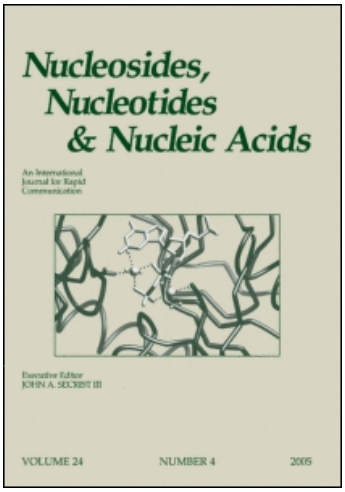


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Iodoaminoimidazole Arabinoside (IAIA): A Potential Reductive Metabolite of the Spect Imaging Agent, Iodoazomycin Arabinoside (IAZA)

Herbert C. Lee[a]; Piyush Kumar[a]; Leonard I. Wiebe[a]; Robert McDonald[b]; John R. Mercer[a]; Kazue Ohkura[c]; Koh-Ichi Seki[c]
[a] Faculty of Pharmacy and Pharmaceutical Sciences, [b] Department of Chemistry, University of Alberta, Alberta, Canada [c] Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Hokkaido, Japan

To cite this Article Lee, Herbert C. , Kumar, Piyush , Wiebe, Leonard I. , McDonald, Robert , Mercer, John R. , Ohkura, Kazue and Seki, Koh-Ichi(1999) 'Synthesis of Iodoaminoimidazole Arabinoside (IAIA): A Potential Reductive Metabolite of the Spect Imaging Agent, Iodoazomycin Arabinoside (IAZA)', Nucleosides, Nucleotides and Nucleic Acids, 18: 9, 1995 — 2016
To link to this Article: DOI: 10.1080/07328319908044860
URL: http://dx.doi.org/10.1080/07328319908044860

NUCLEOSIDES & NUCLEOTIDES, 18(9), 1995–2016 (1999)

SYNTHESIS OF IODOAMINOIMIDAZOLE ARABINOSIDE (IAIA): A POTENTIAL REDUCTIVE METABOLITE OF THE SPECT IMAGING AGENT, IODOAZOMYCIN ARABINOSIDE (IAZA)

Herbert C. Lee,[a] Piyush Kumar,[a] Leonard I. Wiebe,[a] Robert McDonald[b], John R. Mercer*[a], Kazue Ohkura[c] and Koh-ichi Seki[c]

[a]*Faculty of Pharmacy and Pharmaceutical Sciences, and* [b]*Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2E1*
[c]*Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido, Japan 061-0293*

ABSTRACT: The stereospecific synthesis of 1-(5-deoxy-5-iodo-α-D-arabino-furanosyl)-2-aminoimidazole (iodoaminoimidazole arabinoside: IAIA, **2**) is described. The reaction of the protected sugar bromide (**8**) and trifluoroacetamidoimidazole (**10B**) gave the coupled product (**11B**), which gave the free nucleoside (**4**) on deblocking. It was identical with AIA obtained by reduction of AZA (azomycin arabinoside), whose anomeric configuration was found to be α by the X-ray crystallography.

INTRODUCTION

Iodoazomycin arabinoside (IAZA, **1**), labelled with the radioisotope ^{123}I, is being used clinically in cancer patients to mark hypoxic tissue[1,2]. Iodoaminoimidazole arabinoside (IAIA, **2**) (1-(5-deoxy-5-iodo-α-D-arabinofuranosyl)-2-aminoimidazole) is a potential metabolite from the bioreduction of the 2-nitroimidazole moiety in iodoazomycin arabinoside (IAZA, **1**) [3] by nitroreductases[4] in humans. This reductive metabolite could be responsible for the abnormal brain uptake of radioactivity observed in some patients with advanced cancer who had received diagnostic doses of [^{123}I]IAZA[5]. The present paper reports the chemical synthesis of **2** (the α-nucleoside) and the results of investigations on the anomeric configuration of IAIA and IAZA.

Since IAZA has previously been reported to have the β anomeric configuration[3], the chemical synthesis of IAIA initially focused on obtaining the β-nucleoside. Because of the *trans* rule of nucleoside synthesis[6], the preparation of a β-*arabino* (C_1'-C_2' *cis*) nucleoside using benzoyl protective groups proved to be very difficult. Indeed, the present synthetic studies and ^{1}H NMR data of the glycosylated products suggested that IAZA possessed the α anomeric configuration rather than β as previously reported[3]. The α configuration has now been confirmed by examination of the ^{1}H NMR data and by X-ray crystallography.

RESULTS AND DISCUSSION

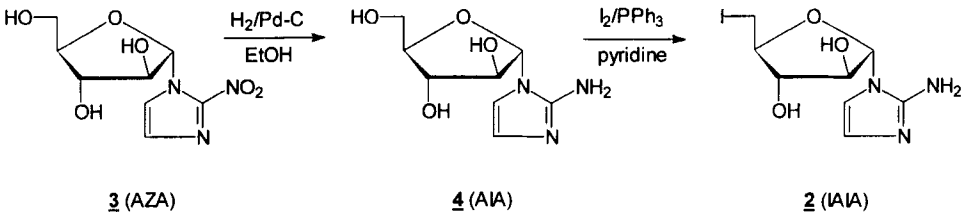
Two synthetic approaches have been used to prepare the target compound, iodoazomycin arabinoside (IAIA, **2**). One method for the synthesis of IAIA involved the chemical reduction of azomycin arabinoside (AZA, **3**) with hydrogen in the presence of palladium-carbon to give aminoimidazole arabinoside (AIA, **4**) in 88% yield. Subsequent iodination with iodine-triphenylphosphine-pyridine afforded **2** in 40% yield (Scheme 1). Although this method gave good yields of **2**, it is not desirable because it involves the degradation of the costly synthetic end product **3**. An alternative synthetic method starting from commercially available D-(-)-arabinose **5** was explored (Scheme 2). Nine glycosylation trials were conducted (Table 1) and five reaction variables are considered.

Glycosylation reaction

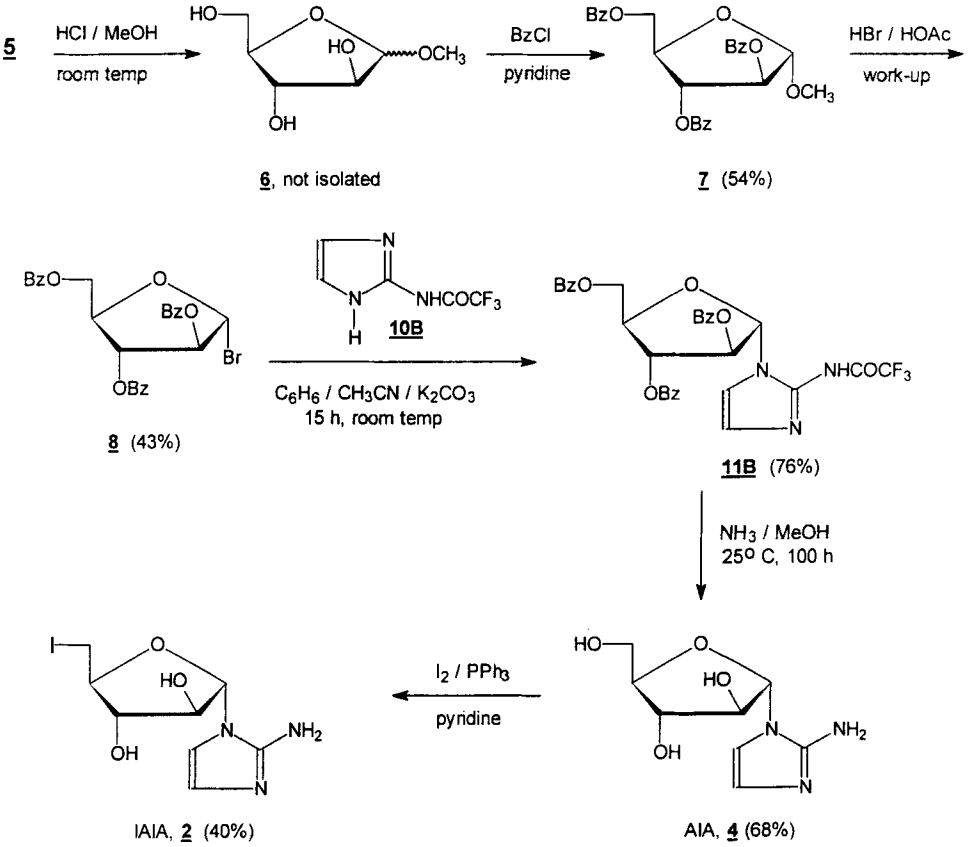
Stability of the sugar bromide

The starting material in the glycosylation reactions listed in Table 1 is the sugar bromide, 1-bromo-2,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (**8**), which was prepared according to standard procedures[7-9] from 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside (**7**). Bromination of **7** with HBr/HOAc gave the blocked α-bromo sugar **8** as a crystalline product in 43% yield. TLC showed a single spot and its melting point was consistent with reported values[7-9]. Its structure was characterized by ^{1}H and ^{13}C NMR. When stored under argon at –20°C, it was stable for months as confirmed by ^{1}H NMR.

