# Synthesis of 2-Carbamoylmethyl-6-β-D-ribofuranosylpyridine with the Aid of a Pd(0)-Catalyzed Reaction



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**Dedicated to the memory of Dr. Roland K. Robins**

D-Allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-ethoxycarbonylmethylpyridine was synthesized from 2-bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine or 2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine by means of a tetrakis(triphenylphosphine)palladium(0)-catalyzed reaction with Reformatsky's reagent. Subsequent ammonolysis and mesylation of the D-altro-ethoxycarbonylmethyl compound gave D-altro-2-carbamoylmethyl-6-(1-*O*-mesyl-2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine which was cyclized to 2-carbamoylmethyl-6-β-D-ribofuranosylpyridine.

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## Introduction.

2-Carbamoyl-6-β-D-ribofuranosylpyridine [1], 3-carbamoyl-5-β-D-ribofuranosylpyridine [2] and 4-carbamoyl-2-β-D-ribofuranosylpyridine [3] have been shown to be mildly cytostatic agents. However 2-carbamoyl-5-β-D-ribofuranosylpyridine [4] was inactive. From these results it seems that biological activity is highly dependent upon the position of the carbamoyl function relative to the D-ribofuranosyl moiety. In order to get more insight in the *in vitro* structure-activity relationship of this particular class of compounds the synthesis of 2-(carbamoylmethyl)-6-β-D-ribofuranosylpyridine (**3**) was planned as is shown in Scheme 1. In this compound the carbamoyl group is disconnected from the pyridine ring by a methylene spacer. As a consequence both electronic and sterical properties are changed significantly.

## Results and Discussion.

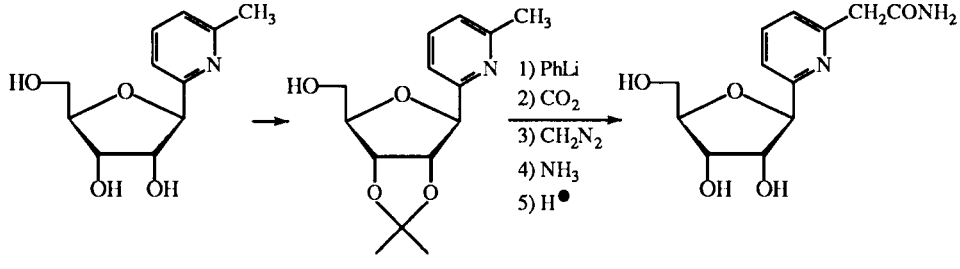
The strategy depicted in Scheme 1 relied on the selective metallation of the methyl group in **2**. Existing methodology was used for the preparation of **1** and **2** [5].

Since the crucial step in Scheme 1 is the lithiation-carboxylation procedure, the conversion of methyl to carbamoylmethyl was first studied on 2-picoline. If the metallation was performed with the aid of phenyllithium at room temperature, 2-carbamoylmethylpyridine was obtained in 31% overall yield. We found that this yield could be increased to (62%) *via* the use of lithium tetramethylpiperidide in 1,2-dimethoxyethane at -78° instead of phenyllithium in diethyl ether at room temperature.

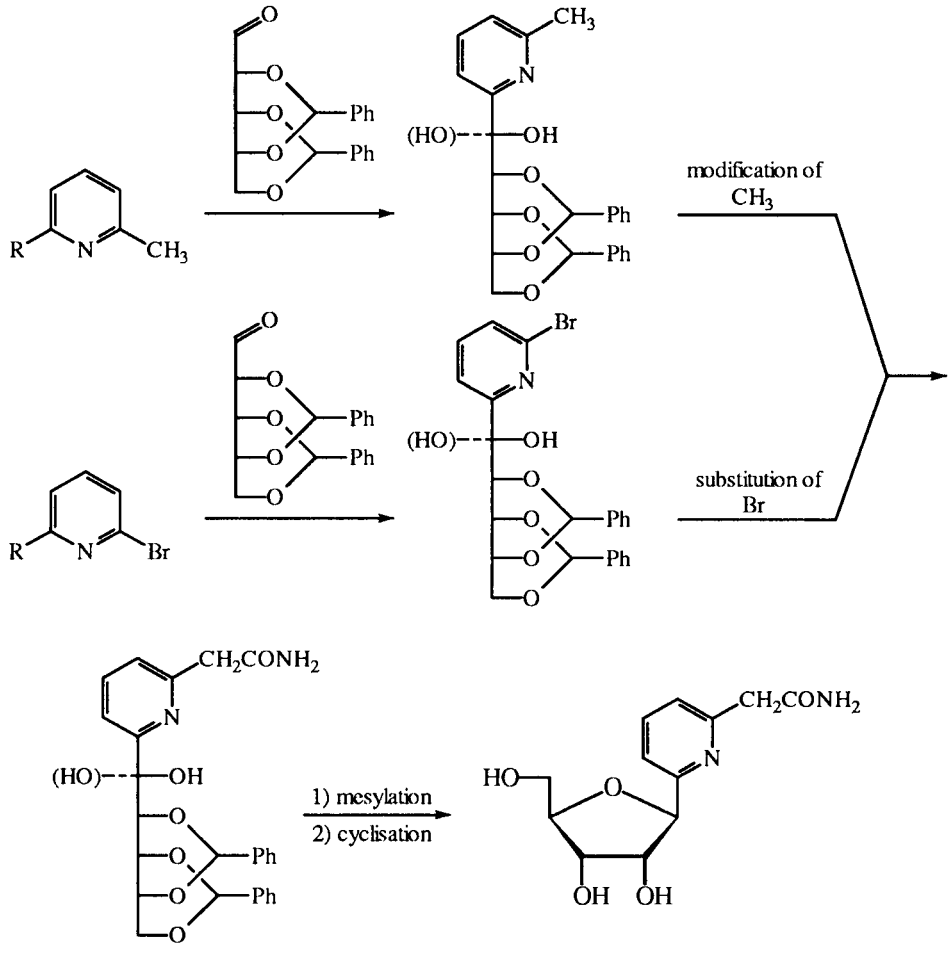
However treatment of the 2',3'-*O*-isopropylidene derivative **2** with lithium tetramethylpiperidide or phenyllithium under identical conditions resulted only in the elimination of acetone and consequently a double bond at C-1' and C-2' was formed [6]. Therefore, an alternative procedure outlined in Scheme 2 was investigated. Preparation of the appropriate pyridine derivative, **4** or **5**, followed by reaction with 2,4:3,5-di-*O*-benzylidene-aldehydo-D-ribose **6** leads to a D-allo/D-altro mixture of **7** or **8** [1,5]. Modification or substitution of the group R should lead to **9** which could then be cyclized after mesylation [5] to the corresponding D-ribofuranosyl compound **3**β.

