

Concise Total Syntheses of Aspalathin
and Nothofagin

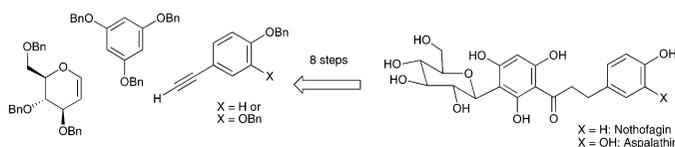
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ABSTRACT



Syntheses of the C-glycosyl flavone natural products aspalathin and nothofagin have been accomplished in eight steps from tribenzyl glucal, tribenzylphloroglucinol, and either 4-(benzyloxy)phenylacetylene or 3,4-bis(benzyloxy)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 tribenzylphloroglucinol, 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 activity³ and has recently been found to inhibit proliferation and infiltration of liver cancer cells.⁴ The structurally related flavonoid nothofagin, typically coisolated 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-benzylglucose-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-tetrabenzylglucose-1-O-trichloroacetimidate with

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(9) (a) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Synth. Commun.* **1996**, *26*, 531. (b) 2,3,4,6-Tetra-O-benzylglucose-1-O-acetate was prepared from dextrose in 60% overall yield by allylation (allyl alcohol, H₂SO₄), benzylation (NaH, BnBr, DMF), deallylation (*t*-BuOK, DMF, 70 °C; 1 N H₂SO₄), and acylation (Ac₂O, Pyr). (c) Prepared in 70% yield by treatment of phloracetophenone with benzyl chloride (3.3 equiv) and K₂CO₃ (5 equiv) in DMF at 80 °C for 1 h.

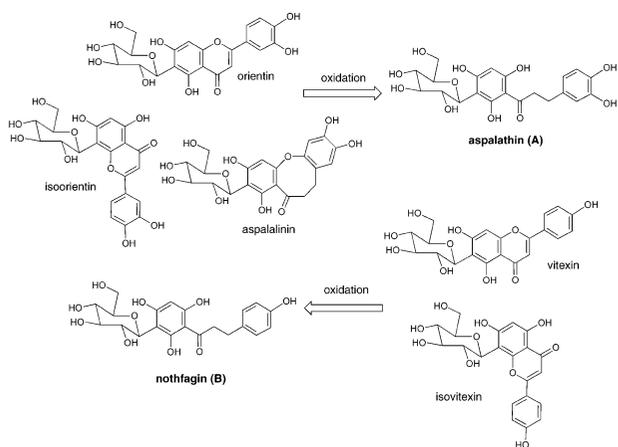


Figure 1. Aspalathin and nothofagin as precursors of other naturally occurring C-glycosyl flavones.

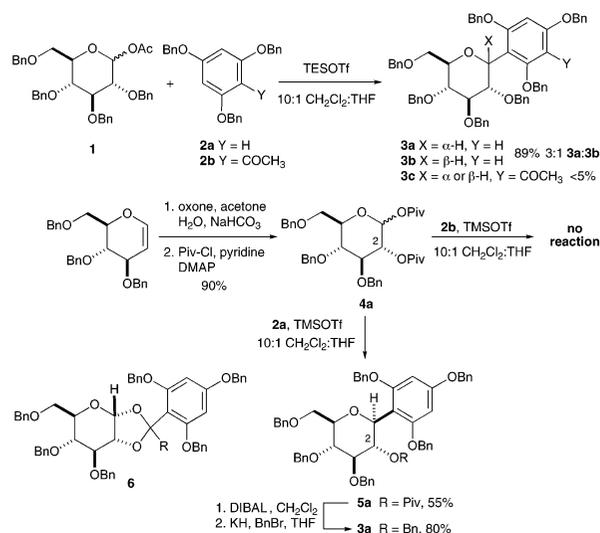
2a.¹⁰ However, attempted coupling of 2,4,6-tris(benzyloxy)acetophenone (**2b**,^{9c} 2 equiv) and **1** in the presence of TESOTf (1–5 equiv) gave only trace quantities (<5%) of the desired C-aryl glycoside product, and unreacted starting materials were recovered in high yield.

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 C2 protecting group.

Seeking to avoid the formation of ketal byproduct observed in reactions involving C2 acetate-protected carbohydrates (ie., **6**, R = CH₃, Scheme 1), we first prepared 1,2-di-*O*-pivaloyl-3,4,6-tribenzylglucose **4a** from tribenzyl glucal by treatment with 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 equiv 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 C2 proton. As anticipated, reaction of **4a** with **2b** under these conditions gave no reaction. Compound **5** could be transformed into **3a** by DIBAL reduction followed by benzylation of the C2 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

Scheme 1. C-Glycosylation of Carbohydrates **1** and **4a**



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 ($t > 1$ h), 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 promoter (≥ 10 equiv) 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 equiv of tribenzylphloroglucinol was 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 equiv 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

(13) Attempts to achieve greater conversions in the C-glycosylation reactions by adding excess Lewis acid (>10 equiv), by elevating the reaction temperature (→25 °C), or by increasing the reaction time (>1h) only led to lower overall yields of **5**, presumably due to acid-induced cleavage of the aromatic benzyl ether protecting groups.