Low yields in the glycosylation reaction were noted when acetonitrile was used to dissolve the bromosugar **8** prior to its addition to the protected 2-aminoamidazole (Table 1, Trials 1-4, 6). This prompted an investigation of the chemical stability of **8** in different



Scheme 1. Chemical synthesis of IAIA (2) from AZA (3).



Scheme 2. Chemical synthesis of IAIA (2) from D-(-)-arabinose (5).

TABLE 1. Glycosylation trials between N^2-protected 2-aminoimidazoles (**10A** or **10B**) with 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide (**8**).

Trial	N^2-protected 2-amino-imidazole	Silylation / $Hg(CN)_2$ / K_2CO_3	Solvent	Reaction condition	Product	Yield %
1*	**10A**	Yes/Yes/ No	CH_3CN	Reflux (82°C), 12 h	Not observed	-
2*	**10A**	No/Yes/ No	CH_3CN	25°C, 3.5 days; 55°C, 24 h; Reflux (82°C), 3 h	Yes, **11A**	15
3A	**10A**	No/Yes/ No	CH_3CN	25°C, 60 h; Reflux (82°C), 3 h	Yes, **11A**	22
3B	**10A**	No/No/ Yes	CH_3CN	25°C, 60 h; Reflux (82°C), 3 h	Yes, **11A**	27
4	**10A**	No/No/ Yes	CH_3CN	25°C, 20 h	Yes, **11A**	17
5	**10A**	No/No/ Yes	C_6H_6/ CH_3CN	25°C, 15 h	Yes, **11A**	27
6	**10B**	No/No/ Yes	CH_3CN	25°C, 2 h	Yes, **11B**	25
7	**10B**	No/No/ Yes	C_6H_6/ CH_3CN	25°C, 15 h	Yes, **11B**	76
8	**10B**	No/No/ No	CH_2Cl_2	25°C, 3.5 days	Yes, **11B**	20
9	**9**	Yes/Yes/ No	C_6H_6	Reflux (80°C), 12h	Not observed	-

*The sugar bromide **8** was prepared by the HBr/CH_2Cl_2 method in an anomeric mixture.

solvents. In acetonitrile, a common glycosylation solvent, ^{1}H NMR showed rapid decomposition of **8**. In "non-participating" solvents such as benzene and dichloromethane, ^{1}H NMR showed no decomposition of **8** after standing overnight (15 h). The low glycosylation yields may therefore be partly due to the chemical decomposition of **8** in acetonitrile. Further evidence in support of this conclusion came from the similarity of the ^{1}H NMR spectra between the decomposed **8** and side products observed in most of the glycosylation trials (Table 1) when acetonitrile was used as the glycosylation solvent. When a solution of **8** in benzene was added dropwise to a solution of the protected 2-aminoimidazole in acetonitrile, decomposition appeared to be minimized. This method appears to be more effective and gave the highest yield of the glycosylated product (Trials 5 and 7).

Protection of the exocyclic N^2-amino group

The reactive primary amino group on the imidazole ring must be modified by a suitable protective group. This prevents competition of the amino group with the N^1 and N^3-nitrogens in the imidazole ring and avoids glycosylation of the exocyclic amine. Such glycosylations have been observed in stannic chloride-catalyzed ribosylation with silylated 2-aminoimidazole, which gave predominately the N^2-nucleoside[10]. Introducing an electron-withdrawing substituent can reduce the reactivity of the exocyclic primary amino group. In this study, the acetyl and trifluoroacetyl groups were selected. The acetyl group is a relatively small substituent and thus could minimize steric effects during glycosylation. With the trifluoroacetyl group the strongly electron-withdrawing fluorine atoms do not significantly contribute to steric effects while their electronic effects could further facilitate amide cleavage. In the trials conducted, the glycosylation reaction involving the trifluoroacetyl group gave higher yields (76%) than the acetyl counterpart (27%) (Table 1). Therefore, the method used in Trial 7 was selected as the preferred synthetic route.

Silylation

Trimethylsilyl groups have been used to activate heterocyclic bases for condensation with glycosyl halides as reported by Nishimura *et al.*[11] to provide a new synthesis of purine and pyrimidine nucleosides. Trimethylsilyl derivatives of 2-nitroimidazole bases[12] and 2-amino-imidazole bases[13] have also been reported. Since the

2-aminoimidazole base in the present reactions contains an exocyclic electron-donating group, base activation by silylation may not be necessary. The effect of silylation of the 2-aminoamidazole on the progress of the glycosylation reaction was examined in Trials 1 and 9 (Table 1). In both reaction trials, numerous unidentified products were observed and the ^{1}H NMR spectra indicated that none of these was the required glycosylation product. Adequate yields of the required coupled products **11A** and **11B** were obtained without activation of the heterocyclic base, although it is not known whether silylation in Trial 7, for example, would further increase the yields.

Mercury salt catalysts

Mercury salts such as mercuric bromide ($HgBr_2$) or mercuric cyanide ($Hg(CN)_2$) are known to function as activators in both nucleoside and oligosaccharide syntheses[14]. During glycosylation, mercury is believed to form a complex with one or more nitrogen atoms on the nucleobase and glycosyl halides are attracted to the nitrogen atoms that bear the mercury groups[15]. Mercury salts did not exert a significant effect in the present glycosylation study. In Trials 3A and 3B, for example, comparable yields and the same stereoselectivity were obtained with or without the use of $Hg(CN)_2$. In glycosylation trials 4-8, **11A** or **11B** were obtained in useful yields without the mercury salt catalyst. Besides acting as base activators, mercury salts also function as acid acceptors similar to the role of molecular sieves[16]. Potassium carbonate (K_2CO_3) was used to replace the highly toxic mercury salt as a solid acid acceptor (Trials 4-7, Table 1) with reasonable yields of the glycosylation products.

Solvent

Acetonitrile is a common solvent for glycosylation but its possible role in the observed decomposition of **8** suggests that it is likely to be a participating solvent. In fact, acetonitrile is known to help direct the stereoselective synthesis of a *trans* glycosylation product[14]. If this were true, it would explain the observed formation of **11A** and **11B** in this study (Trials 2-7). In a polar solvent such as acetonitrile, dissociation of the bromide ion (or other halide ions) from the sugar is more favored and thus the positive charge on the orthoester intermediate is more stabilized. In a less polar solvent such as dichloromethane, however, this dissociation is expected to be less favored, resulting in the formation of a tight ion pair [17] which could hinder the attack by the

nucleobase on the bottom (α) side. The *cis* nucleoside can be predominately formed in this special violation of the *trans* rule. However, this solvent effect appears to be in a delicate balance with the directing effect of the 2' participating group on the sugar. For example, in Trial 8, dichloromethane did not change the stereoselectivity of the glycosylation reactions (^{1}H NMR), even though it is not a participating solvent.

