*O*-pivaloyl-β-D-glucofuranosyl)-adenine (40). When the general method was applied to compound **38** (575 mg, 1.13 mmol), 20 mL of MeOH/NH_3 (10% in NH_3), RC (mixtures of CH_2Cl_2/MeOH) gave of **40** (446 mg, 84%) as a white foam. TLC (CH_2Cl_2/MeOH 20:1): Rf=0.56. $[\alpha]_D^{20}$+116 (*c* 10.4, $CHCl_3$). UV(MeOH): λ_{max}=280nm; ^1H NMR ($CDCl_3$, δ in ppm): 9.37 (s, 1H, H-6), 8.60 (s, 1H, H-2), 8.38 (s, 1H, H-8), 7.94 (d, 2H, J_{orto}=7.2 Hz, H-Ar), 7.58-7.43 (m, 3H, H-Ar), 6.26 (d, 1H, $J_{1',2'}$=2.1 Hz, H-1'), 6.20 (s, 1H, OH), 5.19-5.07 (m, 2H, H-4', H-5'), 4.93 (bs, 1H, H-2'), 4.59 (d, 1H, $J_{3',4'}$=3.6 Hz, H-3'), 4.09 (dd, 1H, $J_{6',5'}$=6.6, $J_{6',6''}$=10.2 Hz, H-6'), 3.90 (dd, 1H, $J_{6'',5'}$=5.4 Hz, H-6''), 1.08 (s, 9H, $(CH_3)_3$); ^{13}C RMN ($CDCl_3$, δ in ppm): 178.1, 165.0 (CO) 152.5 (C-2), 141.7 (C-8), 133.3-127.9 (CH-Ar), 92.7 (C-1'), 87.9, 82.3, 79.6, 73.4, 70.1 (C-2',3',4',5',6'), 38.5 (Me_3C), 26.8 (Me_3C). Anal. calcd. from $C_{23}H_{25}N_5O_6$: C; 59.10; H, 5.35; N, 14.99. Found: C, 59.25; H, 5.36; N, 14.95.

Synthesis of 2'-deoxy-derivatives 33, 41 and 42 by reductive deoxygenation. Genera procedure.

A. **Formation of 2'-*O*-(phenoxythiocarbonyl)-derivatives.** DMAP (0.5 eq/mol) an PhOCSCl (2 eq/mol) were added under argon to a stirred solution of **32**, **39** or **40** in dr CH_3CN or $Cl_2C_2H_4$ (10 mL of solvent/1 mmol of nucleoside). The mixture was stirred fo 40 min-4 h. The reaction mixture was evaporated to dryness and the resultant residue wa partitioned with EtOAc/H_2O and washed with HOAc 1N and NaCl solution. The organi layer was dried with Na_2SO_4 and evaporated. The resultant foam was purified by CC o used without purification in the deoxygenation reaction.

B. **Deoxygenation reaction.** AIBN (35 mg/mmol) and *n*-Bu_3SnH (2.3 eq/mmol) were adde to a stirred solution of the thiocarbonate in dry toluene (previously deoxygenated witl argon). The reaction was carried out in refluxing toluene and controlled by TLC. Th solvent was evaporated and the residue purified by CC or RC.