Consequently, D-allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-methylpyridine (**7**) was treated with 2.2

**Scheme 1 Hypothetical Route to the Title Compound**



**Scheme 2**




equivalents of phenyllithium in diethyl ether at room temperature in an attempt to metallate the 6-methyl group. After 30 minutes the reaction mixture was quenched with dry ice. If the standard work-up procedure was followed [1] the expected D-allo/D-altro-methoxycarbonylmethyl adduct was found to be absent indicating the failure of the metallation-carboxylation sequence. In order to understand this phenomenon, the lithiation-carboxylation reaction as well as the isolation procedure were slightly altered (see Experimental): the reaction mixture was neutralized with 0.1 hydrochloric acid, concentrated *in vacuo* and the residue was analyzed.

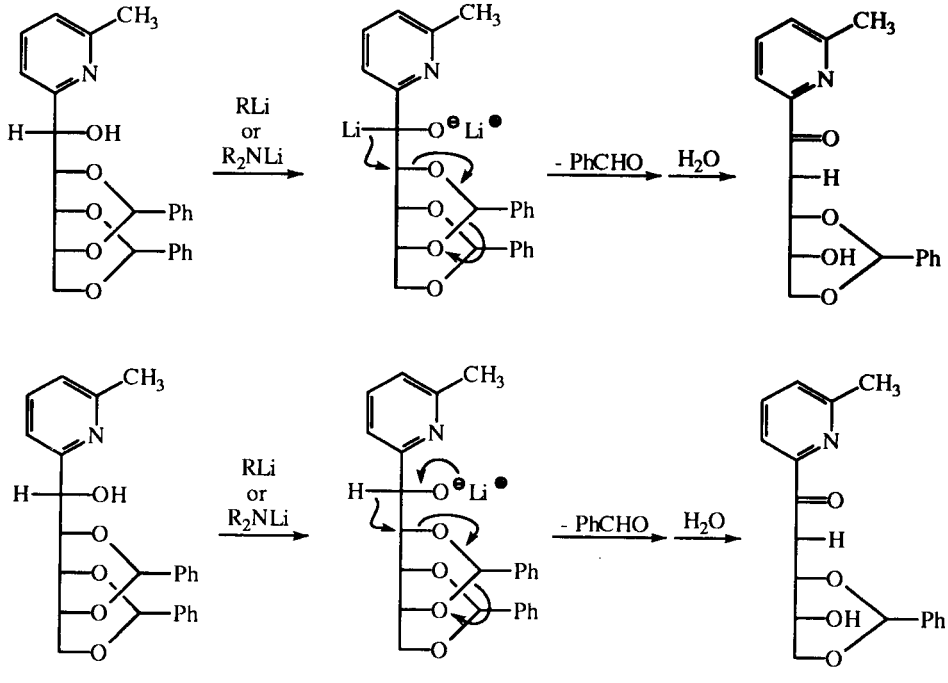
Two compounds were isolated: 60% starting material and 33% of a compound which was identified as (3*S*,4*R*)-2-(3,5-*O*-benzylidene-1-oxo-3,4,5-trihydroxy-1-pentyl)-6-methylpyridine (**9**). The formation of the latter compound can be explained by a proton abstraction on C-1′ followed by the elimination of a molecule of benzaldehyde out of the geminal dilithio compound. In this context we would like to emphasize that the formation of such geminal dilithio compounds is not unusual [7] although a second mechanism involving a hydride shift cannot be excluded. Both mechanisms are shown in Scheme 3.

The same compound **9** was obtained when lithium tetramethylpiperidide in 1,2-dimethoxyethane was used.

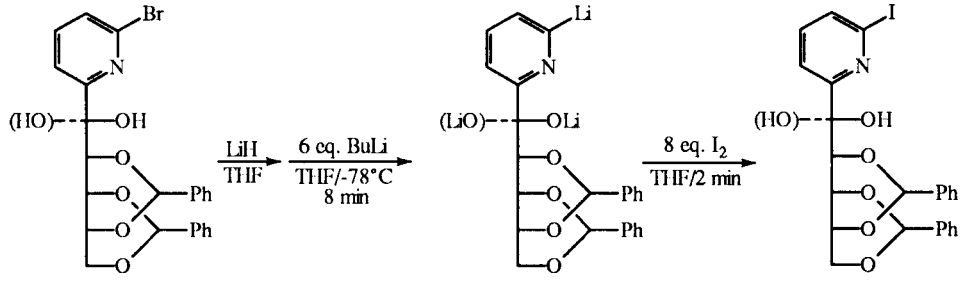
Since this route was not successful we turned to D-allo/D-altro-2-bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-pyridine (**8**) aiming at a methodology based on a nucleophilic displacement reaction of the bromo atom by a $CH_2$-COOEt nucleophile. For this purpose we considered the use of nucleophiles such as lithio ethyl acetate or lithio ethyllithium malonate. However, the yield of the reaction between 2-bromopyridine and sodio diethyl ethylmalonate (*ca.* 19%) did not encourage us to explore this pathway in detail [8].

Instead we decided to explore the Pd-catalyzed substitution of the bromo atom on C-6 in (**8**) with ethoxycarbonylmethyl zinc bromide (**10**). This approach was inspired by the work of Yamanaka *et al.* who studied the Pd-catalysed

**Scheme 3**




**Scheme 4**




"cross-coupling" reaction of halogenated pyrimidines and ethoxycarbonylmethyl zinc bromide [9]. From their experimental data it could be concluded that the iodine derivatives were more reactive than the corresponding bromo- or chloro analogs and that tetrakis(triphenylphosphine)palladium(0) was the catalyst of choice. Since Yamanaka *et al.* assumed that these results were valid for other *N*-heterocycles, only iodopyridines were investigated as substrates.

