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

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

Following the synthesis of 5, in order to access the β-glucopyranose with stereocontrol at the anomeric center, a series of protecting group manipulations were performed from d-glucose. Using the procedure reported by Murai and co-workers, d-glucose (15) was converted to the alcohol in five steps in an overall yield of 57% (Scheme 3). In a similar method to that used by Feldman and Lawlor, the α-trichloroacetimidate was synthesized from using CH₂CN and DBU. This allowed the exploitation

(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.
of trichloroacetimidate acylation chemistry to furnish the desired β-anomer primarily. Thus, in the presence of the protected gallic acid 9, the R-trichloroacetimidate 17 was converted to the ester 18 as a mixture of α and β-anomers (α/β = 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 organocuprate oxidative intramolecular biaryl bond-forming reaction was attempted. Treatment of 2 with isopropylmagnesium chloride, followed by transmetalation with CuBr·SMe2 and subsequent intramolecular cuprate oxidation in the presence of the oxidant 19 gave access to the benzyl-protected sanguiin 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 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. 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, 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 sanguiin H-5 (Scheme 4). Sanguiin H-5 was found to be hydrolytically unstable on silica and alumina, making further purification problematic. The spectroscopic data obtained matched that reported previously for the natural product.

These routes based on organocuprate oxidative biaryl bond formation constitute efficient methods to access sanguiin 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 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.

(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.