Pergamon

Tetrahedron Letters 43 (2002) 4427–4429

TETRAHEDRON LETTERS

Synthesis of β-azomycin nucleosides: 1-(β-D-2-iodo-2-deoxyarabinofuranosyl)-2-nitroimidazole (β-2-IAZA), a novel marker of tissue hypoxia

Piyush Kumar,[a] Leonard I. Wiebe,[a,*] Davood Beiki,[a,†] Kazue Ohkura[b] and Koh-Ichi Seki[b]

[a]*Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8*
[b]*Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan*

Received 25 September 2001; revised 4 December 2001; accepted 1 May 2002

Abstract—This study describes a non-conventional approach to the synthesis of 1-β-D-[2-deoxy-2-iodoarabinofuranosyl]-2-nitroimidazole (β-2-IAZA), a positional and configurational isomer of 1-α-D-[5-deoxy-5-iodoarabinofuranosyl]-2-nitroimidazole (IAZA). [^{123}I]IAZA, a radiopharmaceutical used clinically to image regional tissue hypoxia in a number of pathologies, is synthesized by coupling the appropriately protected 1-α-halo arabinofuranoside, with azomycin, with retention of configuration. To circumvent participation of the C-2′ protecting group, which prevents β-anomer formation during coupling, the riboside 1-β-D-(ribofuranosyl)-2-nitroimidazole (AZR) was elaborated to 1-β-D-(3,5-tetraisopropyldisylyloxy-2-*O*-trifluoromethanesulfonylribofuranosyl)-2-nitroimidazole. Nucleophilic displacement of the 2-*O*-trifluoromethanesulfonyl leaving group by iodide results in inversion of configuration at the ribosyl C-2-position, thereby affording silylated arabinofuranosyl-2′-IAZA, which was desilylated under neutral conditions to afford β-2-IAZA.

The effectiveness of conventional low linear energy transfer (LET) radiation (e.g. X-rays) therapies is seriously reduced by hypoxia in tumor tissue.[1] Appropriate compensation for the presence of hypoxic tissue is considered to be important in improving therapeutic outcomes.[2–4] Assessment of tumor hypoxia has been achieved by non-invasive imaging using [^{123}I]iodoazomycin arabinoside ([^{123}I]IAZA) and other nitroimidazole-based radiosensitizers which, due to their unique reduction potential, are selectively trapped in hypoxic cells.[5–8] Hypoxia-selective uptake of [^{123}I]IAZA has been demonstrated in a number of patients with varying pathological disorders including cancer,[9,10] diabetes,[11] arthritis[12] and peripheral vascular disease,[13] making it the most widely studied hypoxia marker in clinical research.

Iodine in IAZA is covalently bound to a primary carbon atom. Primary iodides are much more susceptible to deiodination than secondary iodides. In pre-clinical and clinical studies, [^{123}I]IAZA undergoes modest deiodination, which unnecessarily increases the radiation dose to the thyroid gland and also contributes to undesired background radioactivity in later-time images.[13] It is also known that IAZA, an α-arabinofuranosyl nucleoside, is not transported by cellular nucleoside transporters,[14] whereas many β-arabinosyl nucleosides are efficiently internalized by these transporters.[15]

The present study reports the synthesis of a novel iodoazomycin nucleoside, which is designed to be chemically more stable than IAZA and to be a substrate for cellular *trans*-membrane transport. Initial attempts to synthesize β-analogs of IAZA, by coupling 1-α-bromo-2,3,5-tri-*O*-benzoyl arabinofuranose with 1-trimethylsilyl-2-nitroimidazole, resulted in the exclusive formation of α-coupled product.[16] The formation of α-isomer is attributed to the electronic involvement of carbonyl function of the benzoyl/acetyl protecting group located at the arabinosyl C-2-β position, with bromine located at the arabinosyl C-1-α-position.[17] Intramolecular interaction of the benzoyl carbonyl oxygen with the electropositive C-1 generates stereochemi-

Abbreviations: β-2-IAZA, 1-β-D-[2-deoxy-2-iodoarabinofuranosyl]-2-nitroimidazole; IAZA, 1-α-D-[5-deoxy-5-iodoarabinofuranosyl]-2-nitroimidazole; AZR, 1-β-D-ribofuranosyl-2-nitroimidazole; α-IAZP, 1-α-D-[4-deoxy-4-iodoxylopyranosyl]-2-nitroimidazole; NOE, nuclear Overhauser effect.