The structures of **11A** and **11B** were assigned as the α configuration by their NMR spectra. They showed signals for $C_{1'}$-H at δ 6.38 (broad s) and 6.43 (d, J=3.9 Hz) with small $H_{1'}$-$H_{2'}$ coupling constants. Their NOEY spectra showed the following cross peaks: $H_{1'}$-$H_{2'}$, $H_{1'}$-$H_{3'}$, $H_{1'}$-H_5, $H_{2'}$-$H_{3'}$, $H_{2'}$-$H_{4'}$, $H_{2'}$-H_5, $H_{3'}$-$H_{4'}$, $H_{3'}$-$H_{5'}$, $H_{4'}$-$H_{5'}$, $H_{4'}$-H_5. These results suggested spatial interactions between the C_5-H proton on the imidazole ring and the three protons on the sugar portion at $H_{1'}$, $H_{2'}$, and $H_{4'}$.

An interesting side product was observed in glycosylation Trials 3-6. This compound was identified to be the benzoylated N^1,N^3-bis(arabinofuranosyl)-2-acetamido-imidazole (**13A**) or its trifluoroacetamido counterpart (**13B**) (Figure 1), depending on the starting 2-aminoimidazole derivative. There is a literature precedent for the formation of such "bis" glycosylation products. Pedersen *et al.*[18] isolated analogous "bis" compounds (α configuration) in the glycosylation reactions between silylated 6-substituted uracils with **7** in the presence of TMS triflate in acetonitrile at room temperature for 5 days. In their study, the yields of the "bis" compounds exceeded those of the desired α nucleoside to such an extent that in one case the yield of the "bis" compound was 81% and that of the α nucleoside was only 1.5%. In the present study, the yield of **13A** was about 16-19% and that of **13B** was 8% while the desired glycosylation products were obtained in 22-27% and 25%, respectively. Thus, in contrast to literature precedents, **13A** and **13B** were not the major products. It was found that the formation of the undesired **13B** was suppressed by the slow addition of the bromosugar **8** to the solution of the imidazole counterpart over a period of 6 hours (Trial 7, Table 1).

The structures assigned to **13A** and **13B** were supported by their ^{1}H NMR data. The imidazole signals converged to a singlet due to the symmetrical nature of each molecule. The integration patterns on the ^{1}H NMR spectra also revealed a 1:1 ratio between the 2 imidazole protons and $C_{1'}$ protons on the sugar, indicating that there were 2 $C_{1'}$ protons present. These 2 $C_{1'}$ protons showed downfield shifts[18] up to 0.24 ppm for

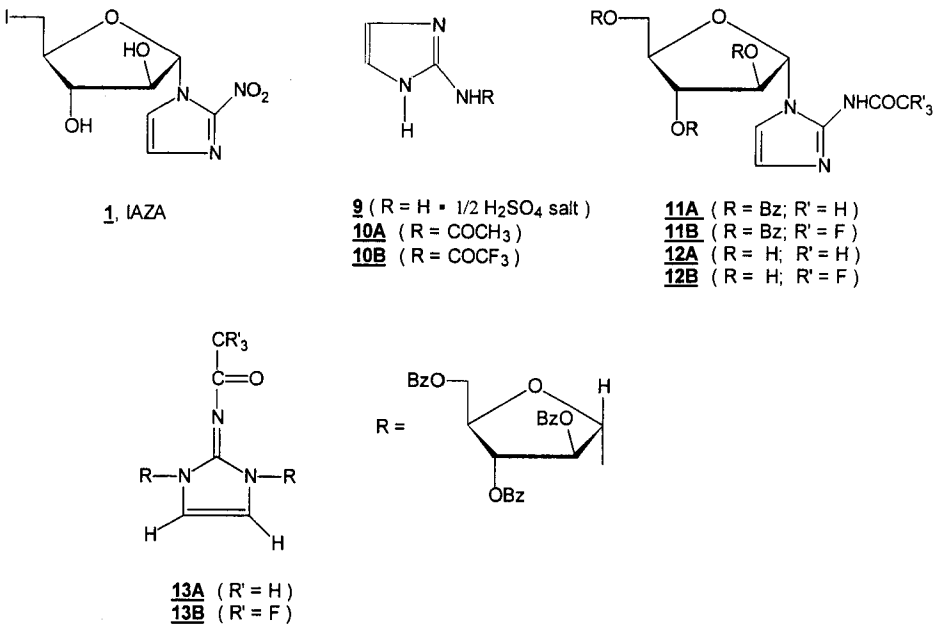


Figure 1. Structure of IAZA (**1**) and synthetic products **10** – **13**.

13A and 0.28 ppm for **13B** relative to their monoglycosylated counterparts. The slight downfield shifts were probably due to the electron-withdrawing effects of the conjugated exocyclic amides, especially in **13B** which contains the trifluoroacetamide. Unambiguous identification of these "bis" compounds was assisted by low-resolution fast atom bombardment (FAB) mass spectra where the $[M+H]^+$ peaks were 1014 and 1068 for **13A** and **13B**, respectively. The reactions outlined in Table 1 gave the α configuration nucleoside stereoselectively, and in no case was formation of the corresponding β-anomer of **11A** and **11B** detected.

Deprotection reaction

Four deprotection reaction trials were performed on selected glycosylation products (Table 2). The deprotection reactions included debenzoylation with NH_3/MeOH on the sugar moiety and amide cleavage on the nucleobase under basic conditions. In the first three reactions the intermediates **12A** or **12B** were isolated prior to further amide cleavage reaction

TABLE 2. Deprotection reactions of selected glycosylation products.

De-protection	Coupled product	De-benzoylation Conditions	Yield of amide (%)	Amide Cleavage condition	AIA (4) yield
1	**11A**	NH_3/MeOH 4°C, 15 h	**12A**, 74%	Et_2NH/CH_3CN reflux, 5 h	Not observed
2	**11A**	NH_3/MeOH 4°C, 22 h	**12A**, 73%	EtOH/KOH/ H_2O, reflux, 3 h	Yes, 65%
3	**11B**	NH_3/MeOH 25°C, 15 h	**12B**, 42%	Not performed	-
4	**11B**	NH_3/MeOH 25°C	ND	NH_3/ MeOH 25°C 100h (total)	Yes, 68%

ND = Not Determined (and not isolated).

The debenzoylation reactions with NH_3/MeOH (at 4 or 25°C) were carried out according to published procedures [3,9,12,13] and were generally successful (Trials 1-3). The cleavage of the amides proved to be more difficult than the debenzoylation reactions. The acetamide **12A** was cleaved in refluxing ethanol and aqueous base to give 65% of **4**. Cleavage of **12B** required less vigorous reaction conditions. In trial 4, trifluoroacetamide **11B** was converted directly into **4** in 68% yield by standing in a solution of ammonia (2 molar) in methanol for 100h at room temperature. The spectral data and chromatographic behaviors of **4** were identical with those of AIA obtained from the reduction of AZA.

The structural assignment of **4** was made essentially on the basis of ^{1}H-NMR spectroscopy (^{1}H-^{1}H COSY and NOE observations). NOE correlation results indicated the spatial interactions between the H_2' proton on the sugar and the C_5-H proton on the imidazole ring (Table 3 and Figure 2). These observations strongly suggest an α nucleoside. If it were β, the strong NOE enhancement signal between C_5-H and H_2' (12.3%) would be very unlikely. Other NOE correlations (H_4' and C_5-H; H_1' and H_3') gave additional support for the α configuration of **4** and was consistent with literature

TABLE 3. ^{1}H NMR data of the AIA (**4**) and IAIA (**2**).

