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Synthesis of Bradyrhizose from D-Glucose

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Abstract

We describe the synthesis of the unusual bicyclic sugar bradyrhizose in 14 steps and 6% overall yield from D-glucose. The synthesis involves the elaboration of a *trans*-fused carbocyclic ring onto the pre-existing glucopyranose framework followed by adjustment of the oxidation levels. Key steps include radical extension of the glucopyranose side chain, ring closing metathesis, allylic oxidation, Luche reduction, hydroxy-directed epoxidation and acid-catalyzed epoxide opening at the more substituted position.

Graphical Abstract

Bradyrhizose, a rare bicyclic sugar, is an important component of the lipopolysaccharide *O*-antigen side chain of *Bradyrhizobium* species (BTail and ORS278 strains). As a molecular signal, it is thought to be involved in facilitating the fixation of nitrogen in tropical leguminous *Aeschynomene* species especially *Aeschynomene indica* and *sensitiva* through a symbiotic process.^{1–5} Isolation and characterization of this sugar revealed that the monomeric unit is made up of an inositol-type backbone which is *trans*-fused to a pyranose ring resulting in a bicyclic compound, whose α -(1 $\rightarrow$ 7)-linked oligomer adopts a compact two-fold right-handed helicoidal structure.⁶

The unusual structural of bradyrhizose coupled with the need to investigate its biological properties have stimulated interest in its chemical synthesis. A first synthesis was achieved

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ASSOCIATED CONTENT

Supporting Information

Complete experimental and characterization details and copies of ¹H and ¹³C NMR spectra of all new compounds.

by Yu and coworkers in 9% overall yield and 26 steps from D-glucal; the key steps being Ferrier rearrangement of a ramified glucopyranoside derivative and subsequent adjustment of the oxidation levels (Scheme 1).⁷ A second synthesis was reported by Lowary and coworkers, who employed *myo*-inositol as starting material, to which a glucopyranose ring was appended with an overall yield of 6% in 25 steps (Scheme 2).⁸ The construction of bicyclic mimetics of bradyrhizose and of related compounds has also been reported.⁹

Our laboratory has been interested in the synthesis of structurally related oxabicyclic motifs in connection with studies on the influence of pyranose side chain conformation on anomeric reactivity,¹⁰ and as analogues of the structurally unique aminoglycoside antibiotic apramycin with its broad spectrum of activity toward multidrug, carbapenem and aminoglycoside resistant enterobacteriaceae and ESKAPE pathogens.^{11, 12, 13} Building on aspects of the chemistry developed in these projects, and inspired by earlier syntheses of apramycin,^{14, 15} and of inositol variants from *cis*-arene glycols by the Carless,¹⁶ Ley,¹⁷ Hudlicky,¹⁸ and Motherwell laboratories,¹⁹ we envisioned a synthesis of bradyrhizose from glucose comprised of i) chain elongation of at the glucopyranose 6-position; ii) annelation of an unsaturated six-membered carbocyclic ring spanning the glucopyranose 4- and 6-positions; and iii) adjustment of the oxidation level in the newly appended ring to afford the target compound. We report here on the reduction of this concept to practice, resulting in a 14 step synthesis of bradyrhizose from D-glucose.

Following the literature protocol, D-glucose **1** was subjected to Fischer glycosylation²⁰ in benzyl alcohol at reflux giving **2**. Subsequent selective installation of a 4,6-*O*-benzylidene acetal under standard conditions gave **3a** in 85% yield and the corresponding β -anomer in 6% yield.²¹ In principle a mixture of the two anomers of **3** could be advanced through the synthesis, but in order to simplify the NMR spectra only the major anomer was taken forward. Thus, the α -anomer of **3** was subjected to benzylation with benzyl bromide and sodium hydride at 0 °C affording **4**.²² Acid-catalyzed removal of the benzylidene acetal,²³ was followed by selective Appel²⁴ iodination of the primary hydroxyl group resulting in compound **6** in excellent yield (Scheme 3).

With **6** in hand, we explored conditions for the side chain elongation with various methallylation protocols. Attempts at cross coupling reactions using methallyl Grignard reagents in the presence of metal catalysts such as (Pd(PPh₃))₄, CuI,²⁵ or Li₂CuCl₄²⁶ resulted only in the recovery of starting materials. Consequently, we turned our attention to the use of radical allylation reactions,²⁷ and in particular the use of methallylsulfones (Table 1). The use of triethylborane²⁸ as initiator in the presence of oxygen at room temperature and below was inefficient and resulted in the formation of significant quantities of the simple reduction product **8**. Attention was therefore focused on thermal conditions, with initiation by lauroyl peroxide, and azoisiobutyronitrile. α,α,α -Trifluorotoluene was selected as an environmentally friendly radical-compatible solvent for these reactions.²⁹ The use of ethyl methallyl sulfone under conditions prescribed by Zard and coworkers³⁰ gave only a low yield of the desired product. The optimum yield of 68% (Table 1, entry 6), however, was obtained under photocatalytic conditions with the blue light irradiation of **6** and 2-pyridyl methallyl sulfone in acetonitrile with *fac*-Ir(ppy)₃ as the catalyst.³¹