9-(3',6'-Anhydro-5'-*O*-benzyl-2'-deoxy-β–D-glucofuranosyl)-inosine (33). The genera procedure for the formation of 2'-*O*-(phenoxythiocarbonyl)-derivatives was applied to **32** (10 mg, 0.27 mmol), CH_3CN (2.8 mL), PhOCSCl (0.07 mL), DMAP (120 mg). After FC (CH_2Cl_2/MeOH 50:1, 20:1) of the 2'-*O*-(phenoxythiocarbonyl)-derivative (88 mg, 64%) wa obtained as a foam. TLC (CH_2Cl_2/MeOH 20:1): Rf=0.44. When applying the deoxygenatio procedure to the 2'-*O*-(phenoxythiocarbonyl)-derivative (88mg, 0.17mmol), toluene (1.4mL) AIBN (6.0mg), *n*-Bu_3SnH (0.1mL, 0.38mmol) the reaction finished in 3.5h. The CC and RC (CH_2Cl_2/MeOH 50:1, 25:1, 10:1) gave of **33** (26 mg, 42%) as a foam. TLC (EtOAc/EtOH 40:1): Rf=0.08. $[\alpha]_D$ +58.4 (*c* 26, MeOH). UV(MeOH): λ_{max}=250nm; IR, 3388, 2929, 2867 1691, 1586, 1210, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, δ in ppm): 8.39 (s, 1H, H-2), 8.21 (s, 1H, H-8) 7.28-7.18 (m, 5H, Ar), 6.50 (m, 1H, H-1'), 4.79 (t, 1H, $J_{5',4'}$=$J_{5',6'}$=4.5 Hz, H-5'), 4.74-4.69 (m 2H, H-6', H-6''), 4.59, 4.43 ("q", 2H, AB system, J_{AB}=11.7 Hz, PhCH_2), 4.22-4.19 (m, 1H, H 4'), 3.89 (d, 1H, $J_{3',4'}$=6.0 Hz, H-3'), 2.80-2.75 (m, 2H, H-2',2''); ^{13}C NMR ($CDCl_3$, δ in ppm) 145.0 (C-2), 139.4 (C-8), 128.2-127.4 (CH-Ar), 85.7 (C-1'), 84.7, 82.6, 78.6 (C-3',4',5'), 72.2 71.9 (C-6', Ph*C*H_2), 36.7 (C-2'). Anal. calcd. from $C_{18}H_{18}N_4O_4$: C, 61.02; H, 5.07; N, 15.82 Found: C, 61.10; H, 5.08; N, 15.86.

1-(3',6'-Anhidro-2'-deoxy-5'-*O*-pivaloyl-β-D-glucofuranosyl)-uracil (41). The genera procedure for the formation of 2'-*O*-(phenoxythiocarbonyl)-derivatives was applied to **39** (60 mg, 1.76 mmol), CH_3CN (17.6 mL), PhOCSCl (0.5 mL) and DMAP (108 mg). To th resultant foam (used without purification) the deoxygenation general method was applied toluene (14 mL), AIBN (61 mg) and *n*-Bu_3SnH (1 mL). The CC (mixtures of CH_2Cl_2/MeOH gave **41** (460 mg, 80%) as white crystals, Mp 199-200 °C (from $CHCl_3$/Pentane); $[\alpha]_D$ +159 (c 4, $CHCl_3$). TLC (CH_2Cl_2/MeOH 25:1): Rf=0.25. UV(MeOH): λ_{max}=262nm; IR, 3151, 3110 3021, 2975, 1730, 1727, 1706, 1682, 1470, 1268, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, δ in ppm); 9.9 (s, 1H, H-3), 7.83 (d, 1H, $J_{6,5}$=8.4 Hz, H-6), 6.32 (dd, 1H, $J_{1',2''}$=8.1, $J_{1',2'}$=3.0 Hz, H-1'), 5.78 (d 1H, H-5), 5.20-5.18 (m, 1H, H-5'), 4.79 (dd, $J_{4',3'}$=3.6, $J_{4',2''}$=5.7 Hz, 1H, H-4'), 4.59-4.57 (m 1H, H-3'), 4.11-4.01 (m, 2H, H-6', H-6''), 2.72 (ddd, 1H, $J_{2'',2'}$=15.6, $J_{2'',3'}$=5.3 Hz, H-2''), 2.31 (dd, 1H, H-2'), 1.19 (s, 9H, Me_3C); ^{13}C NMR ($CDCl_3$, δ in ppm); 179.0, 163.9, 150.7 (CO) 140.6 (C-6), 102.1 (C-1'), 87.2 (C-5), 83.7, 83.0, 74.1, 71.8 (C-3',4',5',6'), 38.1 (C-2'), 38.5 (Me_3C), 26.9(*Me*$_3$C). Anal. calcd. from $C_{15}H_{20}N_2O_6$: C, 55.56; H, 5.17; N, 8.64. Found: C 55.54; H, 5.18; N, 8.64.