	AIA (**4**)	IAIA (**2**)
^{1}H NMR (D_2O)	Imidazole protons (C_4-H & C_5-H): δ6.53 & δ6.81 H_1': δ5.43 ($J_{1',2'}$ = 6.35 Hz) H_2': δ4.36, H_3': δ4.08, H_4': δ4.01, H_5': δ3.68 & 3.59	Imidazole protons (C_4-H & C_5-H): δ6.74 & 6.93 H_1': δ5.64 ($J_{1',2'}$ = 5.2 Hz) H_2' δ4.45, H_3': δ4.10, H_4': δ4.10 H_5': δ3.43 & 3.33
NOE correlation results	(D_2O) H_1'*: C_5-H (1.9%) H_2' (3.3%) H_3' (5.0%) H_5' (1.0%) C_5-H*: C_4-H (5.6%) H_1' (2.6%) H_2' (12.3%) H_4' (2.5%) Structure shown in Figure 2	(CD_3OD): H_1'*: C_5-H (1.6%) H_2' (3.6%) H_3' (2.0%) C_5-H*: H_1' (2.4%) H_2' (5.5%) H_4' (1.0%) Structure shown in Figure 2

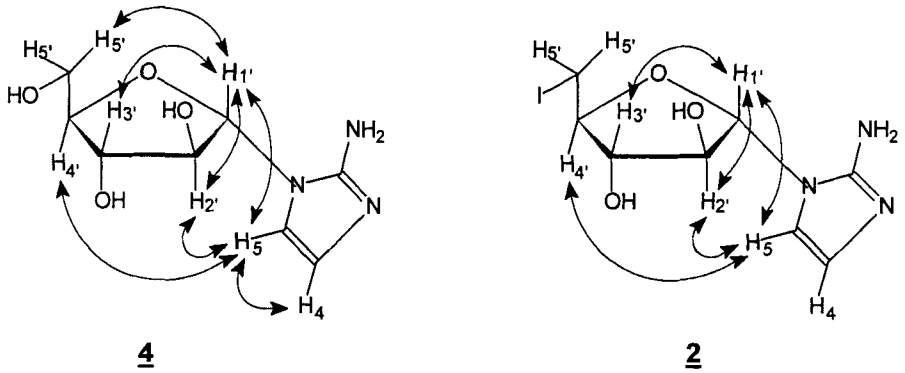


Figure 2. Spatial interactions of hydrogens on compounds **2** and **4** leading to NOE correlations.

observations[19]. Molecular orbital (MO) calculations (PM3 method[20], MOPAC version 94) on **4** predicted that the spatial distances between **C_5-H-H_2'**, C_5-H-H_4' and H_1'-H_3' are **2.073**, 3.563, and 3.916 Å, respectively. Because an NOE signal falls off with the inverse sixth power of distance, protons must be within approximately 5 Å of each other for an NOE between them to be observed[21]. These predicted spatial distances are well within 5 Å and thus are very likely to be observed. The corresponding distances for β-AIA (**4**) were predicted to be **4.716**, 4.468, and 4.126 Å, respectively. These larger spatial distances in the β anomer (especially in C_5-H-H_2' where the distance is more than doubled) are not likely to generate a strong NOE enhancement[19]. It should be emphasized that these MO calculations are performed on molecules in isolation and do not take into account any solvent effects. Nevertheless, these calculations provide a theoretical framework for intramolecular distances.

Subsequent iodination reactions afforded **2** (IAIA) in moderate yield. The structure of **2** was determined by comparison of its NMR spectra with that of **4** and by NOE analysis (Table 3 and Figure 2).

X-ray crystallographic analysis would be the preferred technique to confirm the proposed anomeric configuration of AIA and IAIA. Unfortunately both aminoimidazole derivatives AIA and IAIA were syrupy and could not be crystallized. In contrast, the nitroimidazole derivative AZA gave suitable crystals from alcohol solution. The crystallized AZA was investigated by the X-ray diffraction method. The absolute structure of AZA is shown in Figure 3. The X-ray data show that the anomeric configuration of AZA is α. Because the anomeric configuration of AZA would not be changed during the formation of AIA by the catalytic reduction performed under neutral conditions, the X-ray result of AZA serve to confirm the suggested α configuration for AIA and IAIA.

The synthesis of AZA has been reported by several groups[3, 9, 12]. Schneider *et al.* reported approximately equal yields of both the α and β anomers but did not provide detailed spectroscopic data to support the assignments[9]. Following their method we obtained 1-(2, 3, 5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-nitroimidazole (**14**) the tri-O-benzoyl blocked AZA in 50% yield with no evidence of the β anomer. Some side

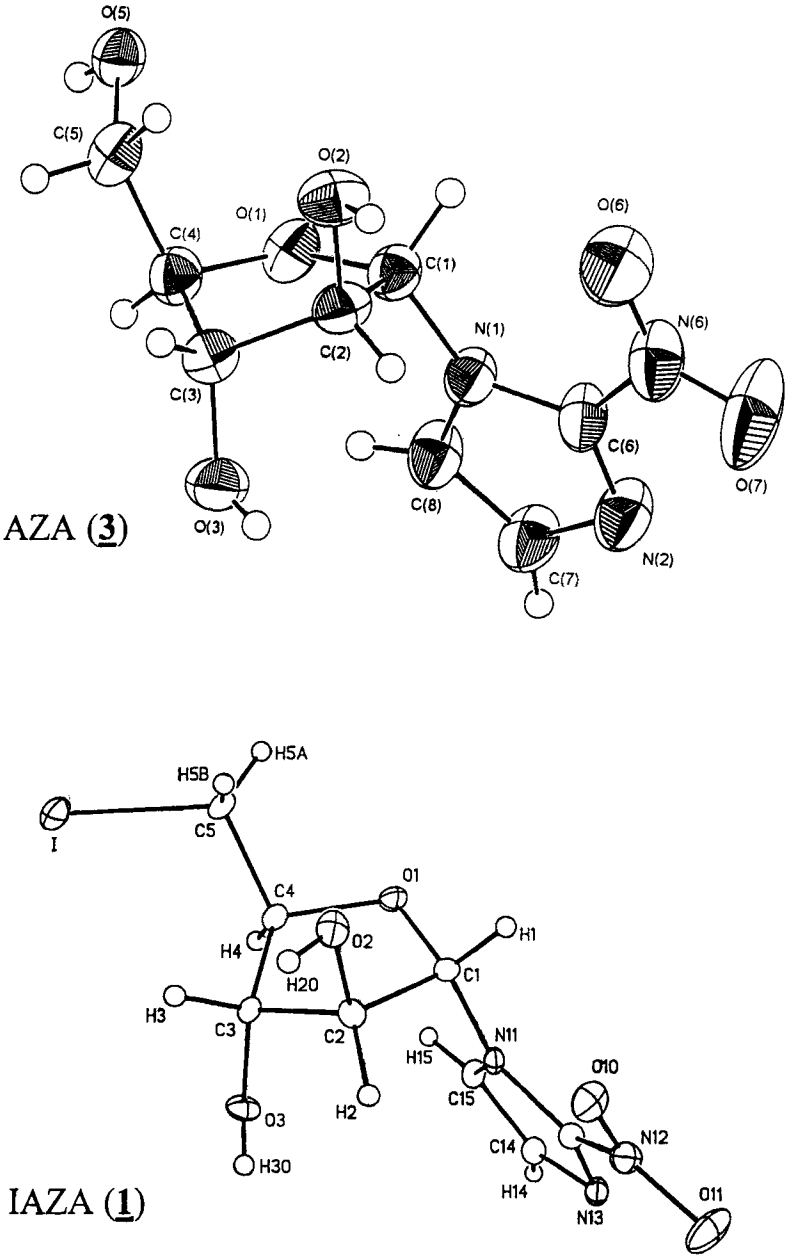


Figure 3. Absolute structures of AZA and IAZA from X-ray crystallographic analysis.

products were observed with Rf values higher than that of the α nucleoside, but none of them was found to be the β nucleoside based on their spectral data.

The results obtained for the absolute configuration of AZA were inconsistent with the previously reported assignment of the β configuration for IAZA (1)[3]. This prompted a reevaluation of the literature data. The reported ^{1}H NMR data for IAZA show H_1'–H_2' coupling constants to be small (<1 Hz) as a strong indication that this compound in fact possesses the α configuration[3]. This configuration has now been confirmed by X-ray crystallography (Figure 3).

