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RESEARCH ARTICLE

Exploring a *de novo* route to bradyrhizose and its diastereomers: synthesis and isomeric equilibrium of reducing bicyclic carbohydrates

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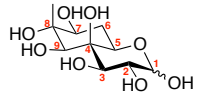
Abstract: A *de novo* asymmetric strategy for the synthesis of D-bradyrhizose diastereomers from an achiral ketoenolester precursor is described. Key transformations used in the stereodivergent approach include two Noyori asymmetric reductions, an Achmatowicz rearrangement, diastereoselective alkene oxidations, and the first example of a palladium(0)-catalyzed glycosylation of a vinylogous pyranone. The isomeric composition of the bicyclic reducing sugars obtained was analyzed and their behaviour was compared to the natural product, revealing key stereocentres that impact the overall distribution.

Introduction

Rhizobia are a class of Gram-negative bacteria that live in symbiosis with legume plants in nitrogen-fixing nodules, a process that is essential for the cycling of atmospheric nitrogen.[1] An important factor in the immunological mediation of microbe–plant interactions is the lipopolysaccharide (LPS) present in the bacterial cell wall.[2,3] In 2011, Molinaro and co-workers reported a unique monosaccharide, D-bradyrhizose, as the only component of the LPS O-chain domain of *Bradyrhizobium* sp. BTAi1 and sp. ORS278, as α-(1→7)-linked homopolymers.[4] D-Bradyrhizose is a ten-carbon monosaccharide with two tertiary hydroxyl groups that is observed predominantly as a pyranose containing heptahydroxy *trans*-oxa-decalin with a 1,5-ring connection (Figure 1). This remarkable bicyclic monosaccharide, as well as its oligo- and polysaccharides, have an unusual immunologically silent nature and are believed to be involved in a unique mechanism of nitrogen-fixing nodule formation.[4]



D-Bradyrhizose
(1,5-pyranose form)

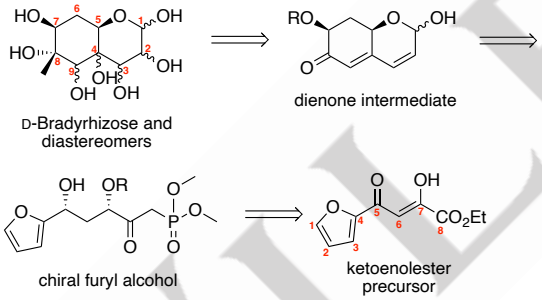
Figure 1. Structure of D-bradyrhizose in its predominant 1,5-pyranose form.

The unusual structural and biological features of D-bradyrhizose have inspired the development of four different synthetic strategies to access the molecule. Yu and coworkers in 2015 first reported the synthesis of the reducing monosaccharide from D-glucal in 26 steps and 9% overall yield [5] and later the synthesis of oligosaccharides containing D-bradyrhizose.[6] Our group then published the synthesis of D-bradyrhizose, and its enantiomer, in 25 steps and 6% overall yield from *myo*-inositol. These compounds were then converted into a panel of disaccharides containing both D- and L-forms of the monosaccharide.[7] Shorter routes to the monosaccharide were then reported by Ngoje and Crich (14 steps and 6% yield from D-glucose),[8] and by Matsushima and coworkers (for the

bradyrhizose methyl glycoside, in 15 steps and 16% yield).[9] Branched octoses that are structurally analogous to D-bradyrhizose have also been prepared.[10]

All previously reported syntheses of D-bradyrhizose used the chiral pool to provide the initial stereochemistry of the molecule. We have had a long-term interest in the use of *de novo* strategies for the synthesis of carbohydrates and polyketide-based compounds from non-chiral precursors.[11–15] This strategy is powerful for the preparation of many natural products of biological interest and analogues that can aid in structure–activity relationship (SAR) studies.[16] Of note, we have shown that the Noyori asymmetric transfer hydrogenation (ATH)[17,18] of α-γ-dioxobutyric acid esters is a powerful reaction in the preparation of stereoisomers of hydroxylated lipids found in avocado.[12]

Motivated by this success, we sought to develop a divergent route that would allow access to the D-bradyrhizose monosaccharide and stereoisomers with varying configuration at some stereocentres (Scheme 1). We envisioned that these products could be obtained from a common protected dienone intermediate, via methyl group addition to the ketone and stereoselective alkene oxidation reactions (*e.g.,* epoxidation/hydration and *syn*-dihydroxylation). The bicyclic pyranone moiety could be formed via Achmatowicz[19] and intramolecular Horner–Wadsworth–Emmons (HWE)[20,21] reactions of a properly functionalized chiral furyl alcohol. This alcohol, in turn, could be obtained from an achiral ketoenolester precursor using a double Noyori ATH as the stereochemistry-determining reaction for the stereogenic centres α and γ to the furan ring.

