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Concise Total Syntheses of Aspalathin and Nothofagin

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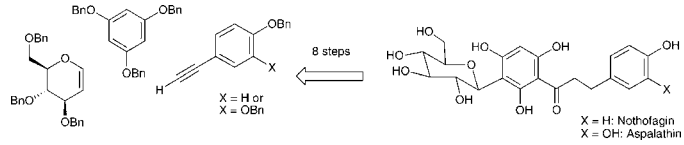
ABSTRACT



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 activity[3] 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 aspalalinin[6] (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 CH_2Cl_2 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 $ZnCl_2$-promoted coupling of 2,3,4,6-tetrabenzylglucose-1-*O*-trichloroacetimidate with

(1) Furuta, T.; Kimura, T.; Kondo, S.; Mihara, H.; Wakimoto, T.; Nakaya, H.; Tsuji, K.; Tanaka, K. *Tetrahedron Lett.* **2004**, *60*, 9375.
(2) Koeppen, B. H.; Roux, D. G. *Biochem. J.* **1966**, *99*, 604.
(3) von Gadow, A.; Joubert, E.; Hansmann, C. F. *J. Agric. Food. Chem.* **1997**, *45*, 632.
(4) Snijman, P. W.; Swanevelder, S.; Joubert, E.; Green, I. R.; Gelderblom, W. C. A. *Mutat. Res., Genet. Toxicol. Environ. Mutagen.* **2007**, *631*, 111.
(5) Krafczyk, N.; Glomb, M. A. *J. Agric. Food Chem.* **2008**, *56*, 3368.
(6) Shimamura, N.; Miyase, T.; Umehara, K.; Warashina, T.; Fujii, S. *Biol. Pharm. Bull.* **2006**, *29*, 1271.
(7) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289.
(8) Schmidt, R. R.; Hoffmann, M. *Tetrahedron Lett.* **1982**, *23*, 409.
(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, H_2SO_4), benzylation (NaH, BnBr, DMF), deallylation (*t*-BuOK, DMF, 70 °C; 1 N H_2SO_4), and acylation (Ac_2O, Pyr) . (c) Prepared in 70% yield by treatment of phloroacetophenone with benzyl chloride (3.3 equiv) and K_2CO_3 (5 equiv) in DMF at 80 °C for 1 h.

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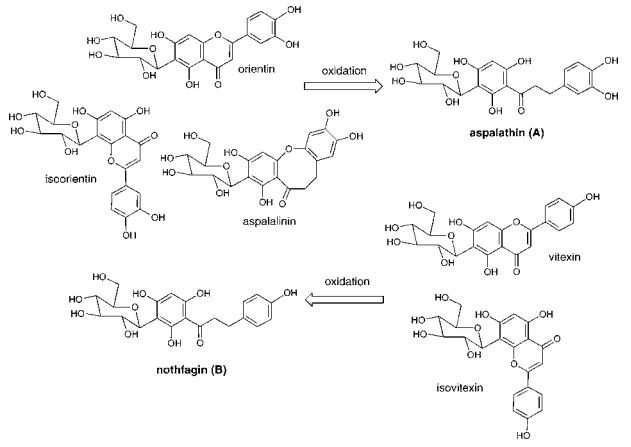
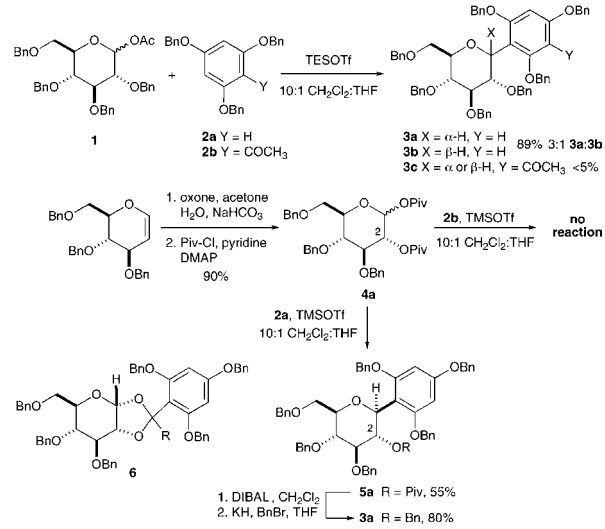


Figure 1. Aspalathin and nothofagin as precursors of other naturally occurring C-glycosyl flavones.

