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Synthesis and Structural Revision of Glyphaeaside C

Brendan J. Byatt,* Atsushi Kato, and Stephen G. Pyne*

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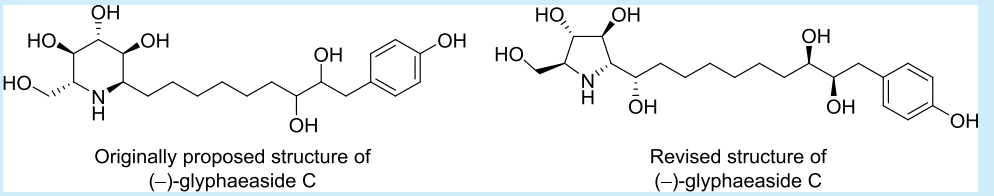

ABSTRACT: The iminosugar core of natural glyphaeaside C, originally assigned as a derivative of the piperidine natural product 1-deoxynojirimycin (DNJ), has been revised as a derivative of 2,5-dideoxy-2,5-imino-L-mannitol (L-DMDP) by the total synthesis of its enantiomer. This revised L-DMDP-derived configuration is the first of its kind to be observed in nature. The prepared iminosugars displayed the nanomolar inhibition of bovine liver β-glucosidase and β-galactosidase.

The glyphaeaside alkaloids are a family of ten iminosugars that were isolated from the roots of *Glyphaea brevis*[1] that have polyhydroxylated phenylalkyl side-chains unique among the carbohydrate-like class of natural products (Figure 1). Such *C*-alkylated iminosugars have been found sparingly in nature, being largely limited to the broussonetine family of alkaloids[2] and sporadic occurrences in various plants.[3−5]

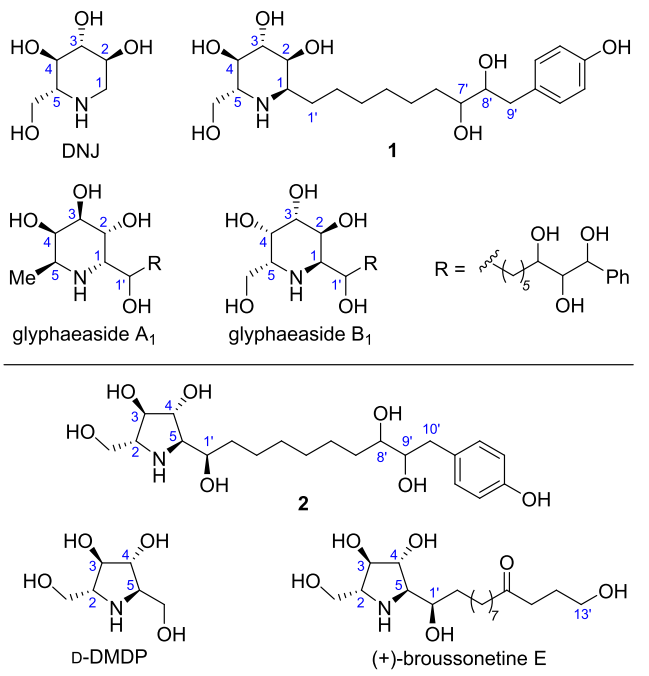

Figure 1. Proposed general structures of glyphaeaside C and related iminosugars.

The glyphaeasides were classified into types A, B, and C according to the configuration of their identified piperidine iminosugar core. Glyphaeaside C, the only one of its type, was assigned as either the 1-deoxynojirimycin (DNJ) derivative **1** (Figure 1) or its enantiomer by analyzing the 1D and 2D NMR spectroscopic data, specifically referencing the large coupling constants ($J_{2,3}$ = $J_{3,4}$ = 6.7 Hz and $J_{4,5}$ = 7.5 Hz) and H2/H4 and H3/H5 ROESY correlations to characterize the two pairs of 1,3-*trans*-diaxial protons in the six-membered ring. Although the side-chain configuration was not determined, the small $J_{1eq,2ax}$ coupling constant (2.5 Hz) suggested a pseudoanomeric α-configuration at C1.