CONCLUSIONS

The synthesis of AIA from D-arabinose was achieved in 5 steps in about 5% overall yield. The glycosylation reaction gave α-nucleoside stereoselectively. The presence of a benzoyl group at C2 would direct the reaction pathway to a C1'-C2' *trans* nucleoside as defined by the trans rule of nucleoside synthesis[6]. The absolute configuration of AZA was determined to be α by X-ray crystallography and the unambiguous relationship between AZA and AIA confirms the α configuration for the nucleoside analogs in the present work. The configuration of IAZA, initially reported to be β[3], has now been reassigned to α based on the X-ray crystallographic analysis. This study may be instructive in the prospective and retrospective determination of anomeric configuration in sugar-coupled imidazoles. Further investigations of radioiodinated IAIA as a SPECT imaging agent are in progress.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) and a Bruker AM 300 MHz spectrometer. ^{1}H-NMR chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard. ^{13}C-NMR chemical shifts are recorded based on residual signals of deuterated solvents. Low and high resolution mass spectra were recorded on a JEOL JMS-HX110 spectrometer for POSFAB MS (matrix: glycerol or 3-nitrobenzyl alcohol), and on a JEOL JMS-DX303 spectrometer for electron impact (EI) MS. Silica gel column chromatography was performed Kieselgel Si-60 (70-230 mesh) (Merck). Thin layer chromatography was

carried out on silica gel 60 F_{254} pre-coated (Merck). Preparative TLC was performed on silica gel 60 F_{254} pre-coated plates (20 x 20 cm) for preparative layer chromatography (Merck). High-pressure liquid chromatography (HPLC) was used to purify selected glycosylation products. Silica gel HPLC was conducted on a Shim-pac PRC-Sil (H) column (25 cm x 20 mm i.d. for preparative scale) (Shimadzu) and on a Shim-pac HRC-SIL column (25 cm x 4 mm i.d. for analytical scale), using a Shimadzu LC-6A apparatus with monitoring at 254 nm. Reverse-phase HPLC was performed on a STR-ODS II (25 cm x 4 mm i.d. for analytical scale) column and a Shim-pac PREP-ODS (25 cm x 20 mm i.d. for preparative scale) eluting with water, using the same Shimadzu apparatus. Molecular orbital (MO) calculations were performed by the PM3 method with CAChe MOPAC version 94 (Release 3.7, CAChe Scientific, Inc) running on a personal computer, Power Macintosh 8100/100AV (Apple Computer).

Methyl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside (7) The title compound 7 was prepared from D-(-)-arabinose 5 (10.0 g, 0.067 mol) according to published procedures [7-9]. Crystalline 7 was obtained from absolute ethanol and was used directly (17.4 g, 54%). Melting point 99-101°C (Lit. 100-101.5°C) [7,8]. TLC R_f = 0.39 (hexane-ethyl acetate 4:1 (v/v)). ^{1}H NMR ($CDCl_3$): δ 7.28-8.13 (15H, m, 3 x C_6H_5), 5.58 (1H, d, $J_{3,4}$ = 4.9 Hz, C_3-H), 5.51 (1H, d, $J_{2,3}$ = 1.2 Hz, C_2-H), 5.18 (1H, s, C_1-H), 4.84 (1H, dd, $J_{5,5'}$ = 12.0 Hz, $J_{5,4}$ = 3.4 Hz, C_5-H), 4.69 (1H, dd, $J_{5',5}$ = 12.0 Hz, $J_{5',4}$ = 4.9 Hz, $C_{5'}$-H), 4.57 (1H, dd, $H_{4,5'}$ = 4.9 Hz, $H_{4,5}$ = 3.4 Hz, C_4-H). ^{13}C NMR ($CDCl_3$): δ 165.8-167.0 (3 x C=O), 128.3-133.5 (3 x C_6H_5), 106.9 (C_1), 82.2 (C_4), 80.9 (C_2), 78.0 (C_3), 63.7 (C_5), 55.0 (OCH_3). ^{1}H-^{1}H NOESY ($CDCl_3$): H_4 had cross peaks with methyl protons in OCH_3, confirming its α configuration.

1-Bromo-2,3,5-tri-O-benzoyl-α-D-arabinofuranose (8) The sugar bromide 8 was prepared from 7 (1.0 g, 2.10 mmol) with 25% hydrogen bromide-acetic acid (9 mL) in a mixture of acetic acid (9 mL) and dichloromethane (2 mL) according to published procedures [7-9]. Crystalline 8 (475 mg, 43%) was obtained from absolute ether (5 mL) after keeping the ethereal solution in the dark for 15 h at 0°C. TLC indicated a single spot (R_f = 0.38 in ethyl acetate-hexane 3:7(v/v)) with no UV active spots at R_f = 0. (Literature TLC[9] R_f = 0.38 in ethyl acetate-hexane 3:7(v/v)). Melting point 100-102°C (Literature mp[7] 103-104°C). ^{1}H NMR ($CDCl_3$): δ 7.28-8.16 (15H, m, 3 x C_6H_5), 6.63 (1H, s, C_1-H), 5.96 (1H,

s, C_2-H), 5.63 (1H, d, $J_{3,4}$ = 4.4 Hz, C_3-H), 4.92 (1H, dd, $J_{5,4}$ = 3.2 Hz, $J_{5,5'}$ = 11.0 Hz, C_5-H), 4.87 (1H, dt, $J_{4,5}$ = 3.2 Hz, $J_{4,5'}$ = 4.4 Hz, C_4-H), 4.78 (1H, dd, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 4.4 Hz, $C_{5'}$-H). ^{13}C NMR ($CDCl_3$): δ 166.0, 165.7, 165.1 (3 x C=O), 128.4-133.8 (3 x C_6H_5), 88.5 (C_1), 85.7 (C_4), 84.6 (C_2), 77.2 (C_3), 62.6 (C_5).

2-Acetamidoimidazole (**10A**) Triethylamine (2.5 mL, 18 mmol) was added to a stirred suspension of finely powdered 2-aminoimidazole sulfate **9** (2.01 g, 15 mmol) in acetic anhydride (20 mL) and the resulting suspension was stirred at 25°C for 42 h. Absolute ethanol (50 mL) was subsequently added to the resulting clear solution and the ethanolic solution was further stirred at 25°C for 15 min and then under reflux (at 80°C) for 20 h. After evaporation of the solvent, the residue was treated with chloroform (30 mL) to afford a crude solid (1.44 g). The mother liquor was concentrated and the resulting syrupy material gave a further 231 mg of crystalline product on standing (total crude yield: 1.67 g, 88%). Recrystallization from 2-propanol (100 mL) gave **10A** as light brown needles (1.28 g, 67%). Melting point 238-240°C (Lit. 287°C[22] and 284-285°C[23]). ^{1}H NMR (CD_3OD): δ 6.77 (2H, s, C_4-H & C_5-H), 2.15 (3H, s, $NHCOCH_3$). TLC R_f = 0.25 in chloroform-methanol 9:1 (v/v). LR (EI) MS *m/z* (%): 125(M^+, 32), 83(100). *Anal.* Calcd. For $C_5H_7N_3O$: C, 47.98; H, 5.65; N, 33.58. Found: C, 48.06; H, 5.64; N, 33.53

2-Trifluoroacetamidoimidazole (**10B**) Triethylamine (3.2 mL, 23 mmol) was added dropwise to a cooled, stirred suspension of finely powdered 2-aminoimidazole sulfate **9** (1.0 g, 7.6 mmol) in trifluoroacetic anhydride (10 mL). The resulting clear solution was stirred at 25°C for 15 h after which the solution was concentrated to thick syrup. 2-Propanol (30 mL) was added and the resulting suspension was filtered to give 0.80 g (60%) of milky white solids that were used directly. An analytical sample was prepared by recrystallization in 2-propanol. Melting point 233-235°C. TLC R_f = 0.33 in ethyl acetate-hexane 3:2 (v/v). ^{1}H NMR (CD_3OD): δ6.94 (2H, s, C_4-H and C_5-H). LR (EI) MS *m/z* (%): 179(M^+, 100). *Anal.* Calcd. For $C_5H_4F_3N_3O$: C, 33.38; H, 2.30; N, 23.37. Found: C, 33.53; H, 2.25; N, 23.46.

