

Total Synthesis of Sanguiin H-5

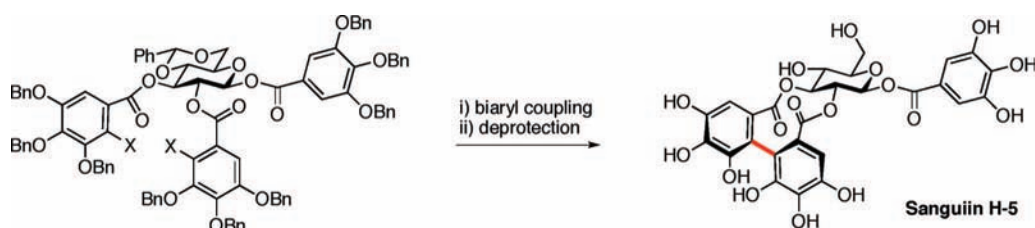
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ABSTRACT



Using an atropdiastereoselective oxidative biaryl coupling as the key step, the total synthesis of the ellagitannin natural product sanguiin 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.

Sanguiin 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 sanguiin 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 sanguiin 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 sanguiin 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 sanguiin 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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(2) (a) Hemingway, R. W.; Laks, P. E. *Basic Life Science. Plant Polyphenols, Synthesis, Properties, Significance*; Plenum Press: New York, 1992. (b) Haslam, E. *Plant Polyphenols. Vegetable Tannins revisited*; Cambridge University Press: Cambridge, 1989.

(3) (a) Nakashima, H.; Murakami, T.; Yamamoto, N.; Sakagami, H.; Tanuma, S.; Hatano, T.; Yoshida, T.; Okuda, T. *Antiviral Res.* **1992**, *18*, 91–103. (b) Xie, L.; Xie, J. X.; Kashiwada, Y.; Cosentino, L. M.; Liu, S. H.; Pai, R. B.; Cheng, Y. C.; Lee, K. H. *J. Med. Chem.* **1995**, *38*, 3003–3008.

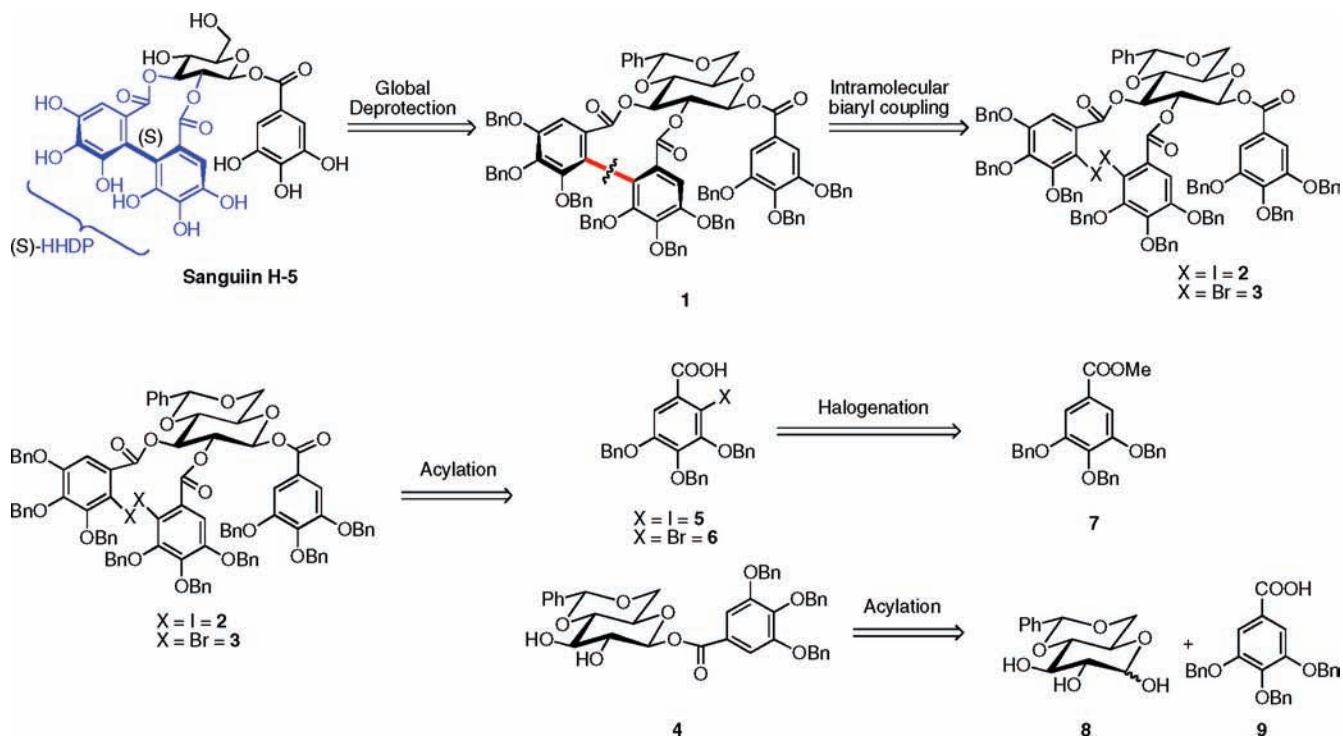
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(5) Khanbabaee, K.; van Ree, T. *Synthesis* **2001**, 1585–1610.