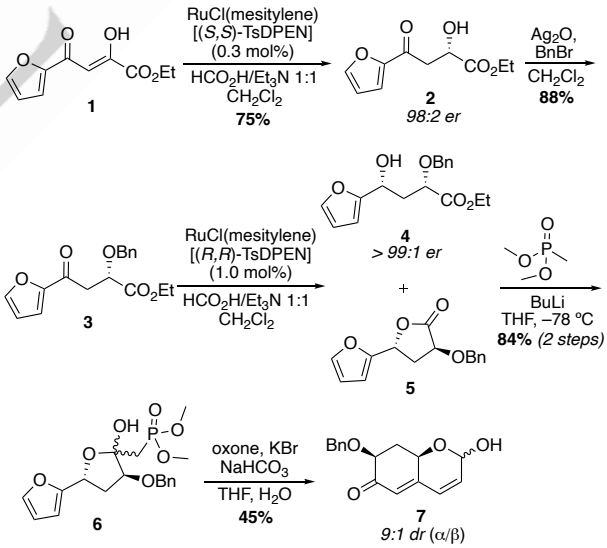


Scheme 1. Retrosynthesis of *de novo* approach to bradyrhizose and diastereomers.

We report here our efforts to implement this approach to synthesize D-bradyrhizose as well as the preparation and equilibrium distribution of three D-bradyrhizose diastereomers with different configurations at C-2, C-4 and C-9. The results provide insights into the feasibility of this approach for synthesizing this unique bicyclic monosaccharide, and related stereoisomers, and reveal that changes in stereochemistry of even a single stereogenic centre significantly impact the equilibrium distribution of cyclic forms.

Results and Discussion

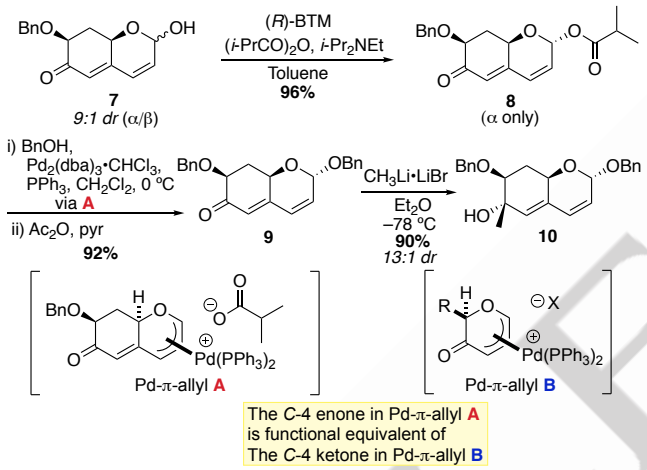
The synthesis started with ketoenolester **1** (Scheme 2), which was prepared in one step from 2-acetylfuran.[22] Reduction to α-hydroxyester **2** occurred in good yield (75%) and excellent enantioselectivity (98:2 *er*), via a modification of a published protocol,[18] using Noyori ATH with RuCl(mesitylene)[(*S*,*S*)-TsDPEN] as a catalyst in a 1:1 formic acid/triethylamine system.[23] The hydroxyl group was then protected as a benzyl ether using silver(I) oxide as a base to afford compound **3** in 88% yield. A second Noyori ATH was then performed to reduce the ketone group, now using RuCl(mesitylene)[(*R*,*R*)-TsDPEN] as a catalyst to afford a mixture of ester **4** and lactone **5**, which were difficult to separate and only partially isolated for characterization (a 1:1 mixture of **4**:**5** was formed based on the crude ^{1}H NMR spectrum). The enantiopurity of the products after the two sequential ATH reactions was determined on pure ester **4** (*er* > 99:1; see data in Supporting Information). The mixture of compounds **4** and **5** was then reacted with lithiated dimethyl methylphosphonate to afford β-ketophosphonate **6**, which was isolated as a 4:1 inseparable mixture of hemiketals in 84% yield over two steps (from **3**). Compound **6** was then subjected to a catalytic Achmatowicz rearrangement[24] to form the dihydropyranone hemiacetal ring and, fortuitously, an intramolecular HWE reaction spontaneously occurred during the basic work-up of the reaction to afford the desired bicyclic dienone **7** as a mixture of anomers (in 45% yield and 9:1 α/β ratio). Even though the yield was not high, this step-saving transformation is complex and is effective at promoting the cyclization without epimerization of the benzyl substituent, a side reaction that was significant in other routes explored. Furthermore, this reaction was optimized so that 30% of starting hemiketal **6** could be recovered during purification and recycled.