While glyphaeaside C was the most potent inhibitor of almond β-glucosidase and snail β-mannosidase out of the isolated compounds, all glyphaeaside alkaloids displayed at least some inhibition of both enzymes seemingly independent of their core configurations.[1] Additionally, glyphaeaside C showed only a mild inhibition of rice α-glucosidase in contrast to similar α-1-*C*-alkylated derivatives of DNJ,[6] and the A-type glyphaeasides—α-1-*C*-alkylated derivatives of 1-deoxyfuconojirimycin (DFJ)—also lacked the substantial bovine kidney α-L-fucosidase inhibition that is characteristic of similar DFJ derivatives.[7] These structure−activity relationships led to a hypothesis that the side-chain functionalization of the glyphaeasides is the primary determinant of their glycosidase inhibition potency and specificity rather than their iminosugar core configuration.[1]

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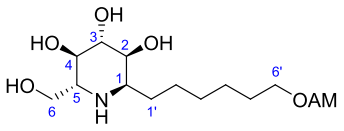
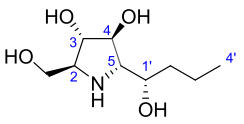
However, upon our analysis of the NMR spectroscopic data of glyphaeaside C, it was noticed that the ring proton coupling constants matched those of 2,5-dideoxy-2,5-imino-D-mannitol (D-DMDP, $J_{2,3} = J_{4,5} = 7.7$ Hz and $J_{3,4} = 7.1$ Hz)[8] more closely than those of DNJ ($J_{2,3} = 8.5$ Hz, $J_{3,4} = 9.0$ Hz, and $J_{4,5} = 9.1$ Hz).[9] Furthermore, the ^{13}C NMR data suggested that C2 (δ_C 66.0) was adjacent to the nitrogen, rather than C1 (δ_C 70.1). These observations led us to hypothesize that glyphaeaside C is in fact a D-DMDP derivative of general structure **2** (Figure 1).[10,11] This alternative structure would also be consistent with the observed ROESY correlations found between the ring protons and might explain, at least in part, the unexpected affinity of glyphaeaside C toward almond β-glucosidase.[2] A comparison of the ^{13}C NMR ring-carbon chemical shifts of glyphaeaside C with those of other reported iminosugars that were also measured in CD_3OD revealed a near-perfect correlation with L-DMDP derivative **4** in contrast to DNJ derivative **3** as an example (Table 1).

Table 1. Selected ^{13}C NMR Spectroscopic Data of Glyphaeaside C and Structurally Related Iminosugars in CD_3OD[a]



3
(Overkleeft *et al.*)



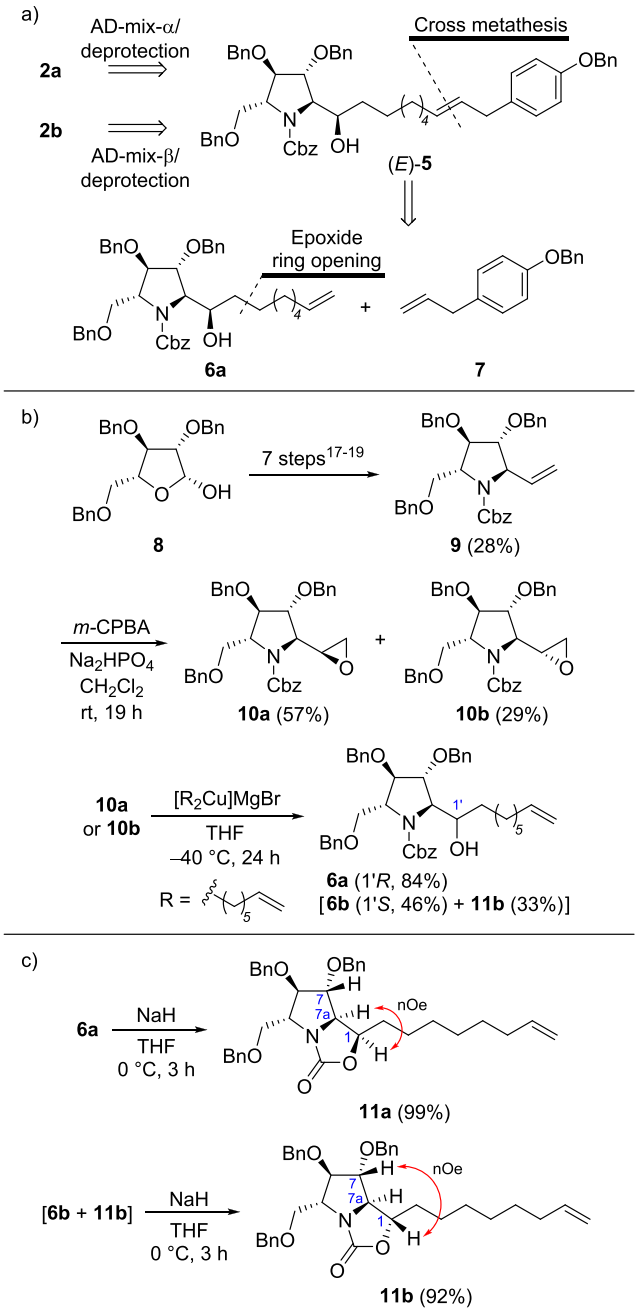
4
(Kato *et al.*)

