

Total Synthesis of Sanguin H-5

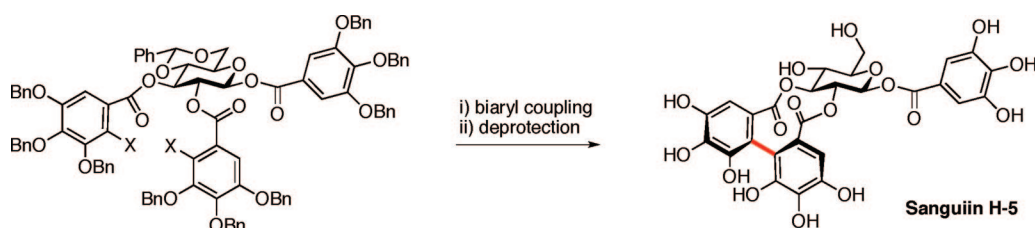
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ABSTRACT



Using an atropdiastereoselective oxidative biaryl coupling as the key step, the total synthesis of the ellagitannin natural product sanguin H-5 is reported. Both organomagnesium and organozinc based metalation methodologies were used to efficiently construct the strained medium-ring core of the natural product.

Sanguin H-5 is a member of the ellagitannin class of hydrolyzable plant polyphenols.¹ In addition to industrial applications,² ellagitannins display a range of useful biological properties including antiviral³ and antitumor activities.⁴ The structural features of sanguin H-5 make it a challenging molecular target.⁵ In addition to the β -glycosidic link at the anomeric center, the characteristic hexahydrodiphenoyl (HHDP) moiety^{1c} common to all ellagitannins is part of a strained medium ring with an (*S*)-configuration about the biaryl bond (Scheme 1).

The only previous synthesis of sanguin H-5 was reported by Feldman and Sambandam and involved an elegant oxidative coupling of pendant aryl groups attached to a central pyranose scaffold.⁶ Although the key coupling step

generated the desired (*S*)-atropoisomer of the HHDP group, the complete reaction pathway suffered from somewhat moderate yields, illustrating the complexity of the target molecule. Since there are only a few reports of the efficient synthesis of biaryl-containing medium rings, we sought to exploit our organocuprate oxidation protocols⁷ to forge the key biaryl bond of sanguin H-5. These coupling methodologies utilized the following general sequence: halogen–metal exchange (either iodine–magnesium^{7a} or bromine–zinc;^{7b} copper salt mediated transmetalation; and finally, organocuprate oxidation and biaryl bond formation.

We envisaged a strategy whereby the globally protected sanguin H-5 precursor **1** could be accessed in an atropdiastereoselective intramolecular biaryl coupling from the appropriate diaryl halide **2** or **3** (Scheme 1).

The precursors **2** and **3** could potentially be synthesized by the diacylation of the diol **4** with the gallic acid derivatives **5** or **6**. Provided the pyranose **4** could be synthesized with a β -configuration at the anomeric center and that the halogenation of **7** is possible, compounds **7**, **8**, and **9** should serve as readily available starting materials (Scheme 1).

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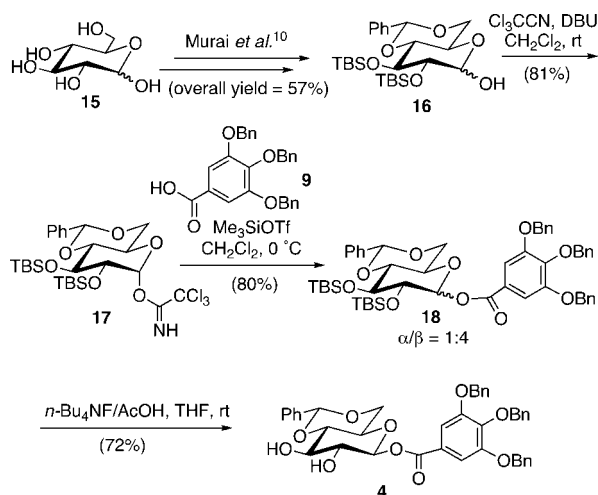
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(S)-HHDP
Sanguin H-5
 Global Deprotection
1
 Intramolecular biaryl coupling
 $X = I = 2$
 $X = Br = 3$
 Acylation
 $X = I = 5$
 $X = Br = 6$
 Halogenation
 $X = I = 7$
 $X = Br = 8$
 Acylation
 $X = I = 9$
 $X = Br = 10$

Scheme 3. Synthesis of the β -Glucopyranose **4**

of trichloroacetimidate acylation chemistry to furnish the desired β -anomer primarily. Thus, in the presence of the protected gallic acid **9**, the α -trichloroacetimidate **17** was converted to the ester **18** as a mixture of α and β -anomers ($\alpha/\beta = 1:4$ by ^1H NMR analysis) in an 80% yield. The desired β -galloylglucose product **4** was isolated in 72% yield by flash column chromatography after desilylation (Scheme 3).