Scheme 2. Synthesis of the bicyclic dienone intermediate **7**.

We then proceeded to functionalize dienone **7** (Scheme 3), starting with the protection of the anomeric position in a fixed configuration. We envisioned this transformation proceeding through an α-selective acylation followed by a net-retentive stereoselective substitution with a benzyloxy group at the anomeric position via palladium–π-allyl catalysis. There was a degree of trepidation with this retrosynthetic plan as, to the best of our knowledge, this would be the first time a dienone substrate

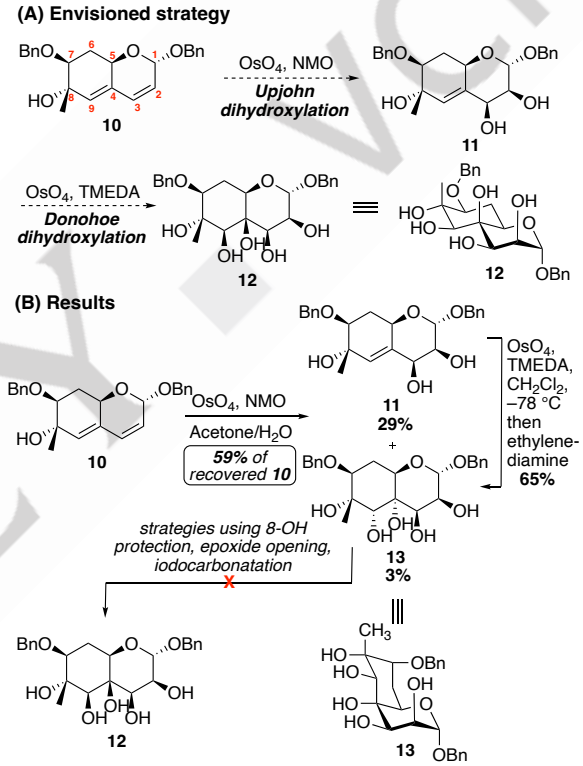
had been used as a donor in these palladium(0)-catalyzed glycosylation reactions. To execute this plan, pyranone **7** was converted, using dynamic kinetic diastereoselective acylation, to isobutyrate ester **8**, yielding the α-anomer only in 96%, using (*R*)-benzotetramisole (BTM) as a catalyst.[25] The acylated pyranone **8** was then used as a donor in a palladium(0)-catalyzed glycosylation[26] reaction of benzyl alcohol, to obtain benzyl glycoside **9** in 92% yield. Treatment of the crude reaction mixture with acetic anhydride and pyridine to acetylate the excess benzyl alcohol was used to facilitate chromatographic purification of the product. Previously, we have found than the C-4 ketone plays a critical role in reactivity and the overall efficiency of the pyranone variant of the palladium(0)-glycosylation. Specifically the C-4 ketone in Pd-π-allyl **B** in parts the requisite electrophilicity to react with with unactivated alcohols.[27–33] Thus, we were pleasantly surprised with the overall facility of this vinylogous pyranone palladium(0)-glycosylation (via Pd-π-allyl **A**), as it compared well to the parent variant (via Pd-π-allyl **B**) in terms of reactivity with unactivated alcohols, and regio- and stereoselectivity.



Scheme 3. Glycosylation with dienone **7** and methyllithium addition to carbonyl group.

The ketone moiety in **9** was then subjected to methyl lithium addition to form tertiary alcohol **10** in 90% yield and 13:1 *dr*, in favour of addition of the methyl group from the top face. The stereochemistry of the addition was determined via 2D-NOESY correlations between the pseudo-axially oriented H-6 and the methyl group hydrogens. We observed that the selectivity of this organolithium addition was in contrast to the reaction using methylmagnesium chloride, which favoured the other diastereomer via addition from the bottom face, presumably due to magnesium-mediated chelation between the ketone carbonyl and the C-7 benzyloxy group.