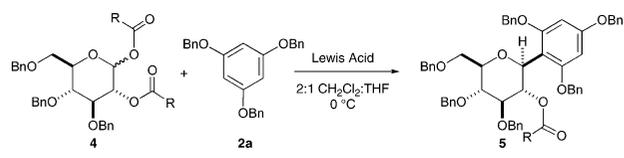
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(15) (a) Prepared in the same manner as **4a**, except with the substitution of isobutryl chloride for pivaloyl chloride in the esterification step. (b) Prepared in the same manner as **4a**, except with the substitution of cyclohexyl carbonyl chloride for pivaloyl chloride in the esterification step.

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(12) Rani, S.; Vankar, Y. D. *Tetrahedron Lett.* **2003**, *44*, 907. While a ~1:1 mixture of anomers at C1 of the carbohydrate is observed in the dihydroxylation reaction, the diastereoselectivity at C2 of the carbohydrate is very high, and we estimate a >95:5 diastereomer ratio at C2 by ¹H NMR analysis of the individual α and β C1 anomers of dipivaloate **4a**.

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)	(CH₃)₂CH	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 of **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 parentheses represents yield based on recovered starting material.

of ~12 equiv of 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 equiv of TMSOTf gave a 43% yield of **5d**, along with ~35% recovered starting material and 12% of an unidentified byproduct 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/AlCl₃ or acetic anhydride in combination with trifluoroacetic acid,¹⁶ phosphoric acid,¹⁷ zinc chloride,¹⁸ indium chloride,¹⁹ 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, POCl₃) 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

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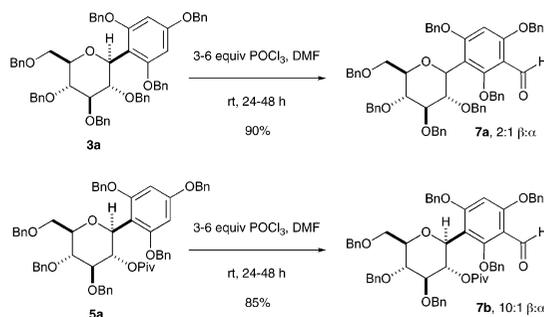
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manner, we chose to investigate the direct formylation of glycoside **5a** containing the C2 pivaloyloxy protecting group.²² Fortunately, aldehyde **7b** was obtained in 85% yield with a 10:1 diastereomer ratio in favor of the desired β-C-aryl glycoside.

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

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 alkylation 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 CH₃MgBr in ether to effect removal of the C2 pivaloyl protecting group. Oxidation of diols **12a,b** with excess MnO₂ in 1:1 CH₂Cl₂/hexanes gave rise to ynone **13** in 93% overall yield from **11a,b**. Finally, hydrogenolysis of the benzyl ether protecting groups (H₂, 10% Pd on C, rt, 18 h) gave an 89% yield of synthetic nothofagin, the spectroscopic and physical data of which (¹H and ¹³C 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

(22) Glycoside **5b** could also be used in the Vilsmeier formylation reaction, providing an 83% yield of the corresponding isobutyryl-protected aryl aldehyde. This substrate was not chosen to advance through the remainder of the synthesis for two reasons: first, the cost of isobutyryl chloride required for the preparation of **4b** (and thus **5b**) is about twice that of pivaloyl chloride, and second, slightly lower overall yields (~55%) were obtained when the isobutyryl-protected aryl aldehyde was subjected to the coupling (with lithiated **10a** and **10b**) and isobutyrate deprotection reactions.

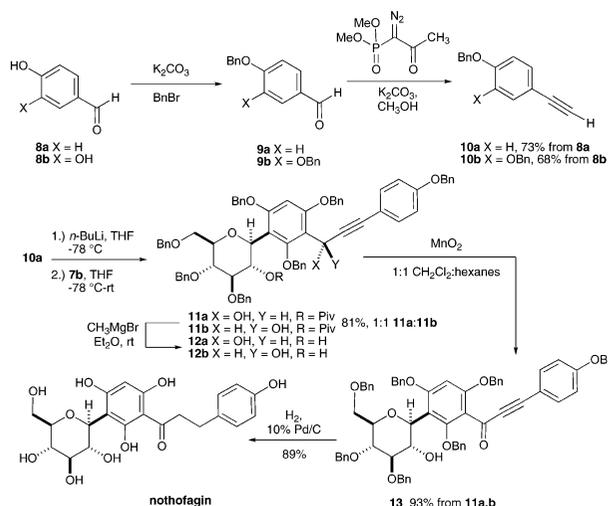
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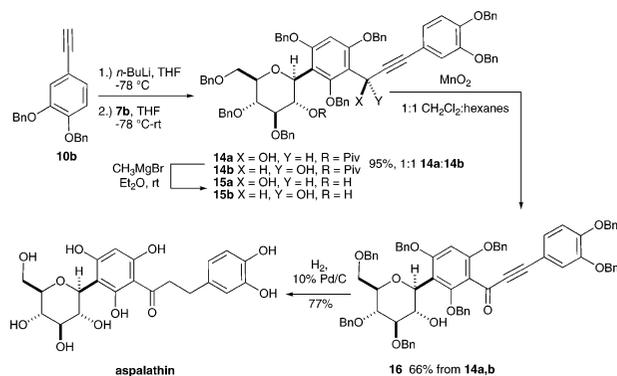
Scheme 3. Completion of the Synthesis of Nothofagin



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, tribenzylphloroglucinol, and either 4-(benzyloxy)phenylacetylene or 3,4-bis(benzyloxy)phenylacetylene. We are currently investigating the oxidative transformation of these

Scheme 4. Completion of the Synthesis of Aspalathin



compounds into other products of potential medicinal and therapeutic value.

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

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