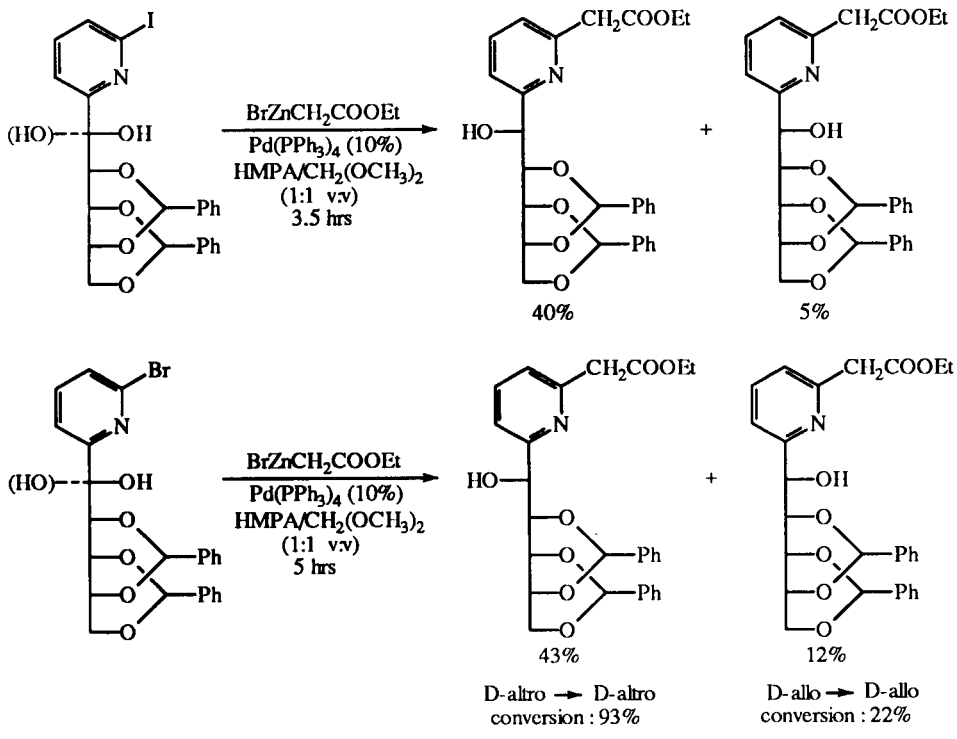
To verify this assumption, D-allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine (**11**) was synthesized starting with 2-bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**8**) (Scheme 4).

The latter compound – as D-allo/D-altro mixture – was treated with 1 equivalent of lithium hydride in tetrahydrofuran for 30 minutes which led to the formation of the lithium salt of the C$_1'$-hydroxyl function. In this way, a defunctionalisation reaction was avoided which is possible if compounds with a free hydroxyl function are used in a Wittig-Gillman reaction [10,11]. The solution was cooled to -78° prior to the addition of 6 equivalents of butyllithium. After 8 minutes the reaction mixture was treated with a large excess of iodine in tetrahydrofuran. After work-up and purification by circular centrifugal preparative layer chromatography, D-allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine (**11**) was isolated in 45 to 50% yield (D-allo/D-altro ratio, 1:13).

Negative effects of the free hydroxyl function at C-1′ in **8** or **11** on the Pd-mediated coupling reaction were not expected since Fauvarque and Jutand were able to achieve such a coupling reaction in the presence of a carboxyl [12].

Before investigating the Pd-catalysed coupling reaction, both D-allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine or D-allo/D-altro-2-bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine were dissolved in ben-

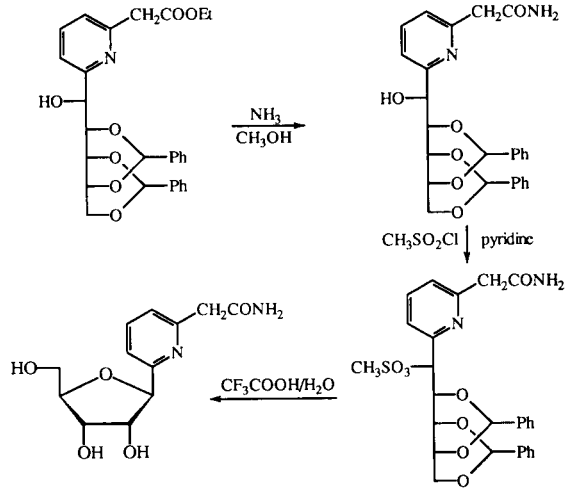
**Scheme 5**




zene or hexane and coevaporated for several times to remove traces of methanol and ethyl acetate. The compounds were then heated to 80° at 0.05 mm Hg to remove all solvent residues. The adducts were dissolved in hexamethylphosphoramide together with tetrakis(triphenylphosphine)palladium(0) and a 1*N* solution of Reformatsky's reagent in dimethoxymethane was added (Scheme 5). The solution was heated in an oil bath at 70° for 3.5 hours [starting from **11**] or 5 hours [starting from **8**]. After the reactions were quenched, the reaction products were purified on a Chromatotron® . The derivatized adducts **12 D-allo** and **12 D-altro** were obtained in 5% and 40%, respectively, if **11** was used as the substrate. It was also noted that the use of the brominated adducts **8** resulted in equal or better yields of **12 D-allo** (12%) and **12 D-altro** (43%). However, a longer reaction time was needed. Consequently, the conversion of the bromo **8** to the iodo adducts **11** prior to the Pd-mediated coupling reaction can be omitted.