3[12]	glyphaeaside C[1]	**4**[13]
55.3 (1)[b]	70.1	69.7 (1′)
70.4 (2)	66.0	66.0 (5)
72.8 (3)	75.1	75.1 (4)
69.5 (4)	76.7	76.7 (3)
59.5 (5)	64.8	64.8 (2)
58.6 (6)	58.6	58.6 (CH_2OH)

[a]Chemical shifts (CD_3OD) are reported in parts per million as per their publication. [b]Carbon atom associated with resonance.

To resolve the observed spectroscopic irregularities and the uncertain side-chain configuration of glyphaeaside C, a total synthesis of general structure **2** was attempted. The natural product was observed to have a negative specific rotation, suggesting an L-configuration.[13,14] However, considering that almost all naturally occurring pyrrolidine iminosugars have a D-configuration, and synthetic L-DMDP showed diminished β-glucosidase inhibition and elevated α-glucosidase inhibition[14] relative to those of the natural enantiomer,[5] the D-DMDP configuration was pursued. The relative ^{1}H NMR chemical shifts of the benzylic methylene (H10′) protons of glyphaeaside C (**2**) matched well with those of the 1,2-dihydroxy-3-(4-hydroxyphenyl)propane moiety of *syn*-configured diolmycin B2[15] and not well with those of the *anti*-configured diolmycin B1, reducing the four possible stereoisomers of **2** down to two: *syn*-8′,9′-diols **2a** and **2b** (Scheme 1a). We planned to utilize complementary Sharpless asymmetric dihydroxylation (ADH) reactions to access both *syn*-diols from the common precursor (*E*)-**5**, which was in turn prepared via the cross metathesis (CM) of pyrrolidine **6a** and *O*-protected allylphenol **7**. We decided to prepare **6a** via an epoxide ring-opening approach rather than a carbonyl addition approach, such as the Brown allylation of a 2-pyrrolidinecarboxaldehyde derivative used in Carriera's synthesis of (+)-broussonetine H,[16] to avoid the

Scheme 1. (a) Retrosynthesis of *syn*-8′,9′-Diols 2a and 2b, (b) Synthesis of Pyrrolidine Fragment 6a, and (c) Synthesis of Oxazolidinones 11a and 11b



potential lack of stereochemical control that is otherwise afforded by the chiral allylborane reagent.

Vinylpyrrolidine **9** was prepared from commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**8**) in a 28% yield over seven steps using reported procedures (Scheme 1b).[16,17] Subsequent epoxidation with *m*-CPBA afforded epoxides **10a** and **10b** in 57% and 29% yields, respectively. The desired isomer **10a** was formed as the major product, albeit only in a moderate excess, and the two epoxides were easily separated by column chromatography—an advantage over methods that afford inseparable mixtures of alcohol products from the reaction of RM (R = allyl; M = ZnBr, MgBr) with related 2-pyrrolidinecarboxaldehydes.[18,19] Epoxide **10a** was then subjected to a ring-opening reaction using the Gilman reagent