1-(2,3,5 Tri-O-benzoyl-α-D-arabinofuranosyl)-2-acetamidoimidazole (**11A**) and 1,3-bis-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-acetamidoimidazole (**13A**). The sugar bromide **8** (30.5 mg, 0.058 mmol) was added to a stirred suspension of 2-acetamidoimidazole **10A** (11 mg, 0.088 mmol) and potassium carbonate (24 mg, 0.17

mmol) in dry acetonitrile (10 mL) under argon atmosphere. The resulting suspension was stirred at 25°C in a sealed reaction flask for 13 h after which a clear solution resulted. TLC indicated the formation of two major products. The solution was stirred at 25°C for an additional 47 h and then under reflux for 3 h. After evaporation of the solvent, the residue was treated with chloroform (20 mL). The filtered chloroform solution was concentrated to give a residue (24 mg) which was purified by preparative TLC using ethyl acetate-methanol (19:1 (v/v)) to give **11A** (9 mg, 28%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 7.35-8.11 (15H, m, 3 x C_6H_5), 7.05 (1H, br s, C_5-H), 6.90 (1H, br s, C_4-H), 6.38 (1H, br s, C_1'-H), 6.10 (1H, br s, C_2'-H), 5.72 (1H, br s, C_3'-H), 4.92 (1H, m, C_4'-H), 4.75 (2H, m, 2 x C_5'-H), 2.11 (3H, s, $NHCOCH_3$). ^{13}C NMR ($CDCl_3$): δ 165.0-166.1 (4 x C=O), 128.4-133.8 (3 x C_6H_5, C_2, C_4 & C_5), 90.0 (C_1'), 83.9 (C_4'), 80.4 (C_2'), 77.9 (C_3'), 63.9 (C_5'), 25.2 ($NHCOCH_3$). LR (EI) MS *m/z* (%): 569(M^+, 0.43), 105(100). HR (FAB) MS ($C_{31}H_{28}O_8N_3$): Calcd. mass 570.1876. Exact mass 570.1854. Another product with a higher R_f value was isolated (**13A**, 11 mg, 19%) and confirmed to be 1,3-bis (2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-acetamidoimidazole. ^{1}H NMR ($CDCl_3$): δ 7.28-8.04 (30H, m, 6 x C_6H_5), 6.94 (2H, s, C_4-H & C_5-H), 6.60 (2H, s, 2 x C_1'-H), 6.00 (2H, s, 2 x C_2'-H), 5.52 (2H, s, 2 x C_3'-H), 4.78 (2H, m, 2 x C_4'-H), 4.72 & 4.63 (4H, m, 2 x C_5'-H), 1.83 (3H, s, $NHCOCH_3$). LR (FAB) MS *m/z* (%): 1014($[M+H]^+$, 15), 105(100).

1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-2-trifluoroacetamidoimidazole (**11B**) and 1,3-bis (2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-trifluoroacetamidoimidazole (**13B**)

A solution of 1-Bromo-2,3,5-tri-O-benzoyl-α-D-arabinofuranose (**8**) (1.594 g, 3.03 mmol) in benzene (200 ml) was added dropwise to a solution of trifluoroacetaminoimidazole (545 mg, 3.04 mmol) in acetonirile (540 mL) in the presence of potassium carbonate (330 mg, 2.39 mmol) over a period of 6 hours, and then kept overnight at room temperature. After purification by silica gel column chromatography with 3% ethyl acetate in dichloromethane, the coupled product 1-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-trifluoroacetamidoimidazole (**11B**) was obtained in 76% yield (1.43 g). TLC R_f = 0.56 in ethyl acetate-hexane (1:1 (v/v)). ^{1}H NMR ($CDCl_3$): δ 11.84 (1H, br s, NH), 7.34-8.11 (15H, m, 3 x C_6H_5), 6.96 (1H, d, J = 2.4 Hz, C_5-H), 6.88 (1H, d, J = 2.4 Hz, C_4-H), 6.43 (1H, d, $J_{1',2'}$ = 3.9 Hz, C_1'-H), 6.20 (1H, t, $J_{2',1'}$ = 3.9 Hz, $J_{2',3'}$ = 3.9 Hz, C_2'-H), 5.86 (1H, t, $J_{3',4'}$ = 4.4 Hz, C_3'-H), 5.08 (1H, ddd, $J_{4',5'a}$ = 4.9 Hz, $J_{4',5'b}$ = 3.9 Hz, C_4'-H), 4.80 (1H, dd,

$J_{5'a,5'b}$ = 12.2 Hz, $J_{5'a,4'}$ = 4.9 Hz, C_5'-H_a), 4.70 (1H, dd, $J_{5'b,5'a}$ = 12.2 Hz, $J_{5'b,4'}$ = 3.9 Hz, C_5'-H_b). ^{13}C NMR ($CDCl_3$): δ 164.3-166.1 (4 x C=O), 149.4 (C_2), 128.3-133.8 (3 x C_6H_5), 112.8 (C_4 & C_5), 89.2 (C_1'), 82.7 (C_4'), 80.8 (C_2'), 77.5 (C_3'), 64.2 (C_5'). LR (FAB) MS *m/z* (%): 624 ($[M+H]^+$, 68), 105(100). HR (FAB) MS ($C_{31}H_{25}O_8N_3F_3$): Calcd. mass 624.1594. Exact mass 624.1581. Another product **13B** with a slightly higher R_f value (0.60 in ethyl acetate-hexane 1:1 (v/v)) was isolated in 7% yield. ^1H NMR ($CDCl_3$): δ 7.35-8.10 (30H, m, 6 x C_6H_5), 7.15 (2H, s, C_4-H & C_5-H), 6.71 (2H, $J_{1',2'}$ = 2.45 Hz, 2 x C_1'-H), 5.93 (2H, t, $J_{2',3'}$ = 2.2 Hz, 2 x C_2'-H), 5.64 (2H, t, $J_{3',4'}$ = 2.4 Hz, 2 x C_3'-H), 4.93 (2H, dt, $J_{4',5'a}$ = 5.9 Hz, $J_{4',5'b}$ = 4.9 Hz, 2 x C_4'-H), 4.81 (2H, dd, $J_{5'a,5'b}$ = 11.9 Hz, $J_{5'a,4}$ = 5.9 Hz, 2 x C_5'-H_a), 4.69 (2H, dd, $J_{5'b,5'a}$ = 11.9 Hz, $J_{5'b,4}$ = 4.9 Hz, 2 x C_5'-H_b). LR (FAB) MS *m/z* (%): 1068($[M+H]^+$, 18), 445(100).

1-(α-D-Arabinofuranosyl)-2-acetamidoimidazole (**12A**) A solution of **11A** (30.5 mg, 0.054 mmol) in absolute methanol (10 mL) was saturated with NH_3 at 0°C for 15 min. The resulting solution was kept at 4°C for 22 h after which the solvent was evaporated. The residue (23 mg) was purified by preparative TLC using chloroform-methanol (7:3 (v/v)) to give **12A** (10.1 mg, 73%) as a syrup. TLC R_f = 0.46 in chloroform-methanol (7:3 (v/v)). ^1H NMR (CD_3OD): δ 7.33 (1H, s, C_5-H), 6.90 (1H, s, C_4-H), 5.60 (1H, d, $J_{1',2'}$ = 3.9 Hz, C_1'-H), 4.28 (1H, dd, $J_{2',3'}$ = 4.8 Hz, C_2'-H), 4.15 (1H, m, $J_{4',5'a}$ = 3.4 Hz, C_4'-H), 4.09 (1H, dd, $J_{3',4'}$ = 5.4 Hz, C_3'-H), 3.75 (1H, dd, $J_{5'a,5'b}$ = 12.1 Hz, $J_{5'a,4'}$ = 3.4 Hz, C_5'-H_a), 3.66 (1H, dd, $J_{5'b,5'a}$ = 12.1 Hz, $J_{5'b,4'}$ = 4.9 Hz, C_5'-H_b), 2.13 (3H, s, $NHCOCH_3$). LR (EI) MS *m/z* (%): 257(M^+, 5.5), 43(100).