Keywords: β-2-IAZA; IAZA; iodoazomycin arabinoside; selective iodination; hypoxia markers.

* Corresponding author. Present address: 3118 Dentistry/Pharmacy Center, University of Alberta, Edmonton, Alberta, Canada T6G 2N8; e-mail: leonard.wiebe@ualberta.ca

† Nuclear Medicine Department, Shariati Hospital, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00845-6

cal hindrance for a nucleophilic (2-nitroimidazole) approach from the β-plane, and consequently results in the exclusive formation of α-azomycin arabinofuranoside.[18] The introduction of alternative protecting groups such as benzyl[19] or substituted silyl (non-carbonylated) groups proceeded sluggishly, and these groups were subject to cleavage during bromination under acidic reaction conditions,[20] and the removal of the benzyl ether protecting groups by catalytic reduction also reduces the nitro substituent on the imidazole ring. It was therefore decided to proceed via the synthesis of AZR,[21] **1**, and to invert the configuration, from ribose to arabinose, during iodination. The synthesis and complete characterization of β-2-IAZA are now reported (Scheme 1).

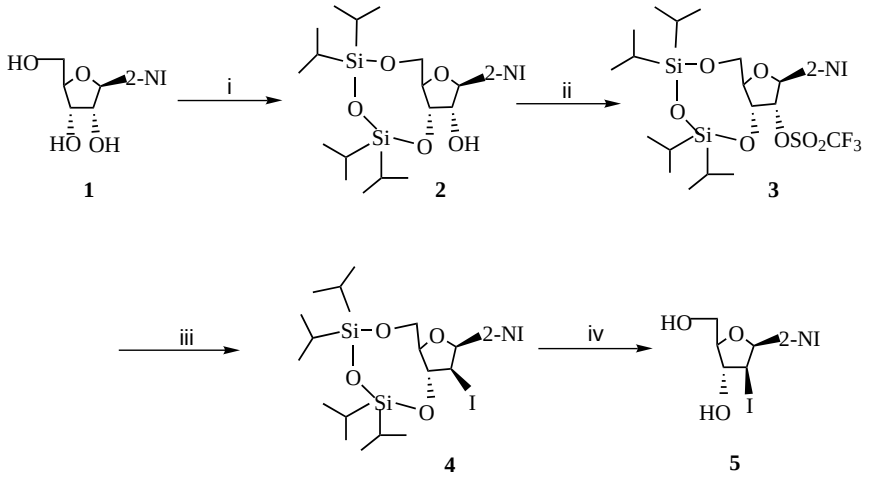
1-β-D-Ribofuranosyl-2-nitroimidazole (AZR) **1** (2.2 g, 8.97 mmol), on treatment with 1,1,3,3-tetraisopropyldisiloxane (3.35 mL, 10.47 mmol) in anhydrous pyridine (30 mL) at 22°C for 16 h, was converted to the corresponding tetraisopropyldisilyloxyribofuranoside **2** in 78% yield (3.4 g). Compound **2** (3.04 g, 6.23 mmol) was treated with trifluoromethanesulfonyl chloride (1.26 mL, 11.84 mmol) and 4-*N*,*N*-dimethylaminopyridine (2.286 g, 18.71 mmol) in anhydrous CH_2Cl_2 (90 mL) for 1.5 h at 0°C to afford corresponding triflate **3** in 88% (3.4 g) yield. Iodination of **3** (63.3 mg, 0.1 mmol) with pulverized sodium iodide (76 mg, 0.51 mmol) in anhydrous 2-pentanone (12 mL) under reflux at 110°C for 1.5 h gave the corresponding tetraisopropyldisilyloxy-2-deoxy-2-iodoarabinofuranoside **4** in 95% yield (58 mg). Deprotection of protective groups in **4** (0.439 g, 0.825 mmol) using ammonium fluoride (87.2 mg, 2.3 mmol) in methanol (40 mL) under reflux for 2.5 h afforded intended β-2-IAZA **5** (0.213 g, 73%).[22]