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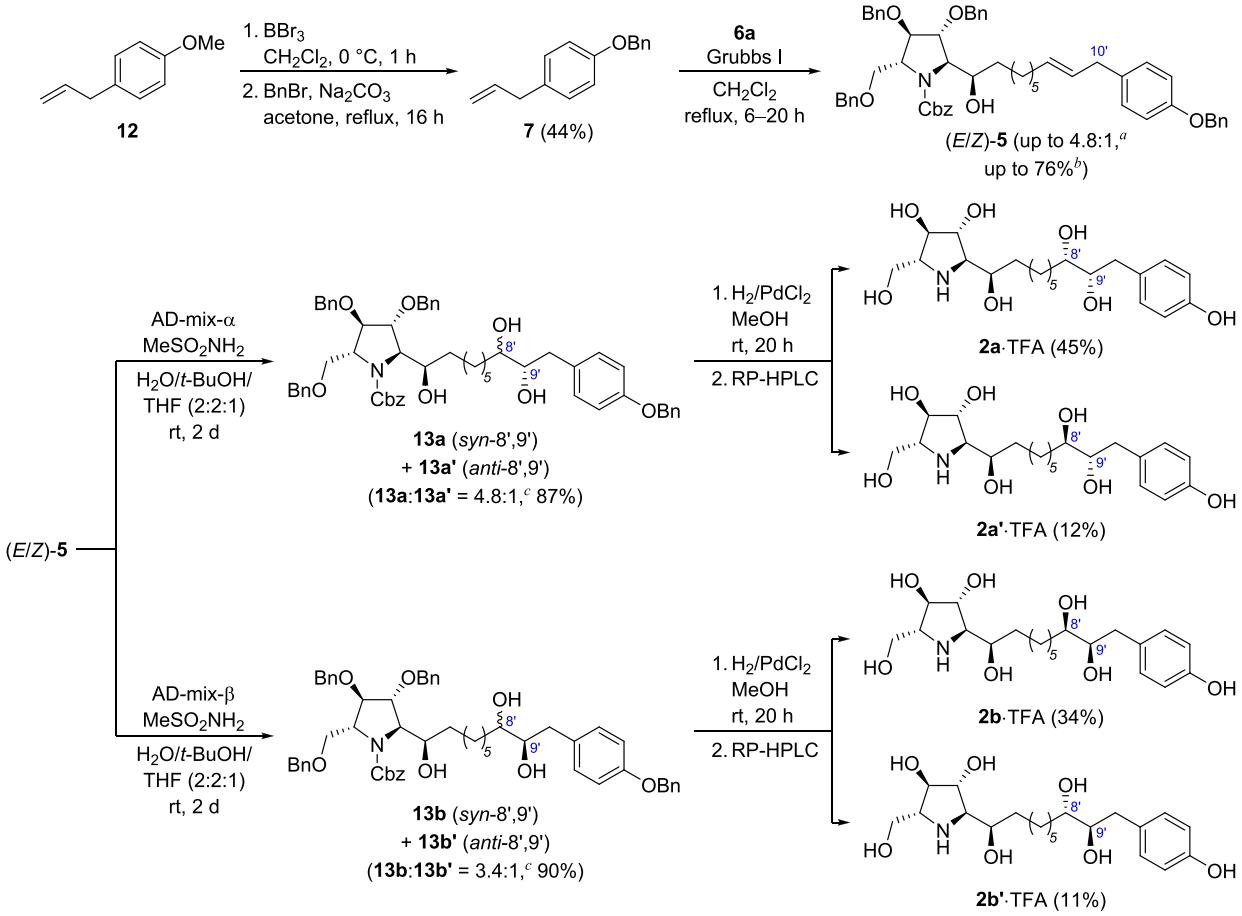
Scheme 2. Preparation and Isolation of the Four Diastereomers of General Structure 2



[a]Measured using the ^{1}H NMR integration of H10′. [b]Yield relative to **6a**. [c]Measured using the HPLC trace of the **2a**/**2b** reaction mixture prior to the *syn*/*anti*-diol separation.

formed at −40 °C from CuBr·DMS and hept-6-en-1-ylmagnesium bromide to afford alcohol **6a** in an 84% yield.

A small quantity of **6a** was treated with NaH to afford the oxazolidinone **11a**, and 1D NOESY analysis enabled the verification of the stereochemical configuration at C1 through an observed H1/H7a correlation (Scheme 1c).[16] The reaction of the minor epoxide **10b** under the same conditions as those of **10a** (Scheme 1b) afforded a mixture of **6b** and the corresponding oxazolidinone **11b**, suggesting that the associated alkoxide intermediate undergoes cyclization faster than the (*R*)-epimer due to the formation of the more favorable *trans*-1,7a-oxazolidinone ring. The **6b**/**11b** mixture was completely converted to **11b** using NaH, and the C1 configuration was similarly determined through an observed H1/H7 1D NOESY correlation (Scheme 1c).