At this point it is worthwhile mentioning that during this coupling reaction also a different reactivity between the D-allo and the D-altro epimers was observed. The lower reactivity of the D-allo epimers **8 D-allo** and **11 D-allo** was reflected by the low yields of **12 D-allo** (12% and 5%) and the recovery of an appreciable amount of unreacted **8 D-allo** (> 10%) and **11 D-allo** (> 15%). To ascertain that during the Pd(0) catalyzed substitution reaction

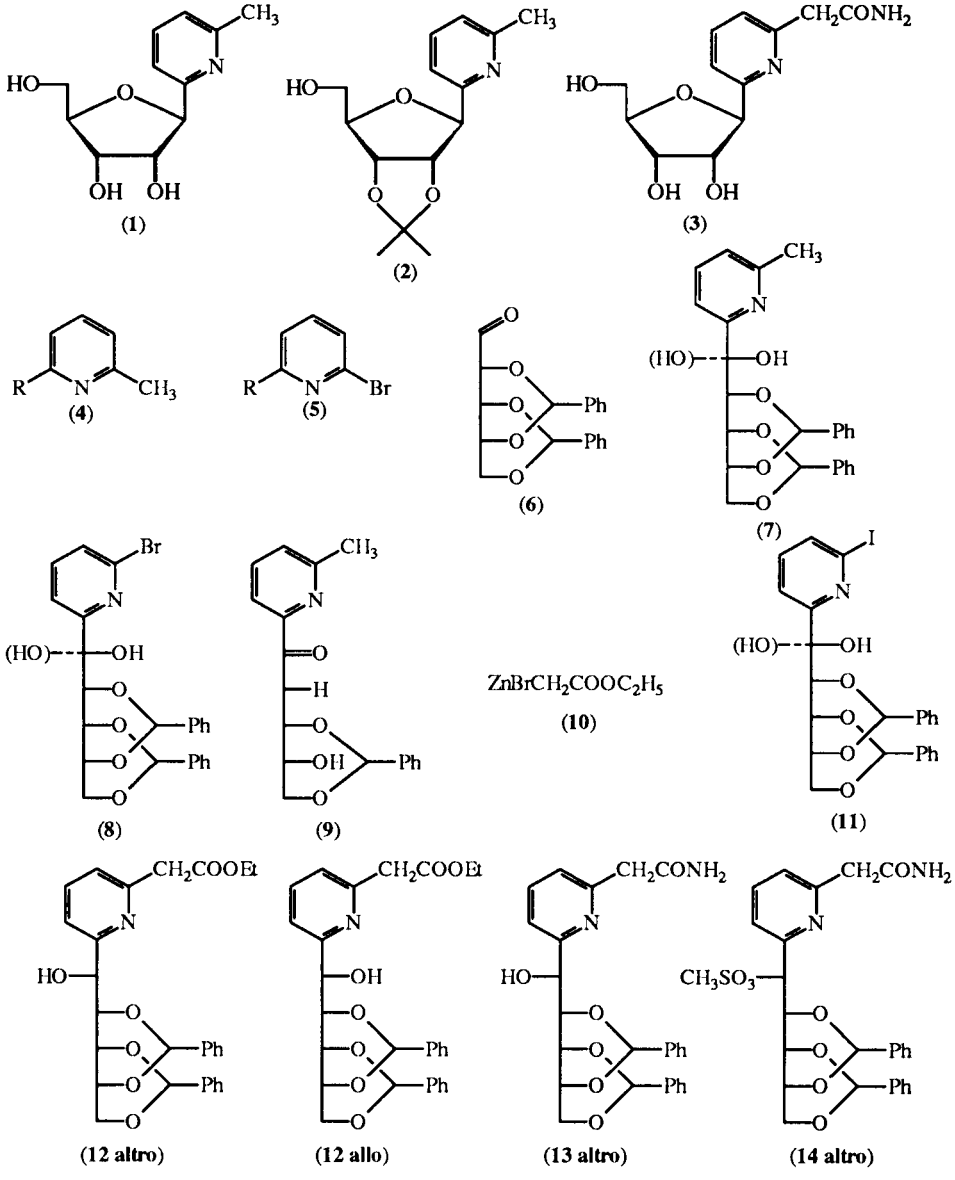
Scheme 6




the configuration at C-1′ was unaffected the reaction was also carried out on the pure D-allo and D-altro epimers of **8**: no epimerization could be detected. Since the D-altro configuration **12 D-altro** will lead to the desired β-anomeric configuration in the C-nucleoside **3** [13], the reaction times were optimized to obtain a maximum amount of D-altro 2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-ethoxycarbonylmethylpyridine (**12**) [93% conversion

out of **8 D-altro**]. The D-allo/D-altro ratio of **8** was 1:2. This epimer was treated with a saturated methanolic ammonia solution to obtain the corresponding carbamoylmethyl analog **13** (yield 100%). The latter was reacted with 3 equivalents of methanesulfonylchloride in dry pyridine for 2 hours and the reaction mixture was poured into a saturated sodium bicarbonate solution. The D-altro-mesylate **14** was extracted with dichloromethane and purified by centrifugal circular preparative layer chromatography. Compound **14** was cyclized in trifluoroacetic acid/water (4/1) for 15 minutes and the mixture was diluted with water. The aqueous layer was extracted with dichloromethane and evaporated to dryness. The residue was dissolved in methanol. Short column chromatography (straight phase) gave a light yellow oil which was purified by hplc on a LiChrosorb 10RP8 column. 2-Carbamoylmethyl-6-β-D-ribofuranosylpyridine **(3)** was collected as a colorless syrup (yield, 85%). The ΔδC-2',C-3'-values of **3** *i.e.* 6.18 ppm (recorded in dimethyl-$d_6$ sulfoxide) and 5.49 ppm (recorded in methyl-$d_3$ alcohol-d) clearly reflect the β-configuration [ΔδC-2',C-3'(α) < 1.6 ppm; ΔδC-2',C-3'(β) > 2.8 ppm]. The anomeric configuration in **3** was also confirmed by means of a NOE-difference experiment (in dimethyl-$d_6$ sulfoxide/methyl-$d_3$ alcohol-d 4/1). Irradiation of H-1' resulted in a NOE signal at H-2' (2%), H-4' (2%) and H-5 (6%) (Scheme 6).