1-(α-D-Arabinofuranosyl)-2-trifluoroacetamidoimidazole (**12B**) A solution of **11B** (17.3 mg, 0.028 mmol) in absolute methanol (5 mL) was saturated with NH_3 at 0°C for 10 min. The resulting solution was kept at 25°C for 15 h after which it was concentrated to dryness. The residue (6 mg) was chromatographed on a column containing silica gel (3 g) using chloroform-methanol (7:3 (v/v)) to give 3.5 mg (42%) of **12B** as an oily residue. TLC R_f = 0.59 in chloroform-methanol (7:3 (v/v)). ^1H NMR (CD_3OD): δ 7.30 (1H, d, J = 2.4 Hz, C_5-H), 6.97 (1H, d, J = 2.4 Hz, C_4-H), 6.04 (1H, d, $J_{1',2'}$ = 3.9 Hz, C_1'-H), 4.36 (1H, dd, $J_{2',3'}$ = 4.4 Hz, C_2'-H), 4.23 (1H, m, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.9 Hz, C_4'-H), 4.14 (1H, dd, $J_{3',4'}$ = 4.9 Hz, C_3'-H), 3.76 (1H, dd, $J_{5'a,5'b}$ = 12.0 Hz, $J_{5'a,4'}$ = 3.9 Hz, C_5'-H_a), 3.68 (1H, dd, $J_{5'b,5'a}$ = 12.0 Hz, $J_{5'b,4'}$ = 4.9 Hz, C_5'-H_b). LR (EI) MS *m/z* (%): 311(M^+, 1), 110(100).

1-(α-D-Arabinofuranosyl)-2-aminoimidazole (AIA, **4**) Method A 1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-2-trifluoroacetamidoimidazole (**11B**) (678 mg, 1.09 mmol) was dissolved in a 2 molar solution of ammonia in methanol (50 mL), and kept in the dark for 100 h at room temperature. The reaction mixture was purified by reverse-phase HPLC, eluting with water to give the deblocked product (AIA) in 68% yield (159.5 mg). ^{1}H NMR (D_2O): δ 6.81 (1H, d, J = 1.95 Hz, C_5-H), 6.53 (1H, d, J = 1.95 Hz, C_4-H), 5.43 (1H, d, $J_{1',2'}$ = 6.35 Hz, C_1'-H), 4.36 (1H, t, $J_{2',1'}$ = 6.35 Hz, $J_{2',3'}$ = 6.35 Hz, C_2'-H), 4.08 (1H, dd, $J_{3',2'}$ = 6.35 Hz, $J_{3',4'}$ = 7.3 Hz C_3'-H), 4.01 (1H, ddd, $J_{4',5'a'}$ = 2.9 Hz, $J_{4',5'b'}$ = 4.9 Hz C_4'-H), 3.68 (1H, dd, $J_{5'a,5'b}$ = 12.7 Hz, $J_{5'a,4'}$ = 2.9 Hz, C_5'-H_a), 3.59 (1H, dd, $J_{5'b,5'a}$ = 12.7 Hz, $J_{5'b,4'}$ = 4.9 Hz C_5'-H_b). ^{13}C NMR (D_2O): δ 150.4 (C_2), 125.0 (C_4), 113.9 (C_5), 87.8 (C_1'), 83.7 (C_4'), 80.1 (C_2'), 75.1 (C_3'), 61.7 (C_5'). LR (FAB) MS *m/z* (%): 216([M+H]$^+$, 69), 185(80), 93(100). HR (FAB) MS ($C_8H_{14}O_4N_3$): Calcd. mass 216.0984. Exact mass 216.0991.

1-(α-D-Arabinofuranosyl)-2-aminoimidazole (AIA, **4**) Method B A solution of **3** (100 mg, 0.41 mmol) in 95% ethanol was reduced under 1 atmosphere of hydrogen at 25^{0}C for 2 h in the presence of palladium/carbon (12.2 mg). The mixture was filtered and the filtrate evaporated to give AIA (**4**) (90 mg, 88%) as a residue that was used directly. ^{1}H NMR and ^{13}C NMR were identical to AIA obtained from Method A.

1-(5-Deoxy-5-iodo-α-D-arabinofuranosyl)-2-aminoimidazole (IAIA, **2**) Iodine (185 mg, 0.73 mmol) and triphenylphosphine (221.5 mg, 0.73 mmol) were added to a solution of **4** (78 mg, 0.36 mmol) in dry pyridine (2 mL) and the resulting solution was stirred at 25^{0}C for 2 h. The solution was concentrated to dryness and the residue was chromatographed on a column containing silica gel using chloroform-methanol (19:1 (v/v)) to give 47 mg (40%) as an oily residue. ^{1}H NMR (D_2O): δ 6.93 (1H, d, J = 2.6 Hz, C_5-H), 6.74 (1H, d, J = 2.6 Hz, C_4-H), 5.64 (1H, d, $J_{1',2'}$ = 5.2 Hz, C_1'-H), 4.45 (1H, dd, $J_{2',3'}$ = 5.5 Hz, C_2'-H), 4.10 (2H, m, $J_{4',5'a}$ = 4.3 Hz, C_3'-H & C_4'-H), 3.43 (1H, dd, $J_{5'a,5'b}$ = 10.0 Hz, $J_{5'a,4}$ = 4.3 Hz, C_5'-H_a), 3.33 (1H, dd, $J_{5'b,5'a}$ = 10.0 Hz, $J_{5'b,4}$ = 5.3 Hz, C_5'-H_b). ^{13}C NMR (D_2O): δ 147.2 (C_2), 114.8 (C_4), 113.8 (C_5), 88.8 (C_1'), 83.8 (C_4'), 79.9 (C_2'), 78.7 (C_3'), 6.6 (C_5'). LR (ESI) MS *m/z* (%): 326([M+H]$^+$, 100). HR (ESI) MS ($C_8H_{13}N_3IO_3$): Calcd. mass 326.000168. Exact mass 326.000624.

Glycosylation reactions with silylated 2-aminoimidazole derivatives (Trials 1 & 9) These glycosylation reactions were modified from published procedures[13]. A suspension of **10A** (15 mg, 0.12 mmol) or finely powdered **9** (16.4 mg, 0.12 mmol) in hexamethyldisilazane (1-5 mL) was refluxed for 2.5-3 h, after which the excess reagent was evaporated to give an oily residue. A solution of the sugar bromide **8** (30 mg, 0.058 mmol), in dry acetonitrile (10 mL) or dry benzene (20 mL), and mercuric cyanide (28.3-49.6 mg, 0.11-0.196 mmol), were added to the silylated residue and the reaction mixture was refluxed for 12 h. After evaporation of the solvent, the filtered chloroform solution (20-30 mL) was successively washed with 30% potassium iodide solution (20-30 mL), saturated sodium bicarbonate (30 mL) and water (20-30 mL). The dried solution (Na_2SO_4) was concentrated to give a residue (15-27.2 mg) which was purified by preparative TLC using ethyl acetate-hexane (4:1 or 3:7 (v/v)). There were 6 major products (0.6-4.4 mg, total 15.8 mg) in Reaction 1 and 9 major products (0.8-4.3 mg, total 19 mg) in Reaction 9. These products showed very complex ^1H NMR data and were not further studied.

Glycosylation in dichloromethane (Trial 8). A solution of the sugar bromide **8** (34 mg, 0.065 mmol) in dry dichloromethane (10 mL) was added to a suspension of **10B** (21 mg, 0.116 mmol) in dry dichloromethane (120 mL) and the resulting suspension was stirred at 25-28°C for 3.5 days. The solvent was evaporated and the filtered solution of chloroform (20 mL) was washed successively with saturated sodium bicarbonate (20 mL) and water (20 mL). The dried solution (Na_2SO_4) was concentrated to give a syrup (50 mg) which was purified by preparative TLC to give 5 major products (0.5-13.2 mg, total 27.8 mg). The glycosylation product **11B** was isolated (8.3 mg, 20%) and was found to be identical by ^1H NMR to that obtained in Trial 7.