(6) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171–8178.

(7) (a) Surry, D. S.; Su, X.; Fox, D. J.; Franckevicius, V.; Macdonald, S. J. F.; Spring, D. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 1870–1873. (b) Su, X.; Fox, D. J.; Blackwell, D. T.; Tanaka, T.; Spring, D. R. *Chem. Commun.* **2006**, 3883–3885. (c) Surry, D. S.; Fox, D. J.; Macdonald, S. J. F.; Spring, D. R. *Chem. Commun.* **2005**, 2589–2590.

Scheme 1. Proposed Retrosynthesis of Sanguiin H-5



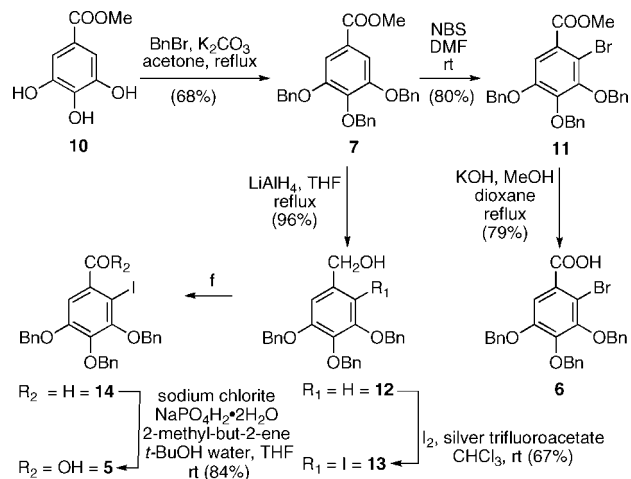
Using the copper-mediated oxidation of an organomagnesium halide, a model system of the strained medium ring core of sanguin H-5 (no hydroxyl substitutions on the aryl rings) had previously been synthesized.^{7a} We were therefore keen to test this methodology in the total synthesis of the more sterically hindered and demanding target (i.e., sanguin H-5). As metalation reaction requires aryl iodides, the gallic acid derivative **5** was needed to facilitate the synthesis of the precursor.

Intriguingly, no previous synthesis of the iodide **5** has been disclosed. Although the bromide **6** could be accessed from methyl gallate **10** (via initial protection to give **7**, bromination to furnish **11** and subsequent ester cleavage (Scheme 2)⁸), neither **7** nor the benzyl ether-protected gallic acid **9** could be iodinated.⁹ However, a stepwise approach from **7** was found to be productive. After the reduction of **7** with LiAlH₄, the resulting alcohol **12** was iodinated in the presence of iodine and silver trifluoroacetate to yield **13**. The iodo alcohol **13** was then converted via a Swern oxidation to the aldehyde **14**; a Pinnick oxidation then furnished the desired benzoic acid **5** (Scheme 2).

Following the synthesis of **5**, in order to access the β -glucopyranose **4** with stereocontrol at the anomeric center, a series of protecting group manipulations were performed

from D-glucose (**15**). Using the procedure reported by Murai and co-workers,¹⁰ D-glucose (**15**) was converted to the

Scheme 2. Synthesis of the Benzoic Acids **5** and **6**



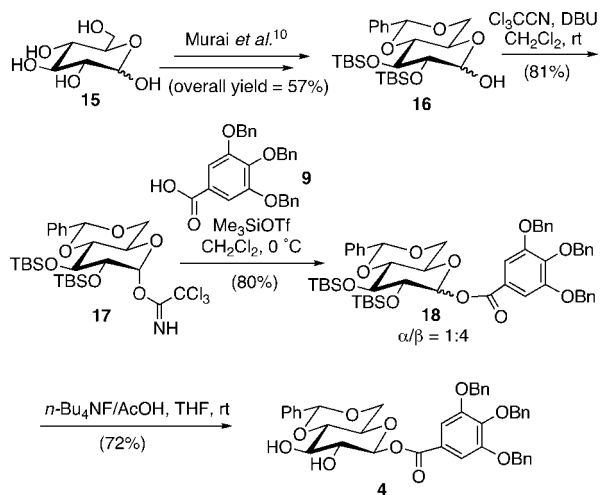
alcohol **16** in five steps in an overall yield of 57% (Scheme 3). In a similar method to that used by Feldman and Lawlor,¹¹ the α -trichloroacetimidate **17** was synthesized from **16** using Cl₃CCN and DBU. This allowed the exploitation