With pyrrolidine **6a** in hand, the complementary CM component was prepared via the BBr_3-mediated *O*-demethylation of commercially available 4-allylanisole (**12**),[20] followed by the benzylation of the resulting allylphenol[21] to afford **7** in a 44% yield (Scheme 2). Although second-generation Grubbs catalysts have seen frequent use in the CM reactions of alkylated iminosugars,[7,16,22] their propensity to catalyze the double-bond migration of allylbenzenes[23] prompted the use of Grubbs' first-generation catalyst.[24] The reaction of **6a** and excess **7** in the presence of 10 mol % catalyst afforded inseparable mixtures of (*E*/*Z*)-**5** in 66−76% yields and (*E*/*Z*)-ratios of 3.4:1−4.8:1; longer reaction times increased the conversion of **6a** and favored the formation of the more thermodynamically stable (*E*)-**5** alkene. The purification of **5** necessitated open-air oxidation[12] and an additional column over silica gel to remove visible ruthenium impurities that have been reported as, and were found to be, detrimental to the subsequent OsO_4-catalyzed dihydroxylation of alkenes.[25]

Separate ADH reactions of alkene mixture **5** with AD-mix-*α* and AD-mix-*β* afforded *syn*/*anti*-8′,9′-diol mixtures **13a**/**13a**′ and **13b**/**13b**′ in 87% (dr 4.8:1) and 90% (dr 3.4:1) yields, respectively, with the *syn*/*anti*-diol ratios reflecting the (*E*/*Z*)-composition of the starting material (Scheme 2). The 8′,9′-diol configurations of **13a** and **13b** were assigned according to the ADH "Sharpless mnemonic", with the (4-(benzyloxy)phenyl)-methyl C9′ moiety considered the "R_L" substituent.[26] Due to the near-insolubility of the hydrophobic alkene substrate in the standard 1:1 H_2O/*t*-BuOH solvent system, a ternary 2:2:1 H_2O/*t*-BuOH/THF solvent system was used for these ADH reactions instead. The global deprotection of **13a**/**13a**′ and **13b**/**13b**′ under hydrogenolysis conditions[27] (H_2/$PdCl_2$) and elution through a plug of RP-18 silica afforded *syn*/*anti*-8′,9′-diol mixtures **2a**/**2a**′ and **2b**/**2b**′, respectively. These diol mixtures were then separated by semipreparative RP-HPLC, affording **2a** and **2a**′ from the first mixture and **2b** and **2b**′ from the second. The aqueous component of the mobile phase was buffered with TFA (pH 2.4) to replicate the conditions used to isolate the natural product.[1] Signals characteristic of the TFA counterion were observed in the ^{19}F NMR (δ_F =

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−76.8 to −77.0 ppm)[28] and negative-ion ESI-MS (m/z: 113, 249) spectra of all final products, and as such their isolated yields and all measurements dependent thereof were calculated as TFA salts.

The ^{1}H and ^{13}C NMR spectroscopic data of **2a** and **2b** in CD_3OD matched perfectly with those reported for natural glyphaeaside C in the same solvent ($\Delta\delta_H$ = 0.00−0.01 ppm and $\Delta\delta_C$ = 0.0−0.1 ppm). While the diastereoisomers **2a** and **2b** were identical by RP-HPLC and NMR analysis in CD_3OD, they were identified as different diastereomers, each with a high diastereomeric purity (>98%), from their NMR analysis in C_5D_5N (see Figures S78 and S79). Thus, a re-examination of NMR profile of the natural product using C_5D_5N may be necessary to determine its absolute 8′,9′-diol configuration.[29]

All four final products displayed positive specific rotations, the first indication that the natural product did, in fact, have a L-arabinose configuration. Although none of the specific rotations perfectly matched the magnitude of the natural product ($[\alpha]_D^{20}$ −0.8 (*c* 1.18, MeOH)), that of **2a** ($[\alpha]_D^{25}$ +3.0 (*c* 0.46, MeOH)) was much closer in magnitude than that of **2b** {$[\alpha]_D^{25}$ +19.9 (*c* 0.42, MeOH)}, which would posit that the structure of natural glyphaeaside C is *ent*-**2a**. While some naturally occurring L-*arabino*-iminosugars have been observed,[2] this revised structure would represent the first example of an L-DMDP derivative to be found in nature and is certainly opposite to that found in the broussonetines (Figure 1, for example).