The stereochemistry of **5** was determined on the basis of nuclear Overhauser effect (NOE) experiments. Irradiation at C-5 imidazole proton affected C-4 imidazole H (6.9%), C-3′ H of the arabinofuranosyl moiety (6.8%) and 5′-CH_2 (1.8%), and significantly, also had minimal impact on C-1′-H (0.7%) of the sugar moiety. This confirms the location of iodine insertion in the arabinose configuration at the C-2 position of the sugar moiety, and the β-configuration of the nitroimidazole moiety in relation to the plane of arabinofuranosyl framework. Additional NOE effects were observed for arabinofuranosyl protons at C-2′ (14.8%), C-4′ (4%), C-5 (2.6%) when the C-1′-H was irradiated. The irradiation at C-2′-H enhanced the signals for C-1′-H (16.9%), C-3′-H (5.3%) and C-4′-H (3.2%), while related enhancements were observed for C-2′-H (1.9%), C-4′-H (1.9%), 5′-CH_2 (2.5%) and C-5-H (6.8%) when C-3′-H was irradiated.

In conclusion, β-2-IAZA, **5**, has been synthesized by nucleophilic substitution at C-2′ of the riboside **2**, with inversion of configuration to form the corresponding arabinoside. This synthesis is not possible by coupling the tri-*O*-benzoylated arabinofuranosyl bromide with 2-nitroimidazole because of the intramolecular participation of these protective groups (during bromination) with the substituent at C-1′.

Acknowledgements

The authors gratefully acknowledge the financial support from Alberta Cancer Board, Edmonton, Canada (grant no. RI-14). We also acknowledge the Islamic Republic of Iran, Ministry of Health and Medical Education, Iran, for providing a doctoral fellowship for Dr. Davood Beiki, and the Health Sciences University of Hokkaido, Hokkaido, Japan, and the Taiho Foundation, University of Alberta, for supporting Associate Professor Dr. Kazue Ohkura, during their respective tenures in Edmonton. We thank Dr. V. Somayaji for his expert assistance with some of the NMR studies and data interpretation.



Scheme 1. Synthesis of β-2-IAZA from AZA. *Reagents and conditions*: (i) 1,1,3,3-Tetraisopropyldisilyloxy 1,3-dichloride/pyridine; (ii) trifluoromethanesulfonyl chloride/DMAP; (iii) NaI/2-pentanone, 110°C; (iv) NH_4F/MeOH and 2-NI = 2-nitroimidazole.