With a route to compound **10** in place, we proceeded to investigate the dihydroxylation of the diene (Scheme 4). We originally envisioned that the C-2–C-3 alkene in **10** would undergo regioselective dihydroxylation from the less hindered top face via the Upjohn procedure (NMO and catalytic OsO_4)[34] to provide 2,3-*cis*-diol **11**. A second C-2 or C-3 hydroxyl-directed Donohoe dihydroxylation (TMEDA and stoichiometric OsO_4)[35] would then afford the oxidation of the C-4–C-9 alkene, also from the top face, to obtain fully hydroxylated *trans*-decalin **12**. Importantly, the pentanol product **12** would only require an inversion at the 2-position to afford the stereochemistry of D-bradyrhizose. Unfortunately, the convex nature of the bicyclic ring system in **11** was too difficult to overcome for the large osmium reagent, even under hydroxy-directing conditions. Thus, when we attempted this strategy, the Upjohn dihydroxylation of **10** was slow and led to a mixture of desired triol **11** and undesired pentol **13**, with a *cis*-decalin-type ring system. When the reaction was run until total consumption of starting material, 20% of **11** was formed, and **13** was the major product (64%). The yield of **11** was maximized to only 29% by using a sub-stoichiometric amount of NMO (0.5 equiv.), which minimized formation of **13** (3%) and enabled the recovery of starting material **10** (59%).



Scheme 4. Envisioned strategy for the dihydroxylation of **10** (**A**) and results obtained (**B**).

The stereochemistry of **13** was assigned via H–H coupling constants $J_{1,2}$ and $J_{5,6a/b}$, which indicate the C-2-hydroxyl group axial orientation ($J_{1,2}$ ~ 2 Hz) and the *cis* nature of the fused decalin system ($J_{5,6a/b}$ ~ 3 Hz). A *trans*-fused ring system (such as **12**) has H-5 and one of the H-6 hydrogens (H-6a) positioned in a dihedral angle of approximately 180° and would show a larger value for $J_{5,6a}$ (Figure 2), typically 8–14 Hz. On the other hand, in the *cis*-decalin (such as **13**) these hydrogens are gauche and the coupling constants would be expected to be smaller (<5 Hz).

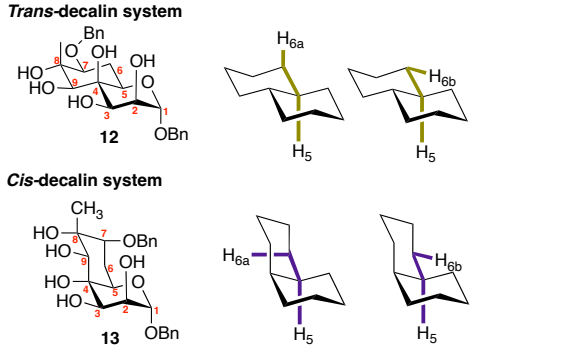
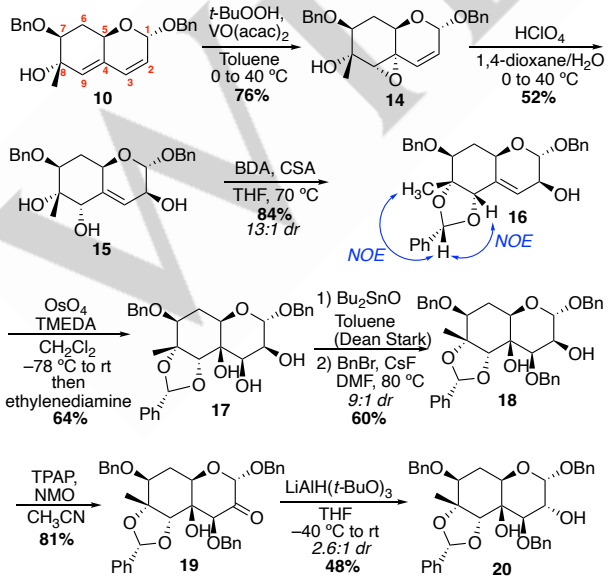


Figure 2. Comparison between the orientation of the H-6 hydrogens in relation to H-5 in *trans*- and *cis*- decalin systems (such as **12** and **13**, respectively).

In an attempt to improve the outcome in favour of the *trans*-decalin system, oxidation of **11** using OsO_4 and TMEDA was explored. However, this reaction led to the same pentol **13** in 65% yield, indicating that the C-2 and C-3 hydroxyl groups cannot direct the dihydroxylation reaction of **11** under these conditions. Further attempts to obtain compound **12** from intermediate **11** using strategies such as dihydroxylation of a C-8-hydroxyl protected derivative, epoxide opening, or iodocarbonatation all failed, suggesting limited reactivity around the C-4–C-9 bond and a high degree of steric hindrance on the top face of the molecule.