N^6-Benzoyl-9-(3',6'-anhydro-2'-deoxy-5'-*O*-pivaloyl-β-D-glucofuranosyl)-adenine (42). The general procedure for the formation of 2'-*O*-(phenoxythiocarbonyl)-derivatives was applied to **40** (70 mg, 0.15 mmol), $Cl_2C_2H_4$ (1.6 mL), DMAP (66 mg), PhOCSCl (0.04 mL). The resultant foam was used in the deoxygenation reaction without purification. From the 2'-*O*-(phenoxythiocarbonyl)-derivative, toluene (1.2 mL), AIBN (5 mg) and *n*-Bu_3SnH (0.09 mL) the general deoxygenation procedure was applied. The CC and RC (mixtures of CH_2Cl_2/MeOH) gave **42** (42 mg, 63%) as a foam. TLC (CH_2Cl_2/MeOH 25:1): Rf=0.16. $[\alpha]_D$ +136.4 (*c* 7.1, MeOH). UV(MeOH): λ_{max}=280nm; IR, 3391, 3104, 2970, 1740, 1710, 1642, 1461, 1250, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, δ in ppm): 9.27 (s, 1H, H-6), 8.80 (s, 1H, H-2), 8.62 (s, 1H, H-8), 8.04 (d, 2H, J_{orto}=6.9 Hz, H-Ar), 7.64-7.51 (m, 3H, H-Ar), 6.67 (dd, 1H, $J_{1',2''}$=7.5, $J_{1',2'}$=2.4 Hz, H-1'), 5.23-5.16 (m, 1H, H-5'), 4.97 (dd, 1H, $J_{4',5'}$=5.4, $J_{4',3'}$=3.9 Hz, H-4'), 4.76-4.74 (m, 1H, H-3'), 4.12-4.01 (m, 2H, H-6',6''), 2.92-2.78 (m, 2H, H-2',2''), 0.98 (s, 9H, Me_3C); ^{13}C NMR ($CDCl_3$, δ in ppm): 179.1 (CO), 152.7 (C-2), 142.2 (C-8), 132.7-127.8 (CH-Ar), 85.3 (C-1'), 84.6, 83.2, 74.1, 71.7 (C-3',4',5',6'), 38.50 (C-2'), 38.5 (C-2', Me_3C), 26.5 (Me_3C). Anal. calcd. from $C_{23}H_{25}N_5O_5$: C, 61.20; H, 5.54; N, 15.52. Found: C, 61.33; H, 5.56; N, 15.55.

9-(3',6'-Anhydro-2'-deoxy-β-D-glucofuranosyl)-adenine (43). A 0.2M solution of **42** (125 mg, 0.27 mmol) in a concentrated aqueous NH_3 solution was heated for 8 h to 55-60 °C. After cooling and evaporation, the residual crude product was purified by RC (CH_2Cl_2/MeOH 10:1) and then recrystallized (from MeOH/Et_2O/mixtures of alcanes) to give **43** (50 mg, 67%) as white crystals, Mp 176.6-178.2 °C. TLC (CH_2Cl_2/MeOH 5:1): Rf=0.6. $[\alpha]_D$ +19.4 (*c* 3.1, MeOH). UV(MeOH): λ_{max}=262nm; IR 3405, 3394, 3001, 2870, 1668, 1580, 1420 cm^{-1}; ^1H NMR (CD_3OD, δ in ppm): 8.48 (s, 1H, H-2), 8.20 (s, 1H, H-8), 6.51 (dd, 1H, $J_{1',2''}$=7.8, $J_{1',2'}$=3.3 Hz, H-1'), 4.80-4.76 (m, 1H, H-3'), 4.66-4.63 (m, 1H, H-4'), 4.41 (ddd, 1H, $J_{5',4'}$=5.0, $J_{5',6'}$=6.45, $J_{5',6''}$=6.1 Hz, H-5'), 3.93 (dd, 1H, $J_{6',6''}$=9.1 Hz, H-6'), 3.68 (dd, 1H, H-6''), 2.85 (ddd, 1H, $J_{2'',3'}$=5.5, $J_{2'',2'}$=15.1 Hz, H-2''), 2.72 (ddd, 1H, $J_{2',3'}$=1.5 Hz, H-2'); ^{13}C NMR (CD_3OD, δ in ppm): 157.5 (C-2), 141.7 (C-8), 87.1 (C-1'), 84.1, 73.9, 49.4 (C-3',4',5'), 73.9 (C-6'), 39.7 (C-2'). Anal. calcd. from $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.94; N, 26.62. Found: C, 50.11; H, 4.95; N, 26.60.

