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Concise Total Syntheses of Aspalathin and Nothofagin

Akop Yepremyan, Baback Salehiani, and Thomas G. Minehan*

Department of Chemistry and Biochemistry, California State University, Northridge, 18111 Nordhoff Street, Northridge, CA 91330

Abstract

Syntheses of the *C*-glycosyl flavone natural products aspalathin and nothofagin have been accomplished in eight steps from tribenzyl glucal, tribenzyl phloroglucinol, and either 4-benzyloxy phenylacetylene or 3,4-dibenzyloxy phenylacetylene. The key step of the syntheses involves a highly stereoselective Lewis-acid promoted coupling of 1,2-di-*O*-acyl-3,4,6-tribenzylglucose with tribenzyl phloroglucinol, which gives rise to the corresponding β -*C*-aryl glycoside in 30–65% yields.

Naturally occurring *C*-aryl glycosides exhibit a range of interesting biological properties. *C*-Glycosyl flavonoids, in particular, have been shown to possess antiviral, cytotoxic, and DNA binding activities.¹ The natural product aspalathin, isolated from the leaves of *aspalathus linearis* and used in the manufacture of rooibos tea,² displays potent antioxidant and radical scavenging activity,³ and has recently been found to inhibit proliferation and infiltration of liver cancer cells.⁴ The structurally related flavonoid nothofagin, typically co-isolated with aspalathin,² also displays antioxidant properties, but to a lesser extent than aspalathin. Both of these compounds can be considered as direct precursors of a variety of other biologically interesting *C*-aryl flavonoid natural products, such as orientin/isoorientin,⁵ vitexin/isovitexin,⁵ and aspalalinin⁶ (Figure 1). In view of their impressive biological profile, we decided to undertake total syntheses of both aspalathin and nothofagin.

Structurally, both natural products consist of a glucopyranosyl unit carbon-linked to a dihydrochalcone moiety, with β -stereochemistry observed at the anomeric carbon atom.² We envisioned that the crucial linkage between the carbohydrate and aromatic subunits could be fashioned by a Lewis-acid promoted Friedel-Crafts-type glycosylation reaction; this process is well-precedented in the literature when highly electron-rich aromatics are employed as nucleophiles,^{7,8} and thus this method seemed a logical starting point for our investigations.

Addition of TESOTf (1 equiv) to a solution of tribenzylphloroglucinol (**2a**,^{9a} 2 equiv) and 2,3,4,6-tetra-*O*-benzyl glucose-1-*O*-acetate^{9b} (**1**) in CH₂Cl₂ at 0°C resulted in a clean conversion to the corresponding *C*-aryl glycoside as a ~3:1 mixture of β : α diastereomers in 89% yield (**3a** and **3b**; Scheme 1). Indeed, Schmidt also previously obtained 3:1 diastereoselectivity in the ZnCl₂-promoted coupling of 2,3,4,6-tetrabenzyl glucose-1-*O*-

* thomas.minehan@csun.edu .

Supporting Information Available Detailed experimental procedures, spectroscopic data, and ¹H and ¹³C NMR spectra for compounds in Table 1 and Schemes 1–4. This material is available free of charge on the Internet at <http://pubs.acs.org>.

trichloroacetimidate with **2a**.¹⁰ However, attempted coupling of 2,4,6-trisbenzyloxy acetophenone (**2b**,^{9c} 2 equiv) and **1** in the presence of TESOTf (1-5 equivalents) gave only trace quantities (<5%) of the desired C-aryl glycoside product, and unreacted starting materials were recovered in high yield.

To circumvent the low diastereoselectivity obtained in the coupling reaction, we explored an alternative approach based on the C-glycosidation studies of Kishi¹¹ involving anchimeric participation by a C.2 protecting group.