Due to the problems in achieving the formation of a *trans*-decalin ring system using the bis-dihydroxylation approach, we then investigated a strategy that started with the functionalization of diene **10** at the C-4–C-9 double bond (Scheme 5). The initial step was a hydroxyl-directed epoxidation of **10**,[36] which led to epoxide **14** in 76% yield. Epoxide opening with aqueous perchloric acid occurred primarily at C-2, with migration of the double bond to C-3–C-4, affording triol **15** in 52% yield. In this reaction, many minor products were observed but not isolated. When the reaction was cooled, it did not proceed. The stereochemistry of the C-2-hydroxyl group was determined based on the small H-1–H-2 coupling constant (1.3 Hz), which suggests a diequatorial orientation of these hydrogens.

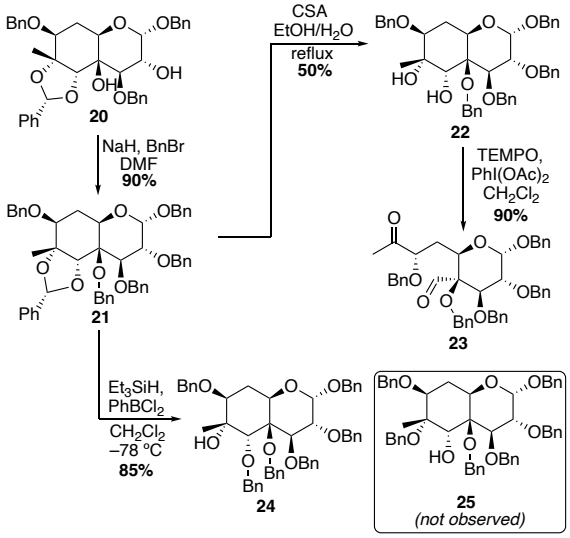


Scheme 5. Synthesis of *trans*-fused decalin **18** and C-2 inversion via oxidation–reduction.

At this stage, we installed a benzylidene acetal on the *cis*-C-8, C-9-diol as an attempt to block the bottom face of the molecule and force the reactivity around the C-3–C-4 double bond from the top face, ultimately leading to a *trans*-fused ring system (Scheme 5). Thus, treatment of **15** with benzaldehyde dimethyl acetal (BDA) and camphorsulfonic acid (CSA) produced **16** in a 13:1 *dr* (based on crude NMR spectrum). From this mixture, a single isomer was obtained in 84% yield. The stereochemistry of the benzylidene acetal was assigned based on the highlighted 2D-NOESY correlations (Scheme 5). The double bond in **16** next underwent hydroxyl-directed dihydroxylation and provided triol **17** in 64% yield, enabling the installation of a *trans*-fused ring system, akin to D-bradyrhizose. The stereochemistry of the ring junction in **17** was confirmed by the $J_{5,6a}$ and $J_{7,6a}$ values (~12 Hz), which indicate an axial–axial relationship, as detailed in Figure 2.

Having established the desired *trans*-decalin system, we proceeded with a strategy to invert the configurations at C-2 and then at C-9, achieving the stereochemistry of D-bradyrhizose. The equatorial C-3 hydroxyl group was subjected to organotin-mediated selective alkylation,[37] yielding 3-*O*-benzylated compound **18** in 60% yield (Scheme 5). Mitsunobu[38] inversion attempts at the C-2-position failed, but a two-step oxidation–reduction approach afforded ketone **19** in 81% yield. Subsequent reduction of the ketone proceeded in moderate selectivity (2.6:1 *dr*) and the desired inverted product **20** was obtained in 48% yield. While the selectivity was modest, **18** and **20** could be easily separated allowing the former to be recycled via the redox process.

With compound **20** in hand, an inversion at the C-9-stereocentre was all that remained to achieve the configuration of D-bradyrhizose. Our attempted strategies (Scheme 6) started with the protection of the remaining hydroxyl groups from **20** as benzyl ethers, to afford compound **21** in 90% yield. Surprisingly, the removal of the benzylidene acetal proved quite challenging, even under rather harsh conditions. The best results were obtained by heating **21** and CSA in a mixture of ethanol and water at reflux. Under these conditions, diol **22** was obtained in 50% yield with the remaining 50% of starting material recovered during purification. Thus, while the yield of **22** was modest, it was possible to recycle **21** to bring through more material. The reasons why the benzylidene acetal in **21** is recalcitrant to hydrolysis remain obscure, particularly because introducing the acetal (*i.e.,* conversion of **15** to **16**) under normal conditions was not problematic. We postulate that the rigid *trans*-decalin ring system in **22** prevents the conformational reorganization needed to accommodate an sp^2-hybridized acetal carbon, which is necessary during hydrolysis. In contrast, in the transformation of **15** into **16**, the analogous sp^2-hybridized carbon is exocylic and thus less impacted by the bicyclic ring system.