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



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 Kishi[11] involving anchimeric participation by a C2 protecting group.

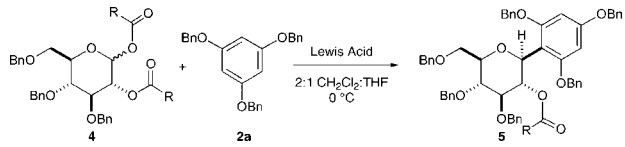
Seeking to avoid the formation of ketal byproduct observed in reactions involving C2 acetate-protected carbohydrates (ie., **6**, R = CH_3, Scheme 1), we first prepared 1,2-di-*O*-pivaloyl-3,4,6-tribenzylglucose **4a** from tribenzyl glucal by Oxone-mediated dihydroxylation,[12] followed by treatment with excess trimethylacetyl chloride in pyridine (60 °C, 24 h). Reaction of **4a** with tribenzylphloroglucinol (**2a**, 4 equiv) at 0 °C in 10:1 CH_2Cl_2/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 1). Due to the sparing solubility of **2a** in acetonitrile and ether at 0 °C, solvent systems chosen for the reaction were admixtures of CH_2Cl_2 with acetonitrile or THF; reactions performed in CH_2Cl_2 alone were slow (t > 1 h), and the optimal solvent combination found was 2:1 CH_2Cl_2/THF. Of the Lewis acids surveyed, only TMSOTf, TESOTf, and $SnCl_4$ (entries 1, 2, 4, 5, 8, and 9) gave rise to the desired product in appreciable yields; the use of BF_3•OEt_2 (entry 3), $InCl_3$, (entry 6), or Et_2AlCl (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 Drian[14] 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

(10) Schmidt, R. R.; Effenberger, G. *Carbohydr. Res.* **1987**, *171*, 59.
(11) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815.
(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 ^{1}H NMR analysis of the individual α and β C1 anomers of dipivaloate **4a**.
(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.
(14) Desmares, G.; Lefebvre, D.; Renevret, G.; Le Drian, C. *Helv. Chim. Acta* **2001**, *84*, 880.
(15) (a) Prepared in the same manner as **4a**, except with the substitution of isobutryl chloride for pivaloyl chloride in the esterificaton step. (b) Prepared in the same manner as **4a**, except with the substitution of cyclohexyl carbonyl chloride for pivaloyl chloride in the esterificaton step.

Table 1. Optimization of the *C*-Glycosylation Reaction[a]



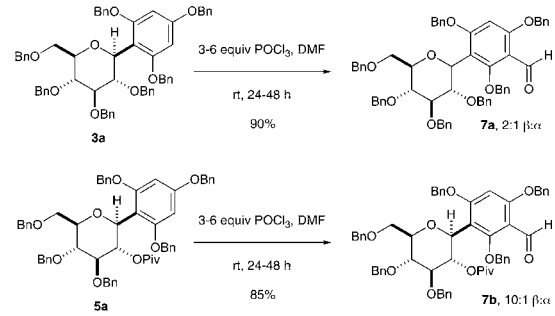
entry	Lewis acid (equiv)	R	4	5	% yield **5** (brsm)[b]
1	TMSOTf (10)	$(CH_3)_3C$	a	a	55 (76)
2	TESOTf (10)	$(CH_3)_3C$	a	a	50 (75)
3	$BF_3{\cdot}OEt_2$ (10)	$(CH_3)_3C$	a	a	<5
4	**TMSOTf (5)**	**$(CH_3)_2CH$**	**b**	**b**	**65 (86)**
5	$SnCl_4$ (5)	$(CH_3)_2CH$	b	b	45 (50)
6	$InCl_3$ (5)	$(CH_3)_2CH$	b	b	<5
7	Et_2AlCl (5)	$(CH_3)_2CH$	b	b	<5
8	TMSOTf (12)	C_6H_{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 ^{1}H 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 = CH_3).

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 chloride,[19] or indium triflate[20] 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 reaction[21] 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 ^{1}H 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 C2 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.