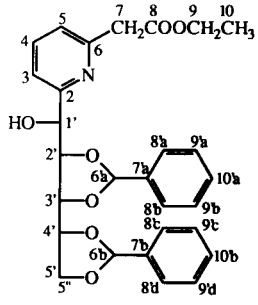
**Formulas**



Biological Activity.

Compound **3** was evaluated for its cytostatic activity against murine leukemia L1210, murine mammary carcinoma FM3A, T-lymphoblast Molt/4F and T-lymphocyte MT-4 cells. However no cytostatic activity was observed. Compound **3** was also evaluated for its inhibitory effect on the replication of a number of DNA viruses [herpes simplex virus type 1 (strain KOS) and type 2 (strain G) and vaccinia virus] and RNA viruses (vesicular stomatitis virus, Coxsackie virus B4, polio virus type 1, parainfluenza virus type 3, reovirus type 1, Sindbis virus, Semliki forest virus and human immunodeficiency virus type 1). No antiviral activity was noted at subtoxic concentrations.

Scheme 7



## EXPERIMENTAL

The $^1$H-nmr spectra and 2D-nmr experiments were recorded at the University of Ghent (Belgium) using a Bruker WH-360 or a Bruker 500 MHz. The NOEDIFF mode of the Bruker software package was used for the NOE difference experiment. The $^{13}$C-nmr spectra were recorded on a Jeol-JNM-FX-100 (25 MHz, RUCA, University of Antwerp (Belgium) connected to a TI-980 B computer system. Samples for nmr measurements were dissolved in deuteriochloroform unless otherwise stated. The proton and carbon numbering system is illustrated in Scheme 7. DCI-mass spectra were run on a Ribermag-10-10B (Nermag S.A.) quadrupole mass spectrometer equipped with a SIDAR data system. Primary ionisation of the reagent gas (ammonia) was performed by 70 eV electrons. The ionisation current was 0.08 mA and the pressure in the ion source was 0.1 mm Hg. Analytical tlc was performed on silica plates (Kieselgel 60 $F_{254}$ Merck, Darmstadt, 0.25 mm) using the same solvent system as used with centrifugal circular preparative layer chromatography unless stated otherwise. Centrifugal circular preparative layer chromatography was carried out on a Chromatotron® (Harrison Research Inc., Palo Alto, CA). Stationary phase: Kieselgel 60 $PF_{254}$ gipshaltig, Merck, Darmstadt, layer thickness 2 mm. Flow rate 6 ml/minute unless stated otherwise. Purities were ascertained by hplc analyses on a Hewlett-Packard HP-1084 apparatus (column: Lichrosorb 10RP8 (25 cm x 4.6 mm)). Reactions involving organometallic reagents were performed in oven-dried glassware under a nitrogen atmosphere. 1,2-Dimethoxyethane, diethyl ether and tetrahydrofuran were dried by distillation from sodium/benzophenone ketyl prior to use. The cytostatic and antiviral activity assays were carried out according to previously published procedures [14-17].

(3*S*,4*R*)-2-(3,5-*O*-Benzylidene-1-oxo-3,4,5-trihydroxy-1-pentyl)-6-methylpyridine (**9**).

To a solution of 500 mg (1.2 mmoles) D-allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-methylpyridine (**7**) in 50 ml of diethyl ether 1.32 ml (2.2 equivalents) of phenyllithium (2.0 *M* in cyclohexane/diethyl ether 70/30 v/v) was added. After 1.5 minutes the turbid solution was poured into a solution containing water (50 ml) and methanol (20 ml). The resulting solution was neutralized with 0.1 *N* hydrochloric acid and evaporated. The crude (3*S*,4*R*)-2-(3,5-*O*-benzylidene-1-oxo-3,4,5-trihydroxy-1-pentyl)-6-methylpyridine (**9**) was purified with centrifugal circular preparative layer chromatography (ethyl acetate/hexane:40/60 v/v); yield, 33%, Rf, 0.52 (ethyl acetate/hexane:1/1 v/v). Simultaneously 60% of the material could be recovered. The analytical data for (3*S*,4*R*)-2-(3,5-*O*-benzylidene-1-oxo-3,4,5-trihydroxy-1-pentyl)-6-methylpyridine are **9**; $^1$H nmr: δ (360 MHz) 2.60 (s, 3H, 7-H), 3.46 (dd, 1H, 2''-H, J = -15.8 Hz, 5.5 Hz), 3.65 (m, 1H, 5''-H, J = -9.8 Hz, 10.0 Hz), 3.70 (m, 1H, 4'-OH, J = 9.1 Hz), 3.87 (dd, 1H, 2'-H), 4.17 (m, 1H, 3'-H, J = 5.1 Hz, 5.5 Hz), 4.31 (dd, 1H, 5'-H, J = 4.0 Hz), 5.52 (s, 1H, 6'-H), 7.30-7.37 (m, 4H, 5-H + 9'a-H + 9'b-H + 10'-H), 7.44-7.49 (m, 2H, 8'a-H + 8'b-H), 7.74 (t, 1H, 4-H, J = 7.7 Hz, 7.7 Hz), 7.87 (d, 1H, 3-H); $^{13}$C nmr: δ 24.01 (C-7), 41.37 (C-2'), 66.13 (C-4'), 71.17 (C-5'), 78.80 (C-3'), 101.02 (C-6'), 119.29 (C-3), 126.05, 127.12, 128.02, 128.70 (C-8', C-9', C-10' and C-5), 137.30 (C-4), 137.56 (C-7'), 152.67 (C-2), 157.89 (C-6), 199.75 (C-1'); ms: m/z 314 ([MH]$^+$).

*Anal.* Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.96; H, 6.13; N, 4.46.

D-Allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-bromopyridine (**8**).