Scheme 6. Attempted strategies for inversion of the C-9 stereocentre.

All that remained to synthesize D-bradyrhizose was the inversion of the C-9 stereocentre (Scheme 6). We envisioned that oxidation of the secondary alcohol in **22** in preference to the tertiary alcohol would provide a ketone that could be reduced with good selectivity from the bottom of the ring (either through chelation of the reducing agent to the C-8 hydroxyl group or due to steric effects of the methyl group) to provide the inverted product. However, our attempts to use the same oxidation–reduction approach employed for C-2 inversion (*i.e.*, transformation of **18** into **20**) were not successful. In particular, instead of selective C-9 oxidation, cleavage of the C-8, C-9-*cis*-diol occurred, using a range of oxidants including TEMPO and (diacetoxyiodo)benzene. The product formed, keto-aldehyde **23**, could be isolated in 90% yield. To circumvent this problem, we explored a regioselective benzylidene ring-opening reaction on compound **20**, to form a compound in which C-9 bears a hydroxyl group and the tertiary alcohol at C-8 is protected as a benzyl ether. However, when we applied conditions (triethylsilane and dichlorophenylborane) that were previously successful for analogous benzylidene acetals,[7] only the undesired regioisomer **24** was produced in 85% yield; the 8-*O*-benzylated compound **25** was not observed. Different reaction conditions that use other Lewis acids were attempted but were also not successful.

At this stage, while we could have considered other approaches to convert **21** into D-bradyrhizose, we instead turned our attention to probe the effect that stereochemical inversion of various stereocentres in these bicyclic monosaccharides had on the distribution of cyclic forms. The compounds needed for this exploration could be accessed by complete deprotection of **13**, **18** and **20**, which was achieved via catalytic hydrogenation to yield 2,4,9-*epi*- (**26**), 2,9-*epi*- (**27**) and 9-*epi*-D-bradyrhizose (**28**), respectively (Scheme 7).

The parent monosaccharide, D-bradyrhizose, exists in D_2O as a mixture of five isomeric forms: 1,5-pyranoses (both α- and β-diastereomers), 1,9-pyranose (β-diastereomer only) and 1,4-furanoses (both α- and β-diastereomers).[5] Given that as many as six possible cyclic forms are possible, these equilibrium mixtures are complex. Detailed cyclization mechanisms and key NMR spectroscopic correlations that were used for structural assignments can be found in the Supporting Information (Figures S1–S6). Perhaps unsurprisingly, for all isomers, there is a predominance of pyranose forms with a *trans*-decalin ring system. Notably, compound **26**, which is fixed in a 1,5-pyranose *cis*-decalin form in benzyl glycoside **13**, rearranges to the 1,9-pyranose form with the more stable ring junction, but in so doing, has three 1,3-diaxial interactions between hydroxyl groups. The great destabilization of the *cis*-decalin forms is further apparent in the distributions for **27**, **28** and D-bradyrhizose, which have less than 10% of the 1,9-pyranose form, a *cis*-decalin-like structure. In the case of **27**, none of this form is found, presumably due to further destabilization by the 1,3-diaxial interaction between the C-2 hydroxyl group and the C-4–C-9 bond. In the case of **26**, it could be imagined that some degree of intramolecular H-bonding (even in an aqueous environment) could help to stabilize what, on the surface, looks to be a very unfavourable arrangement of hydroxyl groups in the 1,9-pyranose form.

Unlike D-bradyrhizose, furanose forms are not observed in **26**–**28**. This is possibly due to the presence of 2,3-*cis*-hydroxyl groups (for **26** and **27**) and of the axial substituent at C-9 (in all cases), which may increase the torsional strain in these isomers. The latter relationship is a 1,3-diaxial-like interaction between the hydroxyl groups on C-9 and C-3. Also of note is the change in the predominant anomers, which are of the α-configuration in the compounds with an axial C-2 substituent (**26** and **27**) and of the β-configuration in the molecules with an equatorial C-2 hydroxyl group (**28** and D-bradyrhizose). This difference can be explained by the repulsion between the axial C-2 substituents and the C-1 hydroxyl groups in β-isomers of **26** and **27**. Similar differences are seen when comparing the equilibrium of the conventional monosaccharides most similar to **26** and **28**, talose and galactose, respectively. In the case of talose, there is a 42:29 α:β ratio (with ~30% furanose forms) and for galactose it is 30:64 α:β (in addition to ~6% furanose forms).[39]

On balance, for the three isomers evaluated here, the C-4 stereochemistry has the most profound impact on the distribution of cyclic forms, given that it determines whether the overall structure will adopt a *cis* or *trans*-decalin like structure. The C-2 stereocentre is less impactful; however, in line with what is known about conventional hexoses, it determines the predominant C-1 diastereomer in the pyranose forms. When the C-2 hydroxyl group is axial, the α-isomer is favoured and when it is equatorial the β-isomer predominates. Finally, the C-9 stereochemistry impacts the ability of the molecules to exist in the 1,4-furanose forms, presumably by destabilization via 1,3-diaxial type interactions that are present when the C-9 hydroxyl group is axial but not when it is equatorial.