Seeking to avoid the formation of ketal by-products observed in reactions involving C.2 acetate-protected carbohydrates (ie., **6**, R=CH₃, scheme 1), we first prepared 1,2-di-*O*-pivaloyl-3,4,6-tribenzyl glucose **4a** from tribenzyl glucal by oxone-mediated dihydroxylation,¹² followed by treatment with excess trimethylacetyl chloride in pyridine (60°C, 24 h). Reaction of **4a** with tribenzylphloroglucinol (**2a**, 4 equiv) at 0°C in 10:1 CH₂Cl₂:THF in the presence of 10 equivalents of TMSOTf afforded glycoside **5** as a single diastereomer in 55% yield. The β-stereochemistry of the carbohydrate was confirmed in the 9.2 Hz coupling constant observed for the carbohydrate C.2 proton. As anticipated, reaction of **4a** with **2b** under these conditions gave no reaction. Compound **5** could be transformed into **3a** by DIBAH reduction followed by benzylation of the C.2 alcohol (KH, BnBr, THF) in 80% overall yield.

Although a stereoselective glycosylation reaction had been found, the moderate yields of product obtained, along with the excess of nucleophile and promoter required, indicated the significantly lower reactivity of carbohydrate **4a** as compared to **1**. We therefore performed an optimization study by altering the reaction promoter, as well as the identity of the acyl protecting groups (R) on glycosyl acceptor **4** (table 1). Due to the sparing solubility of **2a** in acetonitrile and ether at 0°C, solvent systems chosen for the reaction were admixtures of CH₂Cl₂ with acetonitrile or THF; reactions performed in CH₂Cl₂ alone were slow (t > 1h), and the optimal solvent combination found was 2:1 CH₂Cl₂:THF. Of the Lewis acids surveyed, only TMSOTf, TESOTf, and SnCl₄ (entries 1, 2, 4, 5, 8, and 9) gave rise to the desired product in appreciable yields; the use of BF₃•OEt₂ (entry 3), InCl₃, (entry 6) or Et₂AlCl (entry 7) gave negligible amounts of **5** even after prolonged reaction times (>24 h) at ambient temperature. For glycosyl acceptors **4a** and **4c**, excess of the promoter (≥10 equivalents) was required for optimal conversions of the starting material. Furthermore, in all cases, highest yields of **5**¹³ were obtained when 3.5-4.0 equivalents of tribenzyl phloroglucinol were employed; unreacted **2a** could be efficiently recovered (>2 equiv) after column chromatography of the crude reaction mixture.

Le Drian¹⁴ has suggested that the use of the less bulky isobutyryl ester as a carbohydrate protecting group for glycosidation reactions involving anchimeric participation affords higher product yields than similar reactions employing pivaloate-protected sugars. Indeed, coupling of bis-isobutyrate **4b**^{15a} with **2a** (4 equiv) in the presence of 5 equivalents of TMSOTf led to **5b** in 65% yield (86% based on recovered starting material); ketal byproduct **6** (R=*i*Pr) was not formed to any significant extent (>5%) in the reaction. However, reaction of cyclohexyl ester **4c**^{15b} with **2a** (4 equiv) proceeded sluggishly, providing ~30% **5c** after the addition of ~12 equiv TMSOTf (entry 8); **4c** was recovered in 45% yield from the reaction after workup. Reaction of diacetate **4d**¹² with **2a** in the presence of 5 equivalents of TMSOTf gave a 43% yield of **5d**, along with ~35% recovered starting material and 12% of an unidentified by-product presumably derived from acetal **6** (R=CH₃).

It was originally envisioned that benzyl ether **3a** (efficiently prepared from **5a**, Scheme 1) could be advanced toward the natural products by introduction of a carbonyl substituent on the phloroglucinol aromatic ring. Friedel-Crafts acylation approaches employing acetyl

chloride/ AlCl_3 or acetic anhydride in combination with trifluoroacetic acid,¹⁶ phosphoric acid,¹⁷ zinc chloride,¹⁸ indium chloride¹⁹ or indium triflate²⁰ all led to substrate decomposition due to premature loss of the aromatic benzyl ether protecting groups under the acidic reaction conditions. We ultimately found, however, that Vilsmeier-Haack reaction²¹ of **3a** (DMF, POCl_3) smoothly led to aldehyde **7a** in 90% yield (Scheme 2). Attempts to repeat this reaction with *N,N*-dimethylacetamide in place of DMF (to furnish the corresponding aryl ketone) at room temperature or at elevated temperatures gave no reaction. Analysis of the ^1H NMR spectrum of compound **7a** revealed the presence of two diastereomers in a ratio of 2:1. From this observation, we concluded that anomerization was occurring under the Vilsmeier reaction conditions to give a thermodynamic mixture of β - and α -C-aryl glycosides. To avoid compromise of the anomeric stereochemistry in this manner, we chose to investigate the direct formylation of glycoside **5a** containing the C.2 pivaloyloxy protecting group.²² Fortuitously, aldehyde **7b** was obtained in 85% yield with a 10:1 diastereomer ratio in favor of the desired β -C-aryl glycoside.