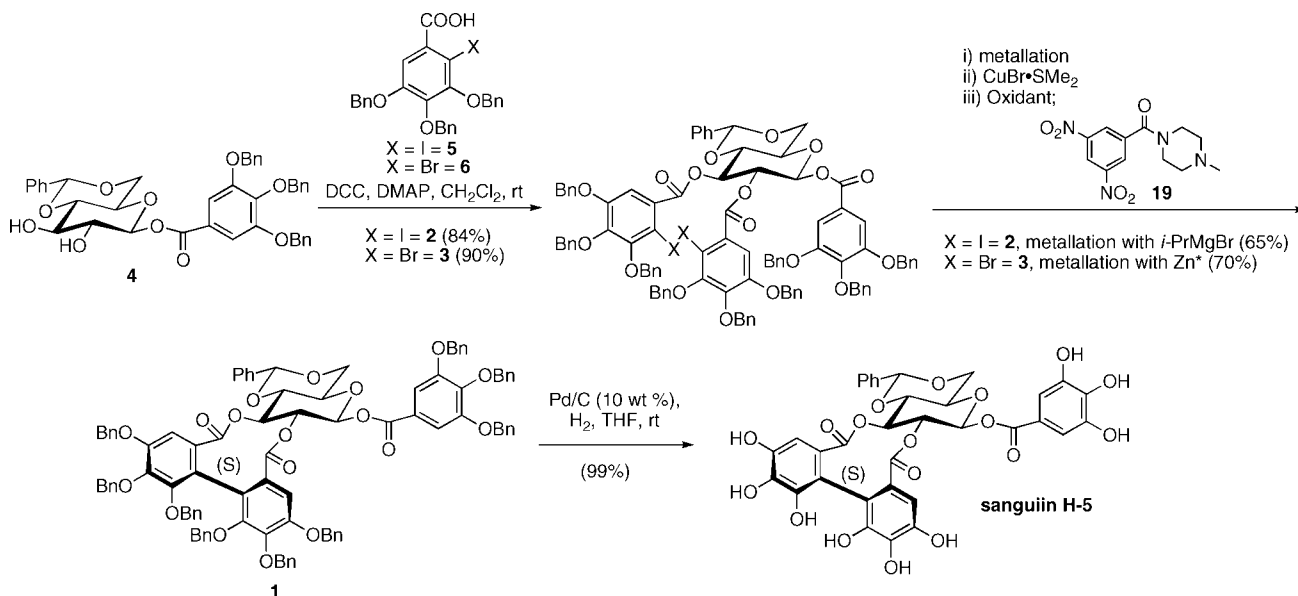
In the presence of DCC, DMAP and the benzoic acid **5**, the β -galloylglucose **4** was converted to the cyclization precursor **2** via a double esterification at O(2) and O(3) in an 84% yield. With **2** in hand, the key orangocuprate oxidative intramolecular biaryl bond-forming reaction was attempted. Treatment of **2** with isopropylmagnesium chloride, followed by transmetalation with $\text{CuBr}\cdot\text{SMe}_2$ and subsequent

intramolecular cuprate oxidation in the presence of the oxidant **19**,⁷ gave access to the benzyl-protected sanguin H-5 **1** (Scheme 4). The reaction proceeded with complete diastereoselectivity and in good isolated yield (65%); pleasingly no dimer side products were observed. This observed selectivity for the (*S*)-atropoisomer in the biaryl coupling step as has been discussed previously,^{1c} is thought to be a result of the structural restraints imposed by the galloylated sugar ring core. Our efforts to determine if this selectivity was as a result of a kinetic or thermodynamic effects were unsuccessful; heating the biaryl **1** led to decomposition and isomerization was not observed.

After demonstrating the effectiveness of the above methodology, the copper catalyzed oxidative organozinc biaryl coupling was examined.^{7b} The milder conditions allow the more readily available aryl bromide coupling precursor to be used in the key C–C bond-forming reaction. Once synthesized,⁸ the bromobenzoic acid **6** was coupled to the β -glucopyranose **4** to give the coupling precursor **3**. After treatment of **3** with Rieke zinc (Zn^*), transmetalation, and oxidation (as before) facilitated the formation of the cyclized product **1** in an optimized 70% isolated yield (Scheme 4). The reaction was highly sensitive to moisture and rigorously anhydrous reaction conditions were required to minimize the formation of the debrominated byproduct.

To complete our total synthesis from the globally protected compound **1** formed via either of the above routes, a Pd/C induced hydrogenolytic deprotection followed by filtration through Celite furnished sanguin H-5 (Scheme 4). Sanguin H-5 was found to be hydrolytically unstable on silica and alumina, making further purification problematic.¹² The spectroscopic data obtained matched that reported previously for the natural product.⁶

These routes based on organocuprate oxidative biaryl bond formation constitute efficient methods to access sanguin H-5

Scheme 4. Intermolecular Biaryl Formation and the Synthesis of Sanguin H-5

and potentially other ellagitannins. In one step after either the initial formation of an organomagnesium or organozinc intermediate, intramolecular oxidative coupling of the resulting diarylcuprate allows diastereoselective and concomitant biaryl bond and medium ring formation. As a result, this approach constitutes a robust and general procedure for the synthesis of natural and unnatural products containing this strained motif. The successful performance of these methodologies in the total synthesis of sanguin H-5 represents a

(12) Chromatography using reversed-phase (C-18) silica could be used if required; however, the filtered, concentrated reaction mixture gave material of ca. 95% purity.

significant advance to complement existing biaryl-coupling strategies.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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