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



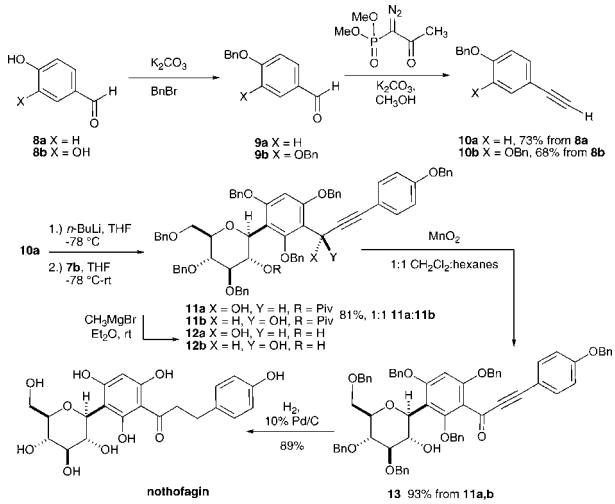
For completion of the natural product syntheses we envisioned addition of an appropriate alkynyllithium species to aldehyde **7b**, followed by benzylic oxidation and protecting group removal. The requisite alkynes **10a**[23] and **10b** for this procedure were fashioned from 4-hydroxybenzaldehyde **8a** and 3,4-dihydroxybenzaldehyde **8b** by benzylation[24] 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 C2 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, 18 h) gave an 89% yield of synthetic nothofagin, the spectrocopic and physical data of which (^{1}H 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

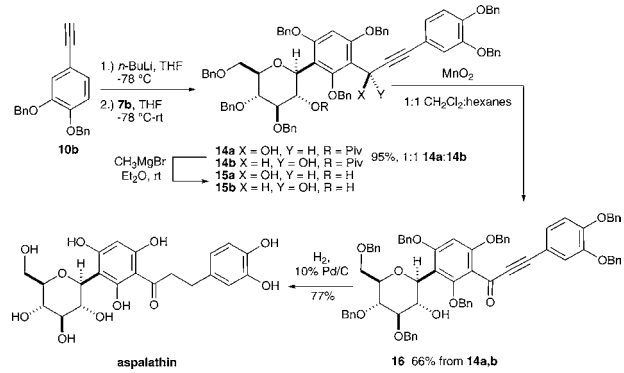
(16) Nay, B.; Arnaudinaud, V.; Vercauteren, J. *Eur. J. Org. Chem.* **2001**, *12*, 2379.
(17) Gjoes, N.; Gronowitz, S. *Acta Chem. Scand.* **1972**, *26*, 1851.
(18) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *J. Wood Chem. Technol.* **1989**, *9*, 35.
(19) Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311.
(20) Koshima, H.; Kubota, M. *Synth. Commun.* **2003**, *33*, 3983.
(21) Jones, A. W.; Wahyuningsih, T. D.; Pchalek, K.; Kumar, N.; Black, D. *Tetrahedron* **2005**, *61*, 10490.

(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.
(23) Maehr, H.; Uskokovic, M. R.; Schaffner, C. P. *Synth. Commun.* **2009**, *39*, 299.
(24) 4-Benzyloxybenzaldehyde: Narasimhulu, M.; Srikanth Reddy, T.; Chinni Mahesh, K.; Sai Krishna, A.; Venkateswara Rao, J.; Venkateswarlu, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3125. 3,4-Bis(benzyloxy)benzaldehyde: Milhazes, N.; Cunha-Oliveira, T.; Martins, P.; Garrido, J.; Oliviera, C.; Rego, A.; Borges, F. *Chem. Res. Toxicol.* **2006**, *10*, 1294.
(25) (a) Muller, S.; Liepold, B.; Roth, R. G.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(26) Melting point and UV data for nothofagin: Hillis, W. E.; Inoue, T. *Phytochemistry* **1967**, *6*, 59. To the best of our knowledge, there exist in the literature no reports of the measurement of the specific rotation ($[\alpha]_D$) of nothofagin.

Scheme 3. Completion of the Synthesis of Nothofagin



Scheme 4. Completion of the Synthesis of Aspalathin



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 (^{1}H 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 compounds into other products of potential medicinal and therapeutic value.

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Supporting Information Available: Detailed experimental procedures, spectroscopic data, and ^{1}H 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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