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22. All new compounds gave satisfactory ^{1}H NMR (300 MHz) spectroscopic and elemental analytical data. Selected data: **2**: 1-β-D-(3,5-*O*-Tetraisopropyldisilyloxy-ribofuranosyl)-2-nitroimidazole: mp 59–61°C. ^{1}H NMR ($CDCl_3$): δ 0.84–1.02 (m, 28H, 4×isopropyl H), 2.45 (br, D_2O exchangeable, 1H, OH), 4.05 (dd, 1H, $J_{4',5'}=2.7$ Hz, Jgem = 13.4 Hz, H-5′), 4.19 (d, $J_{3',2'}=4.3$ Hz, 1H, H-2′), 4.25 (dd, 1H, $J_{3',4'}=9.2$ Hz, $J_{5',4'}=2.8$ Hz, H-4′), 4.32 (d, 1H, Jgem = 13.4 Hz, H-5″), 4.43 (dd, 1H, $J_{2',3'}=4.3$ Hz, $J_{4',3'}=9.3$ Hz, H-3′), 6.3 (s, 1H, H-1′), 7.09 (d, $J_{5,4}=1.1$ Hz, 1H, H-4) and 7.74 (d, $J_{4,5}=1.1$ Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 12.60–13.46 (4 isopropyl CH), 16.87–17.50 (8 isopropyl CH_3), 59.86 (C-5′), 68.19 (C-4′), 76.97 (C-3′), 82.28 (C-2′), 92.33 (C-1′), 122.62 (C-5), 128.39 (C-4), 144.5 (C-2) ppm, Chem. Anal. Calcd: C, 49.256; H, 7.646; N, 8.616; found: C, 49.634; H, 7.39; N, 8.484%. **3**: 1-β-D-(3,5-*O*-Tetraisopropyldisilyloxy - 2 - *O* - trifluoromethanesulfonylribofuranosyl)-2-nitroimidazole: mp 50–52°C. ^{1}H NMR ($CDCl_3$): δ 0.88–1.05 (m, 28H, 4×isopropyl H), 3.99 (dd, 1H, $J_{4',5'}=2.4$ Hz, Jgem = 13.7 Hz, H-5′), 4.17 (dd, 1H, $J_{3',4'}=9.5$ Hz, $J_{5',4'}=2.4$ Hz, H-4′), 4.28 (d, 1H, Jgem = 13.7 Hz, H-5″), 4.53 (dd, 1H, $J_{2',3'}=$ 3.8 Hz, $J_{4',3'}=9.5$ Hz, H-3′), 5.20 (d, $J_{3',2'}=3.8$ Hz, 1H, H-2′), 6.48 (s, 1H, H-1′), 7.13 (d, $J_{5,4}=0.9$ Hz, 1H, H-4) and 7.81 (d, $J_{4,5}=0.9$ Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 12.87–13.40 (4 isopropyl CH), 16.56–17.50 (8 isopropyl CH_3), 59.02 (C-5′), 66.60 (C-4′), 82.30 (C-3′), 88.27 (C-2′), 89.58 (C-1′), 118.43 (CF_3), 122.42 (C-5), 128.83 (C-4), 144.5 (C-2) ppm; Chem. Anal. Calcd: C, 40.698; H, 5.855; N, 6.780; Found: C, 40.939; H, 6.235; N, 7.172. **4**: 1-β-D-(3,5-*O*-Tetraisopropyldisilyloxy-2-deoxy-2-iodoarabinofuranosyl)-2-nitroimidazole: mp 136–138°C. ^{1}H NMR ($CDCl_3$): δ 0.96–1.06 (m, 28H, 4×isopropyl H), 3.74 (ddd, 1H, $J_{3',4'}=8.5$ Hz, $J_{5',4'}=2.8$ Hz, $J_{5'',4'}=1.8$ Hz, H-4′), 4.10 (dd, 1H, $J_{4',5'}=2.8$ Hz, Jgem = 13.4 Hz, H-5′), 4.12 (d, 1H, Jgem = 13.4 Hz, $J_{4',5''}=1.8$ Hz, H-5″), 4.53 (dd, 1H, $J_{2',3'}=9.2$ Hz, $J_{4',3'}=8.5$ Hz, H-3′), 4.65 (dd, $J_{3',2'}=9.2$ Hz, $J_{1',2'}=6.7$ Hz, 1H, H-2′), 6.68 (d, $J_{2',1'}=6.7$ Hz 1H, H-1′), 7.09 (s, 1H, H-4) and 7.63 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 12.49–13.99 (4 isopropyl CH), 16.94–17.31 (8 isopropyl CH_3), 30.27 (C-2′), 60.14 (C-5′), 76.03 (C-4′), 84.04 (C-3′), 86.89 (C-1′), 121.72 (C-5), 128.22 (C-4), 145.5 (C-2) ppm, chem. Anal. Calcd: C, 40.198; H, 6.072; N, 7.031; found: C, 40.480; H, 6.900; N, 7.170. **5**: 1-β-D-[2-Deoxy-2-iodoarabinofuranosyl]-2-nitroimidazole: mp 63–65°C. ^{1}H NMR (CD_3OD): 3.83–3.89 (m, 2H, $J_{3',4'}=7.3$ Hz, $J_{5',4'}=3.5$ Hz, $J_{5'',4'}=3.8$ Hz, Jgem = 13.2 Hz, H-4′ and H-5′), 3.97 (dd, 1H, $J_{4',5''}=3.8$ Hz, Jgem = 13.2 Hz, H-5), 4.52 (dd, 1H, $J_{2',3'}=J_{4',3'}=7.3$ Hz, H-3′), 4.78 (dd, $J_{3',2'}=7.3$ Hz, $J_{1',2'}=6.4$ Hz, 1H, H-2′), 6.69 (d, $J_{2'1'}=6.4$ Hz 1H, H-1′), 7.17 (d, 1H, $J_{5,4}=1.2$ Hz, H-4) and 8.10 (d, 1H, $J_{4,5}=1.2$ Hz, H-5); ^{13}C NMR (CD_3OD): δ 30.39 (C-2′), 60.07 (C-5′), 78.00 (C-4′), 81.37 (C-3′), 84.44 (C-1′), 112.76 (C-5), 126.56 (C-4), 145.20 (C-2) ppm; LR (ESI) MS m/z: 378 (M^++Na), HR (ESI) MS (M^++Na, $C_8H_{10}O_5N_3INa$): Calc. mass 377.95629, exact mass 377.95574.