In a three-necked flask, equipped with a calcium chloride-tube, a dropping funnel and a nitrogen-gas inlet tube 3.08 g (13.0 mmoles) 2,6-dibromopyridine was dissolved in 100 ml of tetrahydrofuran. The solution was cooled to -78° and 8.1 ml (13.0 mmoles) of butyllithium was added in three portions. The solution turned dark-red and after 8 minutes a solution of 2.9 g (8.9 mmoles) of 2,4:3,5-di-*O*-benzylidene-aldehydo-D-ribose, cooled to 5° was added during a period of 15 minutes. After 2 hours at -78°, the reaction mixture was allowed to come to room temperature, whereafter 100 ml of water was added. Extraction with dichloromethane, drying over magnesium sulfate, filtration and concentration yielded D-allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-bromopyridine (**8**) as a foam which is purified and, if needed, separated into its allo/altro components by centrifugal circular preparative layer chromatography (ethyl acetate/hexane 3/7 v/v); the yield of the D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-bromopyridine (Rf, 0.38) was 38%, the yield of D-allo-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-bromopyridine (Rf, 0.44) was 45%.

D-Allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine (**11**).

In a three-necked flask, equipped with a calcium chloride-tube, a dropping funnel and a nitrogen-gas inlet tube 1.94 g (4.0 mmoles) 2-bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**8**) was dissolved in 100 ml of tetrahydrofuran. To this solution 32 mg (4.0 mmoles) of lithium hydride was added and the mixture

was stirred for 30 minutes at room temperature after which it was cooled to -78°. Then 15.0 ml (24 mmoles) of butyllithium (1.6 *M* in hexane) was added in three portions. After 8 minutes a solution of 8.13 g (32 mmoles) of iodine in 30 ml of tetrahydrofuran was added to the red-brown solution during a two-minute period. After 2 hours at -78°, the reaction mixture was allowed to come to room temperature, whereafter 100 ml of tetrahydrofuran/water (7/3) was added. The solution was concentrated to 1/3 of its original volume, poured onto 200 ml of water, decolorized with solid sodium thiosulphate and extracted with diethyl ether. The organic extract was dried over magnesium sulfate and evaporated to a dark viscous oil which was purified by centrifugal circular preparative layer chromatography (ethyl acetate/hexane:1/4 v/v), yield 45-50%; Rf **11 D-allo**, 0.47; Rf **11 D-altro**, 0.40 (ethyl acetate/hexane:3/7 v/v). The analytical data for D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine (**11 D-altro**) are; $^1$H nmr: δ 3.60 (d, 1H, 1'-OH, J = 8.9 Hz), 3.93 (t, 1H, 5''-H, J = -10.3 Hz, 9.5 Hz), 4.02 (m, 1H, 4'-H, J = 4.3 Hz), 4.05 (m, 1H, 3'-H, J = 8.5 Hz), 4.35 (dd, 1H, 2'-H, J = 8.9 Hz), 4.42 (dd, 1H, 5'-H), 5.05 (dd, 1H, 1'-H, J = 2.2 Hz), 5.68 and 5.71 (2s, 2H, 6'a-H and 6'b-H), 7.32 (t, 1H, 4-H, J = 7.6 Hz, 7.7 Hz), 7.34-7.42 + 7.50-7.54 (2m, 9H + 2H, 3-H and phenyl-H), 7.63 (d, 1H, 5-H); $^{13}$C nmr: δ 68.84 (C-5'), 70.97 (C-1'), 72.80 (C-4'), 74.02 (C-3'), 80.29 (C-2'), 101.01, 101.98 (C-6a' and C-6b'), 116.84 (C-6), 120.32 (C-3), 125.98, 126.23 (C-8a' to C-8d'), 128.24 (C-9a' to C-9d'), 129.09 (C-10a' and C-10b'), 133.72 (C-5), 136.95, 137.20 (C-7a' and C-7b'), 137.80 (C-4), 161.56 (C-2); ms: m/z 532 ([MH]$^+$).

The analytical data for D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-iodopyridine (**11 D-allo**) are; $^1$H nmr: δ (360 MHz) 3.7 (bs, 1H, 1'-OH), 3.86 (t, 1H, 5''-H, J = -10.1 Hz, 9.9 Hz), 3.95 (m, 2H, 3'-H and 4'-H), 4.35 (dd, 1H, 5'-H, J = 4.0 Hz), 4.46 (dd, 1H, 2'-H, J = 9.0 Hz), 5.13 (d, 1H, 1'-H, J = 2.9 Hz), 5.52 and 5.79 (2s, 2H, 6'a-H and 6'b-H), 7.14-7.18 (m, 2H, phenyl-H), 7.25 (t, 1H, 4-H, J = 7.7 Hz, 7.7 Hz), 7.29-7.40 (m, 6H, phenyl-H), 7.41 (d, 1H, 3-H or 5-H), 7.47-7.50 (m, 2H, phenyl-H), 7.58 (d, 1H, 3-H or 5-H); $^{13}$C nmr: δ 68.72 (C-5'), 72.43 (C-4'), 72.74 (C-1'), 73.83 (C-3'), 80.84 (C-2'), 101.13, 101.49 (C-6a' and C-6b'), 116.36 (C-6), 120.38 (C-3), 125.86, 126.23 (C-8a' to C-8d'), 127.93, 128.23 (C-9a' to C-9d'), 128.79, 129.15 (C-10a' and C-10b'), 133.35 (C-5), 136.95 (C-7a' and C-7b'), 137.62 (C-4), 160.52 (C-2); ms: m/z 532 ([MH]$^+$).

*Anal.* Calcd. for $C_{24}H_{22}INO_5$: C, 54.25; H, 4.17; N, 2.64. Found: C, 54.29; H, 4.15; N, 2.62.

D-Allo/D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-ethoxycarbonylmethylpyridine (**12**) from 2-Bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**8**).

In a three-necked flask, equipped with a calcium chloride-tube, a dropping funnel and a nitrogen-gas inlet tube 400 mg (0.83 mmole) of 2-bromo-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-pyridine (**8**) and 96 mg (0.086 mmole) of tetrakis(triphenylphosphine)palladium(0) was dissolved in 20 ml of hexamethylphosphoramide. To this solution 17 ml of Reformatsky's reagent (1 *N*) in dimethoxyethane was added whereafter the mixture was placed in a heating bath (70-73°) during 5 hours. Then the reaction mixture was poured onto 100 ml of aqueous saturated ammonium chloride and thrice extracted with 40 ml of diethyl ether. The combined organic phases were washed with water, dried with magnesium sulfate and concentrated *in vacuo*. The acetates were further purified and separated by centrifugal circular preparative layer chromatography (ethyl acetate/dichloromethane:8/92), yield of **12 D-altro** 43%, Rf, 0.55; yield of **12 D-allo** 12%, Rf, 0.40.