(8) Feldman, K. S. Personal communication. Feldman, K. S.; Quideau, S.; Appel, H. M. *J. Org. Chem.* **1996**, *61*, 6656.

(9) (a) Methods examined: (i) Electrophilic iodination: Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533. (b) Orito, K.; Hatakeyama, T.; Takeo, M.; Sugimoto, H. *Synthesis* **1995**, 1273. (c) van Laak, K.; Scharf, H. D. *Tetrahedron* **1989**, *45*, 5511(ii) Suzuki's oxidative conditions: (d) Suzuki, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2871(iii) Directed ortho-lithiation and iodine quench: (e) Gohier, F.; Mortier, J. J. *Org. Chem.* **2003**, *68*, 2030.

(10) Tanaka, H.; Kawai, K.; Fujiwara, K.; Murai, A. *Tetrahedron* **2002**, *58*, 10017–10031.

(11) Feldman, K. S.; Lawlor, M. D., *J. Am. Chem. Soc.* **2000**, *122*, 7396–7397, NB: NaH was used as the base in this reported synthesis.

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).

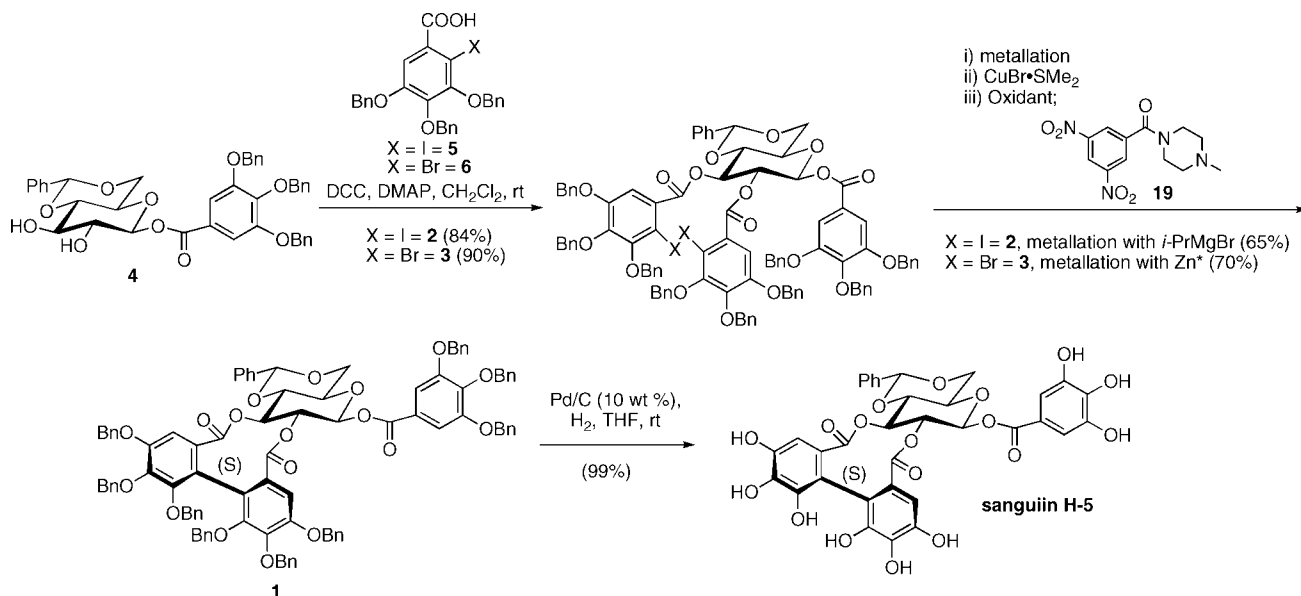
In the presence of DCC, DMAP and the benzoic acid **5**, the β -galloylglucose **4** was converted to the cyclization precursor **2** via a double esterification at O(2) and O(3) in an 84% yield. With **2** in hand, the key orangocuprate oxidative intramolecular biaryl bond-forming reaction was attempted. 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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