1-(3',6'-Anhydro-2'-deoxy-β-D-glucofuranosil)-uracil (44). 100 mg (0.31 mmol) of compound **41** were dissolved in 10 mL of MeOH and treated with Amberlite IRA- 402 basic resin, and stirred at rt for 16 h. After neutralizing with AcOH, the residue was concentrated to dryness and purified by CC (CH_2Cl_2/MeOH 20:1) to give **44** (quantitative) as a foam. TLC (CH_2Cl_2/MeOH 10:1): Rf=0.2 (CH_2Cl_2/MeOH 15:1). $[\alpha]_D$ +56.6 (*c* 5.6, MeOH). UV(MeOH): λ_{max}=270nm. IR 3438, 3401, 3140, 3124, 2942, 1732, 1662, 1475, 1390, 1275 cm^{-1}; ^1H NMR (CD_3OD, δ in ppm): 8.11 (d, 1H, $J_{6,5}$=8.1 Hz, H-6), 6.30 (dd, 1H, $J_{1',2''}$=7.9, $J_{1',2'}$=3.7 Hz, H-1'), 5.71 (d, 1H, H-5), 4.64-4.61 (m, 1H, $J_{3',4'}$=3.9 Hz, H-3'), 4.52-4.43 (m, 2H, H-4',5'), 3.95 (dd, 1H, $J_{6',5'}$=6.3, $J_{6',6''}$=9.0 Hz, H-6'), 3.75 (dd, 1H, $J_{6'',5'}$=5.7 Hz, H-6''), 2.69 (ddd, 1H, $J_{2'',3'}$=6.0, $J_{2'',2'}$=15.0 Hz, H-2''), 2.25 (dd, 1H, H-2'); ^{13}C NMR (CD_3OD, δ in ppm): 143.6 (C-6), 102.5 (C-5), 88.7 (C-1'), 86.2, 83.9, 74.0, 73.5 (C-3',4',5',6'), 39.1 (C-2'). Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00%; H, 5.00%; N, 11.69%. Found: C, 50.09%, H, 4.99%, N, 11.69%.