Subsequently, oxidation of **7** under Parikh-Doering conditions³² gave ketone **9** in good yield, which on treatment with vinyl magnesium bromide afforded alcohol **10** in 97% yield as a single diastereoisomer consistent with earlier observations in related systems.³³ The requisite bicyclic scaffold was obtained by ring closing methathesis with the Grubbs 2nd generation catalyst in dichloromethane at 45 °C, affording **11** in 85% yield (Scheme 4), and consistent with the literature precedent for the effective formation of trisubstituted cyclohexenes from methallyl type precursors.³⁴

Allylic oxidation of **11** with SeO₂ in 1,4 dioxane at 80 °C gave enone **12** in 70% yield, with regioselectivity in agreement with Guillemonat's rules and subsequent work.³⁵ Regio- and stereoselective reduction of the enone derivative **12** was achieved under Luche's conditions,³⁶ resulting in the isolation of the allylic alcohol **13** in 86% yield as a single diastereomer. Treatment of **13** with *m*-CPBA at room temperature in dichloromethane gave epoxide **14** in 83% yield as a single diastereoisomer, as a result of steering by hydrogen bonding by either of the two allylic alcohols (Scheme 5).³⁷ The relative configuration of **14** was confirmed by the observation of strong NOE correlations of H9 with each of the C8-methyl group, H3, H5 and H7.

The regioselective opening of **14** was explored under a variety of acidic conditions (Table 2). In dry solvents the enone **12** was returned as the only product, as the result of a 1,2-hydride shift followed by β -elimination. Reactions did not proceed under simple aqueous acidic conditions without excessive heating for reasons of insolubility. The use of aqueous 1,4-dioxane as solvent proved more successful when the mixture was adjusted to contain the maximum amount of water consistent with a homogeneous solution. The desired regio- and stereoselective ring opening of the epoxide was best achieved by employing sulfuric acid as catalyst in a 1:3 dioxane:water mixture at 65 °C (Table 2, entry 4) when the tetraol **15** was obtained in 50% yield alongside 45% of the enone **12**, which could be recycled. The relative configuration of **15** rests on the spatial proximity of H9 to H3, H5 and H7, and of the axial C8 methyl group to H6_{axial}, as established by the presence of strong NOE correlations.

While the regiochemical outcome of the epoxide opening under acid-catalyzed conditions deviates from the Fürst-Plattner rule,³⁸ it was anticipated on the basis of the well-known anti-attack of nucleophiles at the more substituted position of trisubstituted epoxides under acidic conditions (Scheme 6).³⁹

The synthesis of bradyrhizose was completed by hydrogenolysis of the benzyl ethers over 10% Pd/C in methanol in essentially quantitative yield (Scheme 5). The spectral data of the synthetic material were consistent with the literature data and the existence of bradyrhizose as a mutarotating mixture of the two pyranose forms and two furanose forms, rich in the former.⁷

In conclusion, we have succeeded in developing an effective synthesis of bradyrhizose from D-glucose in 14 steps and 6% overall yield. The approach employed differs conceptually from the existing syntheses in that it is based on the elaboration of the carbocyclic ring onto an existing pyranose framework rather the fusion of a pyranose ring onto a preformed inositol skeleton; it is also some ten steps shorter than either of the two existing syntheses.

Relatively minor variations on the sequence of reactions from the key bicyclic intermediate **12** are expected to afford a variety of stereoisomers of bradyrhizose itself.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Key steps of the Yu synthesis from D-glucal

Scheme 2.

Key steps of the Lowary synthesis from *myo*-inositol

Scheme 3.
Derivatization of D-glucose

Scheme 4.
Construction of the bicyclic scaffold

Scheme 5.

Adjustment of oxidation levels and completion of the synthesis.

Scheme 6.
Regio and stereoselective epoxide ring opening

Table 1.

Radical homologation of 6 to give 7

entry	sulfone (R)	initiator	solvent	temp (°C)	% yield 7	% yield 8
1	2-pyridyl	Et ₃ B	PhCF ₃	0	40	51
2	2-pyridyl	lauroyl peroxide	PhCF ₃	80	54	36
3	2-pyridyl	AIBN	PhCF ₃	80	0	0
4	3-pyridyl	lauroyl peroxide	PhCF ₃	80	50	38
5	ethyl	AIBN	heptane/PhCl	80	10	6
6	2-pyridyl	<i>fac</i> -Ir(ppy) ₃ (5 mol%), Bu ₃ N	acetonitrile	rt	68 ^a	13

^a) Conducted under argon with irradiation by 12V blue LED strips at room temperature.

Table 2.

Optimization of the epoxide ring opening

entry	reagent	temp (°C)	solvent	% yield 13	% yield 16	
1	wet triflic acid	0–45	dichloromethane	0	0	
2	conc H ₂ SO ₄	65	1,4-dioxane:water (1:1)	20	68	
3	conc H ₂ SO ₄	65	1,4-dioxane:water (1:2)	37	35	
4	conc H ₂ SO ₄	65	1,4-dioxane:water (1:3)	50	45	
5	conc H ₂ SO ₄	65	1,4-dioxane:water (1:4)	13	0	
6	conc H ₂ SO ₄	65	1,4-dioxane:water (1:6)	10	0	
7	Sc(SO ₃ CF ₃) ₃	rt–45	THF	0	0	