The analytical data we found for D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-ethoxycarbonylmethylpyridine (**12 D-altro**) are; $^1$H nmr: δ 1.21 (t, 3H, 10-H, J = 7.1 Hz), 3.85 (s, 2H, 7-H), 3.93 (t, 1H, 5''-H, J = -10.1 Hz, 9.9 Hz), 4.00 (m, 1H, 4'-H, J = 4.4 Hz), 4.07 (t, 1H, 3'-H, J = 9.0 Hz), 4.11 (q, 2H, 9-H), 4.31 (dd, 1H, 2'-H, J = 9.1 Hz, 2.1 Hz), 4.41 (dd, 1H, 5'-H), 5.09 (bs, 1H, 1'-H), 5.64 and 5.72 (2s, 2H, 6'a-H and 6'b-H), 7.23 and 7.29 (2d, 2H, 3-H and 5-H), 7.31-7.41 + 7.50-7.54 (2m, 8H + 2H, phenyl-H), 7.68 (t, 1H, 4-H, J = 7.8 Hz, 7.6 Hz); $^{13}$C nmr: δ 14.13 (C-10), 43.80 (C-7), 60.92 (C-9), 68.84 (C-5'), 70.48 (C-1'), 72.92 (C-4'), 74.08 (C-3'), 80.72 (C-2'), 101.01, 101.80 (C-6a' and C-6b'), 119.22 (C-3), 122.57 (C-5), 125.98, 126.17 (C-8a' and C-8d'), 128.12 (C-9a' and C-9d'), 128.91 (C-10a' and C-10b'), 137.07 (C-4), 137.07, 137.37 (C-7a' and C-7b'), 153.21 (C-6), 158.39 (C-2), 170.45 (C-8); ms: m/z 492 ([MH]$^+$).

The analytical data for D-allo-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-ethoxycarbonylmethylpyridine (**12 D-allo**) are; $^1$H nmr: δ 1.21 (t, 3H, 10-H, J = 7.1 Hz), 3.79 and 3.83 (2d, 2H, 7a-H and 7b-H, J = -15.5 Hz), 3.86 (t, 1H, 5''-H, J = -10.0 Hz, 9.8 Hz), 3.93 (m, 1H, 4'-H, J = 4.2 Hz), 3.98 (t, 1H, 3'-H, J = 9.0 Hz), 4.11 (q, 2H, 9-H), 4.34 (dd, 1H, 5'-H), 4.44 (dd, 1H, 2'-H, J = 8.9 Hz), 5.15 (d, 1H, 1'-H, J = 2.7 Hz), 5.53 and 5.78 (2s, 2H, 6'a-H and 6'b-H), 7.06-7.10 (m, 2H, phenyl-H), 7.23 and 7.32 (2d, 2H, 3-H and 5-H), 7.25-7.30 + 7.35-7.40 + 7.46-7.49 (3m, 3H + 3H + 2H, phenyl-H), 7.66 (t, 1H, 4-H, J = 7.7 Hz, 7.7 Hz); $^{13}$C nmr: δ 14.13 (C-10), 43.80 (C-7), 60.92 (C-9), 68.78 (C-5'), 72.60 (C-1' and C-4'), 74.02 (C-3'), 81.39 (C-2'), 101.01, 101.68 (C-6a' and C-6b'), 119.65 (C-3), 122.39 (C-5), 125.74, 126.29 (C-8a' and C-8d'), 127.93, 128.24 (C-9a' and C-9d'), 128.72, 129.15 (C-10a' and C-10b'), 137.07 (C-4), 137.07 (C-7a' and C-7b'), 153.09 (C-6), 157.48 (C-2), 170.33 (C-8); ms: m/z 492 ([MH]$^+$).

*Anal.* Calcd. for $C_{28}H_{29}NO_7$: C, 68.42; H, 5.95; N, 2.85. Found: C, 68.46; H, 5.91; N, 2.84.

D-Altro-2-carbamoylmethyl-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**13**).

In 40 ml of ice-cold, saturated methanolic ammonia 400 mg of D-altro-2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)-6-ethoxycarbonylmethylpyridine (**12 D-altro**) was dissolved. The reaction vessel was closed and was allowed to warm up to room temperature. After 20 hours the solution was concentrated *in vacuo*, yield 100%, Rf, 0.44 (dichloromethane/methanol 9/1 v/v). The analytical data for D-altro-2-carbamoylmethyl-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**13**) are; $^1$H nmr: δ 3.56 and 3.74 (2dd, 2H, 7a-H and 7b-H, J = -15.5 Hz), 3.97 (m, 2H, 4'-H and 5''-H), 4.11 (dd, 1H, 2'-H, J = 9.3 Hz), 4.16 (bs, 1H, N-H), 4.21 (t, 1H, 3'-H, J = 8.8 Hz), 4.40 (dd, 1H, 5'-H, J = 4.8 Hz, -10.0 Hz), 5.11 (d, 1H, 1'-H, J = 1.4 Hz), 5.55 and 5.77 (2s, 2H, 6'a-H and 6'b-H), 6.34 (bs, 1H, N-H), 7.15 and 7.25 (2d, 2H, 3-H and 5-H), 7.31-7.43 + 7.52-7.55 (2m, 8H + 2H, phenyl-H), 7.67 (t, 1H, 4-H, J = 7.6 Hz, 7.7 Hz); $^{13}$C nmr: δ 45.08 (C-7), 68.84 (C-5'), 69.81 (C-1'), 73.04 (C-4'), 73.84 (C-3'), 81.39 (C-2'), 102.04 (C-6a' and C-6b'), 119.34 (C-5), 123.06 (C-3), 126.23, 126.53 (C-8a' to C-8d'), 128.36 (C-9a' to C-9d'), 129.21, 129.70 (C-10a' and C-10b'), 136.95, 137.19 (C-7a' and C-7b'), 138.11 (C-4), 154.55 (C-2), 158.76 (C-6), 171.00 (C-8); ms: m/z 463 ([MH]$^+$).