The four final products were tested against a panel of glycosidases to ascertain their corresponding inhibitory effects (Table 2). In general, glycosidase inhibition was independent of the side-chain configuration; in cases where the IC_{50} was determined (compounds that showed >50% inhibition at a 100 μM inhibitor concentration), the enzyme that experienced the greatest variation of inhibition was human lysosomal β-glucosidase, where the IC_{50} values of **2a** (33 μM) and **2b** (195 μM) differed by a factor of 5.9. Concerning mammalian β-glucosidase activity, the compounds showed a far greater inhibitory activity toward bovine liver, where **2b** was the strongest inhibitor (IC_{50} = 0.019 μM) and showed an increase in potency of four orders of magnitude compared to that of human lysosomal. All compounds displayed the nanomolar inhibition of bovine liver β-galactosidase (IC_{50} = 0.019−0.043 μM), a trait shared with many of the broussonetine alkaloids and particularly those with the D-DMDP configuration ((+)-broussonetine E, IC_{50} = 0.0020 μM).[2] While not tested against this specific enzyme, natural glyphaeaside C displayed only mild inhibition of *Aspergiullus oryzae* β-galactosidase (82% at 1000 μM), providing further evidence of its L-DMDP-configuration.[14] Regarding almond β-glucosidase inhibition, **2b** was also the strongest inhibitor, though it was 5.1× less potent than natural glyphaeaside C (IC_{50} = 0.15 μM). The difference between the synthesized compounds and the targeted natural product is further exemplified by their inhibition of snail β-mannosidase, specifically that the synthesized compounds were weaker by approximately an order of magnitude.

Table 2. Concentrations of Glyphaeaside C Stereoisomers Giving a 50% Inhibition of the Selected Glycosidases[a]

	IC_{50} (μM)				
enzyme	natural[1]	**2a**	**2b**	**2a′**	**2b′**
***α*-glucosidase**					
rice	13%[b]	21.3%[c]	5.7%[c]	3.0%[c]	4.2%[c]
***β*-glucosidase**					
almond	0.15	0.92	0.77	0.99	0.82
bovine liver	-[d]	0.037	0.019	0.060	0.038
human lysosome	-[d]	33	195	36	55
***β*-galactosidase**					
bovine liver	-[d]	0.031	0.020	0.043	0.019
A. oryzae	82%[b]	-[d]	-[d]	-[d]	-[d]
***β*-mannosidase**					
snail	4.5	48	30	56	35

[a]See the Supporting Information for complete assay data. [b]Inhibition percet at 1000 μM. [c]Inhibition percent at 100 μM. [d]Not tested.

In conclusion, a comparison of the NMR spectroscopic data of glyphaeaside C with similar reported compounds led to the determination that the originally proposed structure **1** was incorrect and more likely a stereoisomer of general structure **2**. As part of a total synthesis investigation, the 5-*C*-hydroxyalkyl moiety of **2** was accessed via the ring-opening of epoxide **10a**, a novel synthesis route that should find future useful applications in azasugar synthesis. The four 8′,9′-diol diastereomers of **2** were prepared utilizing the complementary ADH reactions of (*E*/*Z*)-**5** and the eventual separation by semipreparative HPLC after global deprotection. The biological activity profiles of the prepared compounds are relatively conserved with respect to their side-chain configurations and consistent with similar D-DMDP-derived alkaloids. However, they are notably different from the natural product, which is now believed to possess the L-DMDP configuration. A comparison of specific rotation data suggests that natural glyphaeaside C is the enantiomer of **2a**, although further studies, such as a reisolation of the natural product, are needed to unambiguously confirm this assertion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01248.

Experimental procedures and characterization data (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a**, **2a′**, **2b**, **2b′**, (*E*/*Z*)-**5**, **6a**, **6b**, **7**, **9**, **10a**, **10b**, **11a**, **11b**, **13a**, **13a′**, **13b**, and **13b′** (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

Stephen G. Pyne − *School of Chemistry and Molecular Bioscience, University of Wollongong, Wollongong, New South Wales 2522, Australia*; orcid.org/0000-0003-0462-0277; Email: spyne@uow.edu.au

Brendan J. Byatt − *School of Chemistry and Molecular Bioscience, University of Wollongong, Wollongong, New South Wales 2522, Australia*; Email: bbyatt@uow.edu.au

Author

Atsushi Kato − *Department of Hospital Pharmacy, University of Toyama, Toyama 2630, Japan*; orcid.org/0000-0001-8022-196X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01248

Notes

The authors declare no competing financial interest.

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(10) Following the numbering convention of the broussonetine alkaloids, compound **2** is considered a C5-alkylated 2-(hydroxymethyl)pyrrolidine derivative; consequently, the ^{13}C NMR chemical shifts previously assigned as C1 and C2 now correspond to C1′ and C5, respectively.

(11) Applying the same structural rearrangement to the B-type glyphaeasides would suggest a shared 2,5-dideoxy-2,5-imino-D (or L-)-altritol (DIA) core structure and, by extension, a 1-deoxy-DIA core shared by the A-type glyphaeasides (see the Supporting Information for further discussion).

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