These results allow the prediction of the equilibrium distribution of other D-bradyrhizose stereoisomers. For example, the C-3 epimer (**29**, Figure 3), may, similar to **27**, **28** and D-bradyrhizose, behave like its parent hexose, gulose, which adopts predominantly the β-pyranose form.[39] Similarly, it might be predicted that stereochemical inversions at C-7 and C-8 (*e.g.,* **30** and **31**) would have relatively little impact on the overall distribution compared to D-bradyrhizose, unless also coupled with inversion at another centre, as they are located relatively remotely from the possible sites of cyclization.

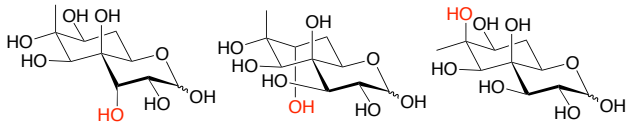
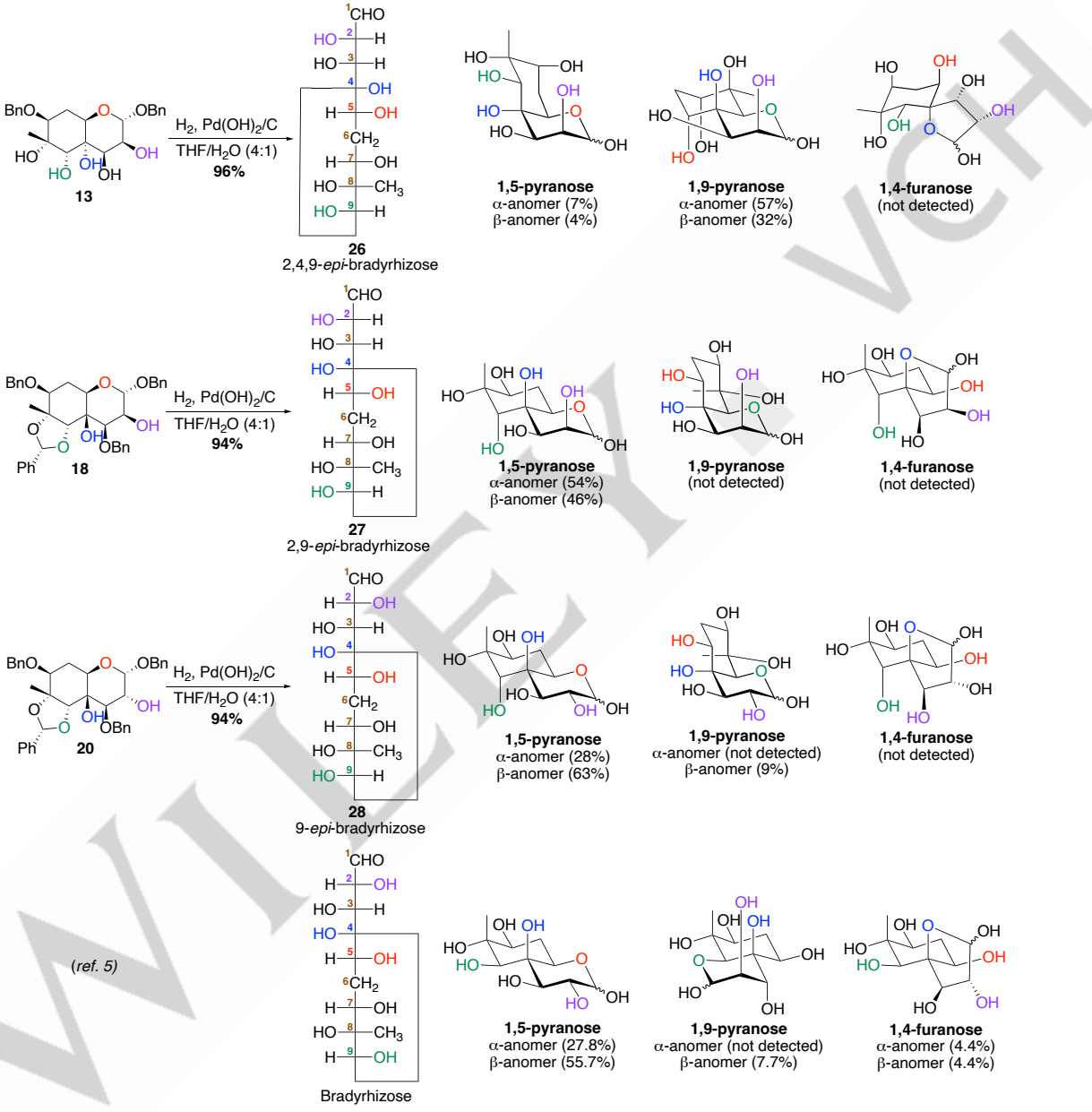