1-(3',6'-Anhydro-2'-deoxy-β-D-glucofuranosyl)-cytosine (46). 1-mesyl-3-nitro-1,2,4-triazole (MSNT) (433 mg, 1.46 mg) and diphenyl phosphate (35.5 mg, 0.14 mmol) were added to a solution of **41** (102 mg, 0.31 mmol) in dry pyridine (1.5 mL). The reaction mixture was stirred for 8h. After concentrating to dryness the residue was purified by FC and RC using mixtures of CH_2Cl_2 and MeOH, to give 16 mg of starting material and **45** (74 mg, 66%) as solid. **45** was treated with MeOH/NH_4OH conc. for 3 days, after CC (CH_2Cl_2/MeOH 20:1 10:1) resulted in **46** (38 mg, 91%), as white crystals, Mp 216-218° C (from MeOH/Et_2O). TLC (CH_2Cl_2/MeOH 10:1): Rf=0.14. $[\alpha]_D$ +116.4 (*c* 1.2, MeOH). UV(MeOH): λ_{max}=272nm. IR 3380, 3117, 3072, 1656, 1606, 1478, 1366, 1136 cm^{-1}; ^1H NMR (CD_3OD, δ in ppm): 8.16 (d, 1H, $J_{6,5}$=7.5 Hz, H-6), 6.24 (dd, 1H, $J_{1',2''}$=7.6, $J_{1',2'}$=3.7 Hz, H-1'), 5.90 (d, 1H, H-5), 4.58 (dd, 1H, $J_{3',2''}$=5.6, $J_{3',2'}$=1.5, $J_{3',4'}$=3.9 Hz, H-3'), 4.54-4.44 (m, 2H, H-4', H-5'), 3.94 (dd, 1H, $J_{6',5'}$=6.6, $J_{6',6''}$=9.0 Hz, H-6'), 3.72 (dd, 1H, $J_{6'',5'}$=6.0 Hz, H-6''), 2.70 (ddd, 1H, $J_{2'',2'}$=15.0 Hz, H-2''), 2.18 (ddd, 1H, H-2'); ^{13}C NMR (CD_3OD, δ in ppm): 143.4 (C-6), 95.9 (C-5), 89.8 (C-1'), 86.2, 84.2, 73.7 (C-3',4', 5'), 74.2 (C-6'), 40.2 (C-2'). Anal. calcd. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.44; N, 17.57. Found: C, 50.18; H, 5.45; N, 17.53.

Acknowledgements. We thank the Ministerio de Educación y Cultura (MEC) for financial support. P.M. Thanks MEC for a grant. Authors thanks Dr. G. Gosselin (U. Montpellier II) for suggestions and for facilitating the perfomance of the biological testing. Thanks are given to the Servei de Recursos Científics (URV) for its support.

REFERENCES

1 Mitsuya, H.; Yarchoan, R.; Broder S. *Science*, **1990**, 249, 1533.

2 a) Bolli, M.; Leumann, C. *Angew. Chem. In. Ed. Engl.* **1995**, 34, 694. b) Tarkoy, M.; Bolli, M.; Leumann, C. *Helv. Chim. Acta.* **1994**, 77, 716. c) Tarkoy, M.; Bolli, M.; Schweizer, M.; Leumann, C. *Helv. Chim. Acta.* **1993**, 76 481. d) Altmann, K-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, 34, 4881.

3 a) Van Roey, P.; Taylor, E. W.; Chu, C. K.; Schinazi, R. F. *Ann. NY Acad. Sci.* **1990**, 616, 29. b) Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *Antiviral Chem. Chemother.* **1990**, 1,163.

4 a) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Barchi Jr, J. J. *Tetrahedron Lett.* **1993**, 34, 6233. b) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi Jr, J. J. *J. Med. Chem.* **1994**, 37, 3389.

5 a) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.*, **1989**, 30, 2203. b) Beard, A. R.; Butler, P. I. Mann, J.; Partlett, N. K. *Carbohyd. Res.*, **1990**, 205, 87.

6 Webb, T. R.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1988**, 31, 1475.

7 Counde, O-Y.; Kurz, W.; Eugui, E. M.; Mc Roberts, M. J.; Verheyden, J. H. P.; Kurz, L. J.; Walker, K. A. M. *Tetrahedron Lett.*, **1992**, 33, 41.

8 Bjorsne, M.; Szabó, T.; Samuelsson, B.; Classon, B. *Bioorg. Med. Chem.* **1995**, 3, 397.

9 Chao, Q.; Zhang, J.; Pickering, L.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1998**, 54, 3113.

10 Herdewijn, P. *Liebigs Ann.* **1996**, 1337.

11 Hrebabecky, H.; Dockal, J.; Holy, A. *Collect. Czech. Chem. Commun.* **1994**, 59, 1408.

12 a) Tronchet, J. M.; Zsély, M.; Capek, K.; Komaromi, I.; Geoffroy, M.; De Clercq, E.; Balzarini, J. *Nucleosides Nucleotides*, **1994**, 13(9), 1871. b) Tronchet, J. M.; Zsély, M.; Sultan, N. *Nucleosides Nucleotides*, **1994**, 13(10), 2071.