*Anal.* Calcd. for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.55; H, 5.64; N, 6.03.

D-Altro-2-carbamoylmethyl-6-(1-*O*-mesyl-2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**14**).

To a stirred solution of 100 mg (2.16 $10^{-4}$ moles) of D-altro-2-carbamoylmethyl-6-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**13**) in 20 ml of dry pyridine 50 ml (6.48 x $10^{-4}$ moles) of methanesulfonyl chloride was added. After 2 hours the solution was poured into an excess aqueous saturated sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, concentrated and further evaporated under high-vacuum (0.05 mm Hg) during 2 hours to remove residual pyridine. Further purification by centrifugal circular preparative layer chromatography (dichloromethane/methanol 98/2 to 95/5 v/v) yielded a transparent high-viscous oil, yield, 82%, Rf, 0.56 (dichloromethane/methanol 9/1 v/v). The analytical data for D-altro-2-carbamoylmethyl-6-(1-*O*-mesyl-2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**14**) are; $^1$H nmr: $\delta$ 2.99 (s, 3H, C$H_3SO_3$), 3.659 and 3.713 (2d, 2H, 7a-H and 7b-H, J = -15.4 Hz), 3.95 (t, 1H, 5''-H, J = -9.7 Hz, 9.9 Hz), 4.00 (m, 1H, 4'-H), 4.05 (t, 1H, 3'-H, J = 8.6 Hz), 4.433 (dd, 1H, 5'-H, J = 3.9 Hz), 4.463 (dd, 1H, 2'-H, J = 9.0 Hz), 5.19 (bs, 1H, N-H), 5.64 and 5.65 (2s, 2H, 6'a-H and 6'b-H), 5.96 (d, 1H, 1'-H, J = 3.4 Hz), 6.86 (bs, 1H, N-H), 7.21 (d, 1H, 3-H, J = 7.4 Hz), 7.34-7.42 (m, 10H, phenyl-H), 7.46 (d, 1H, 5-H, J = 7.8 Hz), 7.72 (t, 1H, 4-H); $^{13}$C nmr: $\delta$ 38.81 (C$H_3SO_3$), 45.02 (C-7), 68.78 (C-5'), 72.74 (C-4'), 74.08 (C-3'), 78.83 (C-2'), 79.62 (C-1'), 101.80 (C-6a' and C-6b'), 121.11 (C-5), 124.03 (C-3), 126.04, 126.17 (C-8a' to C-8d'), 128.36 (C-9a' to C-9d'), 129.21, 129.39 (C-10a' and C-10b'), 136.58, 136.77 (C-7a' and C-7b'), 137.92 (C-4), 155.16, 155.74 (C-2 and C-6), 171.43 (C-8); ms: m/z 541 ([MH]$^+$).

*Anal.* Calcd. for $C_{27}H_{28}N_2O_8S$: C, 59.99; H, 5.22; N, 5.18. Found: C, 59.97; H, 5.21; N, 5.19.

2-Carbamoylmethyl-6-$\beta$-D-ribofuranosylpyridine (**3**).

In a flask of 50 ml, 80 mg (1.5 $10^{-4}$ moles) of D-altro-2-carbamoylmethyl-6-(1-*O*-mesyl-2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine (**14**) was dissolved in 20 ml of trifluoroacetic acid. Then 5 ml of water was added and the solution was stirred for 15 minutes whereafter the solution was poured into 100 ml of water. Washing with dichloromethane and evaporation of the aqueous phase gave a pale yellow oil which was dissolved in methanol and subsequently neutralized with methanolic ammonia. Evaporation and short-column chromatography (Kieselgel 60 $F_{254}$ Merck, Darmstadt, column: 15 cm x 1 cm I.D., eluent: dichloromethane/methanol 4/1 v/v) yields 2-carbamoylmethyl-6-$\beta$-D-ribofuranosylpyridine which was further purified by hplc (LiChrosorb$^{TM}$ 10RP8, column: 25 cm x 22 mm I.D., eluent: water/methanol 9/1 v/v, 6 ml/minute, $t_R$: 30 minutes), yield, 85%, Rf, 0.32 (dichloromethane/methanol 4/1 v/v). The analytical data for 2-carbamoylmethyl-6-$\beta$-D-ribofuranosylpyridine (**3**) are; $^1$H nmr (dimethyl sulfoxide-$d_6$): $\delta$ 3.53 (m, 1H, 5''-H, J = -11.8 Hz), 3.56 (s, 2H, 7-H), 3.66 (dt, 1H, 5'-H), 3.85 (m, 1H, 4'-H, J = 3.2 Hz, 4.1 Hz), 3.89 (q, 1H, 3'-H, J = 5.3 Hz), 3.98 (q, 1H, 2'-H, J = 4.7 Hz), 4.70 (d, 1H, 1'-H, J = 4.5 Hz), 4.85 (d, 1H, 2'-OH, J = 4.9 Hz), 4.98 (t, 1H, 5'-OH, J = 5.1 Hz, 5.8 Hz), 5.05 (d, 1H, 3'-OH, J = 5.2 Hz), 6.97 (bs, 1H, N-H), 7.23 (d, 1H, 3-H), 7.42 (d, 1H, 5-H), 7.52 (bs, 1H, N-H), 7.71 (t, 1H, 4-H, J = 7.6 Hz, 7.6 Hz); $^{13}$C nmr (dimethyl sulfoxide-$d_6$): $\delta$ 44.68 (C-7), 61.98 (C-5'), 71.10 (C-3'), 76.90 (C-2'), 84.64 (C-1'), 85.31 (C-4'), 119.43 (C-5), 123.02 (C-3), 137.46 (C-4), 155.55 (C-6), 160.06 (C-2), 171.88 (C-8); ms: m/z 179 (Base + 44$^+$), 269 (MH$^+$).

*Anal.* Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.93; H, 5.81; N, 10.38.

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