Azomycin arabinoside (AZA, **3**) The coupling reaction of protected sugar bromide **8** with nitroimidazole in the presence of mercuric cyanide was performed according to Schneider's method.[9]. The reaction mixture was purified by HPLC on silica gel with 25% ethyl acetate in hexane to give the coupled product, 1-(2, 3, 5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-nitroimidazole (**14**) in 50% yield. The spectral data and chromatographic behaviors of **14** were identical with literature values[9,12]. The subsequent deblocking reaction of **14** (490 mg, 0.88 mmol) was performed in a 2 molar solution of ammonia in methanol (60 mL) at 4°C for 24 h. After removal of the solvent, the residue

was submitted to silica gel column chromatography using 10% methanol in chloroform as eluent to give AZA (197 mg, 91%). The ^{1}H NMR spectrum was identical with published data[3, 9, 12]. Single crystals for X-ray crystallographic analysis were obtained by recrystallization from ethanol. Mp 155-156°C (lit.153-155°C[9], 160°C[12])

X-ray Crystallography of AZA (3) The diffraction experiment was carried out using a colorless transparent prism with dimensions of 0.9 x 0.6 x 0.1 mm. The diffractometer, Mac Science MXC18K, was used with monochromated CuKα radiation (λ=1.5418 Å). The unit cell dimensions were determined from angular settings of 22 reflections (2θ values in the range of 50-60°), affording the following crystal data: $C_8H_{11}N_3O_6$, Mr = 245.00, a = 10.012(3), b = 7.186(2), c = 7.453(3)Å, ß = 103.89(3)°, V = 520.5(3)Å^3, monoclinic, $P2_{1/a}$, Z = 2, Dx = 1.563 g/cm^3. 1189 unique reflections ($2\theta \leq 140°$) were measured, of which 1047 with $|F0| \geq 3.00\sigma$ (F0) were considered as observed. The structure was solved by maXus. The refinement of atomic parameters was carried out using the block diagonal least-squares method with anisotropic temperature factors. The atomic scattering factors were taken from International Tables for X-ray Crystallography (1974). The final R factor is 0.031.

X-ray Crystallography of IAZA (1) A colorless crystal of 5-deoxy-5-iodo-(2'-nitro-1'-imidazolyl)-α-D-arabinofuranose ($C_8H_{10}IN_3O_5$) with dimensions 0.9 x 0.8 x 0.3 mm was selected and X-ray diffraction data were collected on a Siemens P4/RA instrument with Mo Kα radiation (λ = 0.71073 Å) at –60^{0}C. The compound crystallizes in the monoclinic space group $P2_1$ (No. 4) with a = 11.6446(3) Å, b = 11.9457(6) Å, c = 9.4735(3) Å, V = 1317.79(9) Å^3, Z = 4, ρ_{calcd} = 1.141 g cm^{-3}, μ = 1.418 mm^{-1} (where unit cell parameters were determined from least-squares refinements using the setting angles of 32 centered reflections having $29.7^o < 2\theta < 30.0^o$). The structure was solved via direct methods (*SHELXS*-86) and the model further refined using full-matrix least-squares calculations on F^2 (*SHELXS*-93). The final model with 1717 unique data used and 138 parameters varied, converged to values of R_1 (F_o) = 0.0319 (for 1645 data with $F_o^2 > 2\sigma(F_o^2)$) and $wR_2(F_o^2)$ = 0.0792 (all data). The absolute stereochemistry of the molecule could be unambiguously established from the X-ray data (refinement in the opposite configuration resulted in significantly poorer residuals).

ACKNOWLEDGEMENTS

We thank Dr. Angelina Morales-Izquierdo for her kind assistance in ESI mass spectrometry. This work was supported in part by a Research Initiative Program Grant (RI-14) from Alberta Cancer Board, Edmonton, Alberta, Canada, and from the Taiho Endowed Research Fund.

REFERENCES

1. Parliament, M.B.; Chapman, J.D.; Urtasun, R.C.; McEwan, A.J.; Goldberg, L.; Mercer, J.R.; Mannan, R.H.; Wiebe, L.I. *Brit. J. Cancer,* **1992** ***65***, 90-95.
2. Groshar, D.; McEwan, A.J.B.; Parliament, M.B.; Urtasun, R.C.; Goldberg, L.E.; Hoskinson, M.; Mercer, J.R.; Mannan, R.H.; Wiebe, L.I.; Chapman, J.D. *J. Nucl. Med.* **1993** ***34***, 885-888.
3. Mannan, R.H.; Somayaji, V.V.; Lee, J.; Mercer, J.R.; Chapman, J.D.; Wiebe, L.I. *J. Nucl. Med.*, **1991** ***32***, 1764-1770.
4. Edwards, D.I. *J. Antimicrob. Chemother.*, **1993** ***31***, 9-20.
5. Lee, H.C.; Kumar, P.; McEwan, A.J.; Wiebe, L.I.; Mercer, J.R. *Radiat Res.*, (MS in preparation).
6. Baker, B.R.; Joseph, J.P.; Schaub, R.E. *J. Am. Chem. Soc.*, **1955** ***77***, 5905-5910.
7. Ness, R.K.; Fletcher, H.G .Jr. *J. Am. Chem. Soc.*, **1958** ***80***, 2007-2010; Fletcher, H.G. Jr. *Methods Carbohydr. Chem.*, **1963** ***2***, 228-230.
8. Wright, R.S.; Khorana, H.G. *J. Am. Chem. So.c*, **1958** ***80***, 1994-1998.
9. Schneider, R.F.; Engelhardt, E.L.; Stobbe, C.C.; Fenning, M.C.; Chapman, J.D. *J. Labelled Compd Radiopharm.*, **1997** ***39***, 541-557.
10. Prisbe, E.J.; Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.*, **1978** ***43***, 4774-4783.
11. Nishimura, T.;Shimizu, B.; Iwai, S. *Chem. Pharm. Bull*, **1963** ***11***, 1470-1472.
12. Sakaguchi, M.; Larroquette, C.A.; Agrawal, K.C. *J. Med. Chem.*, **1983** ***26***, 20-24.
13. Prisbe, E.J.; Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.*, **1978** ***43***, 4784-4794.
14. Khan, S.H.; Hindsgaul, O. "Chemical Synthesis of Oligosaccharides". in "Frontiers in Molecular Biology - Molecular Glycobiology",: Editors; Fukuda, M. and Hindsgaul, O., IRL Press, 206-229 (1994).

15. Montgomery, J.A .; Thomas, H.J. *J. Org. Chem.*, **1966** ***31***, 1411-1413.

16. Glaudemans, C.P.J.; Fletcher, H.G. Jr. *J. Org. Chem.*, **1963** ***28***, 3004-3006.

17. Watanabe, K.A.; Hollenberg, D.H.; Fox, J.J. *J. Carbohydr. Nucleosides Nucleotides*, **1974** ***1***:1-37.

18. Jorgenson, P.T.; El-Barbary, A.A.; Pedersen, E.B. *Liebigs Ann. Chem.*, **1993**, 1-5.

19. Rosenmeyer, H.; Toth, G.; Seela, F. *Nucleosides and Nucleotides*, **1989** ***8***, 585-597; Bourgeois, W.; Seela, F. *J. Chem. Soc., Perkin Trans I*, **1991**, 279-283.

20. Stewart, J.J.P.; *J. Comput. Chem.*, **1989** ***10***, 209-220

21. Eliel, E.L.; Wilen, S.H.; Mander, L. "Stereochemistry of Organic Compounds", John Wiley and Sons, NewYork:, 991-1118 (1994).

22. Fargher, R.G .; Pyman, F.L. *J. Chem. Soc. Trans*, **1919** ***115***, 217-260.

23. Heinisch, G.; Reusser, W. *Sci. Pharm.*, **1974** ***42***, 19-33.

Received 8/25/98
Accepted 4/28/99