Journal & Proceedings of the Royal Society of New South Wales, vol. 157, part 1, 2024, pp. 141–142. ISSN 0035-9173/24/010141-02

Thesis abstract

Synthesis of glyphaeaside C and structural revisions of the glyphaeaside alkaloids

Brendan J. Byatt

Abstract of a thesis submitted to the University of Wollongong

In 2015, ten C-alkylated iminosugars were isolated from the roots of *Glyphaea brevis* (Malvaceae). The alkaloids were purported to possess 1,5-dideoxy-1,5-iminohexitol cores, with the A-, B-, and C-type glyphaeasides bearing L-*fuco*, D-*galacto*, and D-*gluco* configurations, respectively; as well as unprecedented di-, tri-, and tetra-hydroxylated nine-carbon side chains with terminal aryl substituents. Glyphaeaside C — the only member of its type — was found to be a potent and competitive inhibitor of almond β-glucosidase (IC_{50} = 0.15 μM, Ki = 0.031 μM), which was especially remarkable considering the absence of any significant α-glucosidase inhibition, for which other related iminosugars with the same configuration — including α-homonojirimycin, α-1-C-(*n*-octyl)-1-deoxynojirimycin, and α-1-C-(8-hydroxyoct-1-yl)-1-deoxynojirimycin — are known to possess.

The structural uniqueness and peculiar glycosidase inhibitory activity of glyphaeaside C thus prompted a total synthesis investigation of its purported structure. The α-aza-C-glycoside unit was accessed via a stereoselective Grignard addition to a protected D-glucosylamine, eventually followed by a reductive amination-cyclisation to afford the D-*gluco* piperidine ring analogous to reported methods. After a cross-metathesis reaction to install the terminal phenol substituent, the side chain alkene moiety was subjected to complementary Sharpless asymmetric dihydroxylation reactions, followed by global deprotection to afford the two 7′,8′-*threo*-diols as the major products. While the NMR spectroscopic data of the afforded C-alkylated piperidine iminosugars were in agreement with similar compounds reported in the literature, they were notably dissimilar to that of natural glyphaeaside C. The iminosugars prepared from this pathway were found to be good inhibitors of human lysosomal α glucosidase and α-galactosidase, as well as of related glycosidases from other sources.

After examining the NMR spectroscopic data of the natural product, it was hypothesised that glyphaeaside C was in fact a 2,5-dideoxy-2,5-iminohexitol derivative of D-*manno* configuration — a motif more commonly found among natural C-alkylated iminosugars than that of the purported structure. To confirm this hypothesis, a total synthesis of the revised structure was attempted via preparation of a known vinylpyrrolidine precursor. Installation of the side chain moiety was achieved by epoxidation of the vinyl substituent, affording a mixture of diastereomers that were separable by column chromatography. Fortuitously, the major epoxide diastereomer was found to possess the desired configuration, conferring an inherent advantage over analogous carbaldehyde addition strategies

that have been previously reported. After ring-opening with a Gilman-like reagent, the resulting 8-nonenylic alcohol was subjected to a sequence of reactions analogous to that employed in the previous pathway, followed by semi-preparative HPLC to afford the four side chain diastereomers. The NMR spectroscopic data of the major *threo* products were identical to that of the natural product, thus confirming the revised pyrrolidine-based structure of glyphaeaside C. Although the configuration of the side chain diol moiety relative to the iminosugar core can be deduced with reasonable confidence, the absolute configuration of the natural product cannot be unequivocally assigned from the available data. The products synthesised by this method displayed potent inhibition against bovine liver β-glucosidase (IC_{50} values of 0.019–0.060 μM) and β-galactosidase (IC_{50} values of 0.019–0.043 μM), and moderate inhibition of human lysosomal β-glucosidase (IC_{50} values of 33–195 μM); importantly, no significant inhibition of rice α-glucosidase was observed, although the relatively strong inhibition against almond β-glucosidase (IC_{50} values of 0.77–0.99 μM) was less than that displayed by the natural product. The novel epoxide strategy used to access the revised structure of glyphaeaside C represents a potentially useful synthetic pathway towards similar C-alkylated pyrrolidine iminosugars, including several of the related broussonetine alkaloids, and could be conceivably applied to the synthesis of other pyrrolidine iminosugars with different ring configurations.

Dr. Brendan J. Byatt
Research Assistant at ANFF Materials
https://www.anffmaterials.org/team
Australian National Fabrication Facility

E-mail: bb795@uowmail.edu.au

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