Figure 3. Structure of 3-*epi*- (**29**), 7-*epi*- (**30**) and 8-*epi*-D-bradyrhizose (**31**) in their 1,5-pyranose forms.



Scheme 7. Synthesis of D-bradyrhizose diastereomers from protected intermediates and their isomeric composition in D_2O, determined by ^1H NMR spectroscopy, in comparison with D-bradyrhizose.

Conclusion

In conclusion, we have developed a novel *de novo* strategy to synthesize bicyclic monosaccharides akin to D-bradyrhizose from a readily obtained achiral ketoenolester precursor (**1**). Noyori ATH reactions were used as the key stereochemistry-determining steps (the transformation of **1** into **4**) and other key steps were an Achmatowicz rearrangement and diastereoselective alkene oxidations. The route also features the first example of a palladium(0)-catalyzed glycosylation on a dienone substrate (*i.e.,* **8**). The potential of this glycosylation was not further explored here. However, it represents a potentially attractive strategy for

introducing these bicyclic motifs, containing a rich degree of functionality that can be modified (as shown here), into more complex frameworks. The synthesis of the natural compound D-bradyrhizose has not yet been achieved using this approach, but three diastereomers with one (**28**), two (**27**), or three (**26**) stereocentres inverted, were successfully prepared. Although a previous report described the synthesis of L-bradyrhizose and disaccharides incorporating the enantiomeric form of the natural monosaccharide,[7] **26**–**28** represent the only other stereoisomeric derivatives described to date. Accessing these compounds was made possible by the *de novo* nature of the route reported, which, unlike previous syntheses of the natural product, does not rely upon the chiral pool. Accessing derivatives of this sort from the chiral pool would be significantly less efficient. Modification of the approach will enable the synthesis of the natural product, and other stereoisomers, the latter of which are perhaps more interesting in probing structure–activity relationships. Analysis of the ring forms populated by the three analogs synthesized, **26**–**28**, and a comparison to those present at equilibrium by D-bradyrhizose, provided insights into the structural features in the molecule that influence the distribution. These insights provide a basis upon which to predict the populations of other analogs, which could be synthesized via modification of the general route described here.

Supporting Information

The authors have cited additional references within the Supporting Information.[40]

Acknowledgements

The authors gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada (RGPIN-2018-04365), the Canadian Glycomics Network (SD-1), the National Science Foundation (CHE-2102649), the National Institutes of Health (AI142040 and AI154860) and intramural funding from Academia Sinica for support. We thank NMR facilities at Academia Sinica (Institute of Biological Chemistry, Institute of Biomedical Sciences and National Biotechnology Research Park) for NMR spectroscopic data, the Synthetic Core Facility in the Institute of Biological Chemistry for optical rotation data and the Mass Spectrometry facility in the Academia Sinica Institute of Chemistry for mass spectrometric data.

Keywords: asymmetric synthesis • bradyrhizose • carbohydrates • *de novo* synthesis • total synthesis

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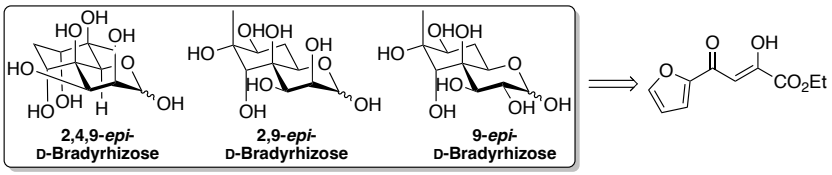

A *de novo* approach to synthesize D-bradyrhizose diastereomers from an achiral ketoenolester is presented. The strategy uses transfer hydrogenation, an Achmatowicz rearrangement and alkene oxidations as key steps in the synthesis. The effect of the configuration at C-2, C-4 and C-9 on the isomeric composition of the reducing sugars in water was analyzed and compared with the natural product.

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