For completion of the natural product syntheses we envisioned addition of an appropriate alkynyllithium species to aldehyde **7b**, followed by benzylic oxidation and protecting group removal. The requisite alkynes **10a**²³ and **10b** for this procedure were fashioned from 4-hydroxybenzaldehyde **8a** and 3,4-dihydroxybenzaldehyde **8b** by benzylation²⁴ and alkynylation with the Bestmann-Ohira reagent (Scheme 3).²⁵ Treatment of alkyne **10a** with 0.9 equiv of *n*-BuLi, followed by addition of aldehyde **7b** gave rise to a ~1:1 mixture of diastereomeric propargylic alcohols (**11a** and **11b**, 81%) which was immediately treated with CH_3MgBr in ether to effect removal of the C.2 pivaloyl protecting group. Oxidation of diols **12a,b** with excess MnO_2 in 1:1 CH_2Cl_2 :hexanes gave rise to ynone **13** in 93% overall yield from **11a,b**. Finally, hydrogenolysis of the benzyl ether protecting groups (H_2 , 10% Pd on C, rt, 18h) gave an 89% yield of synthetic nothofagin, the spectroscopic and physical data of which (^1H and ^{13}C NMR, UV, and melting point) matched those reported for the natural compound.^{5, 26}

The synthesis of aspalathin was accomplished in an analogous manner (Scheme 4) by coupling lithiated **10b** with **7b**, followed by pivaloyl deprotection, benzylic oxidation, and benzyl ether hydrogenolysis; synthetic aspalathin was obtained in 51% overall yield from **14a,b**. The spectroscopic and physical data for the synthetic material (^1H and ^{13}C NMR, UV, IR, $[\alpha]_D$, and melting point) was identical in all respects to those reported for the natural product.^{2,5}

In summary, eight-step syntheses of the natural glycosyl flavonoids nothofagin and aspalathin have been accomplished in 28% and 20% overall yield, respectively, from tribenzyl glucal, tribenzyl phloroglucinol, and either 4-benzyloxy phenylacetylene or 3,4-dibenzyloxy phenylacetylene. We are currently investigating the oxidative transformation of these compounds into other products of potential medicinal and therapeutic value.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Aspalathin and nothofagin as precursors of other naturally occurring C-glycosyl flavones

Scheme 1.
C-glycosylation of carbohydrates **1** and **4a**.

Scheme 2.
Formylation of glycosides **3a** and **5a**

Scheme 3.
Completion of the synthesis of nothofagin.

Scheme 4.
 Completion of the synthesis of aspalathin

Table 1

Optimization of the C-glycosylation reaction^a

entry	Lewis acid (equiv)	R	4	5	% yield 5 (brsm) ^b
1	TMSOTf (10)	(CH ₃) ₃ C	a	a	55 (76)
2	TESOTf (10)	(CH ₃) ₃ C	a	a	50 (75)
3	BF ₃ •OEt ₂ (10)	(CH ₃) ₃ C	a	a	<5
4	TMSOTf (5)	(CH ₃) ₂ CH	b	b	65 (86)
5	SnCl ₄ (5)	(CH ₃) ₂ CH	b	b	45 (50)
6	InCl ₃ (5)	(CH ₃) ₂ CH	b	b	<5
7	Et ₂ AlCl (5)	(CH ₃) ₂ CH	b	b	<5
8	TMSOTf (12)	C ₆ H ₁₁	c	c	30 (54)
9	TMSOTf (5)	CH ₃	d	d	43 (66)

^a Optimal yields were obtained using 3.5–4.0 equiv **2a**. The optimal reaction concentration was 0.33 M relative to **4**. For entries 1–8, <5% ketal byproduct **6** was formed, as assayed by ¹H NMR of the crude reaction mixture.

^b Yield in parenthesis represents yield based on recovered starting material.