13 Stoss, P.; Kaes, E. *Nucleosides Nucleotides* **1980**, 2, 213.

14 a) Pickering, L.; NAir, V. *Nucleosides Nucleotides* **1997**, 16, 1435. b) Pickering, L.; Nair, V. *Nucleosides Nucleotides* **1996**, 15, 1751.

15 Zou, R.; Matteucci, M. D. *Tetrahedron Lett.*, **1996**, 37(7), 941.

16 a) Calvo-Flores, F. G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Santoyo- González, F. *J. Org. Chem.*, **1997**, 62, 3944. b) Calvo-Asín, J.A.; Calvo-Flores, F.G.; Exposito-López, J.M.; Hernández-Mateo, F.; García-López, J.J.; Isac-García, J.; Santoyo-González, F.; Vargas-Berenguel, A. *J. Chem. Soc., Perkin. Trans. 1* **1997**, 1079. c) Vargas-Berenguel, A.; Santoyo-González, F.; Calvo-Asín, J.A.; Calvo-Flores F.G.; Exposito-López J.M.; Hernández-Mateo F.; Isac-García J.; Giménez-Martínez J.J. *Synthesis*, **1998**, 1778. d) Isac-García, J.; Calvo-Flores, F. G.; Hernández-Mateo, F.; Santoyo-González, F. *Chem. Eur. J.* **1999**, 5, 1512.

17 Fuentes, J.; Angulo, M.; Pradera, M.A. *Tetrahedron Lett.* **1998**, 39, 7149.

18 Gourlain, T.; Wadouachi, A.; Beaupère, D. *Synthesis* **1999**, 290.

19 a) Köll, P.; John, H. G.; Kopf, J. *Liebigs Ann. Chem.* **1982**, 639. b) Köll, P.; Komander, H.; Meyer, B. *Liebigs Ann. Chem.* **1983**, 1310.

20 a) Kim, K.S.; Joo, Y.H.; Kim, I.W.; Lee, K.R.; Cho, D.Y.; Kim, M.; Cho, I.H. *Synth. Commun.* **1994**, 24, 1157.

21 Mootoo, D.R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1570. b) Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A.R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, 33, 3607. c) Yang, B.-H.; Jiang, J.-Q.; Ma, K.; Wu, H.-M. *Tetrahedron Lett.* **1995**, 36, 2831. d) Beauchamp, T.J.; Powers, J.P.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **1995**, 117, 12873.

22 a) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis*, **1981**, 396. b) Kocienski, P. J. in *Protecting Groups*, Thieme, **1994**, 46. c) Greene, T. W. in *Protective Groups in Organic Synthesis*, John Wiley & Sons, **1981**, 29:31. d) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron*, **1986**, 42(11), 3021.

23 a) Ikemoto, N.; Schreiber, S.L. *J. Am. Chem. Soc.*, **1992**, 114, 2524. b) Oikawa, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.*, **1985**, 26, 1541. c) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.*, **1986**, 27, 3647.

24 a) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.*, **1987**, 28(33), 3823. b) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.*, **1989**, 54, 1346. c) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett*, **1993**, 663.

25 a) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.*, **1983**, 105, 4059. b) Génu Dellac, C.; Gosellin, G.; Imbach, J.-L. *Tetrahedron Lett.*, **1991**, 32(1), 79. c) Robins, M. J Madej, D.; Hansske, F.; Wilson, J. S.; Gosselin, G.; Bergogne, M.-C.; Imbach, J.-L Balzarini, J.; De Clercq, E. *Can. J. Chem*, **1988**, **66**, 1258.

26 a) Jones, S. S.; Rayner, C. B.; Reese, C. B.; Ubasawa, A.; Ubasawa, M. *Tetrahedron* **198** 36, 3075. b) Reese, C. B.; Ubasawa, A.; *Tetrahedron Lett.* **1980**, 21, 2265. c) Divakar, K J.; Reese, C. B. *J. Chem. Soc. Perkin 1*, **1982**, 1171.

27 a) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, 94, 8205. b) Altona, C Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, 95, 2333.