Synthesis of Biaryl-Containing Medium-Ring Systems by Organocuprate Oxidation: Applications in the Total Synthesis of Ellagitannin Natural Products

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Abstract: In this feature article we discuss the construction of biaryl-containing medium-sized rings by organocuprate oxidation and the application of this chemistry in the synthesis of members of the ellagitannin family of natural products. A concise and efficient total synthesis of the ellagitannin sanguiin H-5 is highlighted. Studies towards the synthesis of elaeocarpusin are also presented.

Key words: cuprates, total synthesis, ring-closing, natural products, biaryls

1 Introduction

The importance of biaryl-containing medium-sized[1] rings in organic chemistry is exemplified by their being the structural core of a large number of natural products, pharmaceutical agents, catalysts and ligands (Figure 1). Consequently, the development of synthetic procedures towards medium-ring biaryls has attracted considerable interest.[2] However, there remain few widely-applicable methods for the synthesis of structures of this type; no single set of conditions has been reported that shows truly broad utility and careful optimisation is typically required on a case-by-case basis. Thus, new methodology that can be applied to close a biaryl medium-sized ring is clearly timely and powerful, with potential applications in both target-oriented and diversity-oriented syntheses.[3]

Within our own group we have developed methodologies for the synthesis of sterically hindered functionalized biaryls, including highly strained medium-ring-containing biaryls, by the intramolecular oxidative coupling of diarylcuprates (Scheme 1).[7] These coupling protocols utilize the following general sequence: halogen–metal exchange (either iodine–magnesium or bromine–zinc); copper salt mediated transmetallation to form an intermediate organocuprate; and finally, organocuprate oxidation and biaryl bond formation.[8] Organomagnesium and organozinc halides are less reactive than the organolithium precursors that are typically used to generate organocuprates by transmetallation.[9] Thus, the oxidative organocuprate coupling protocols developed within our group allow an expansion in the substrate scope as moderately electrophilic groups can now be tolerated.

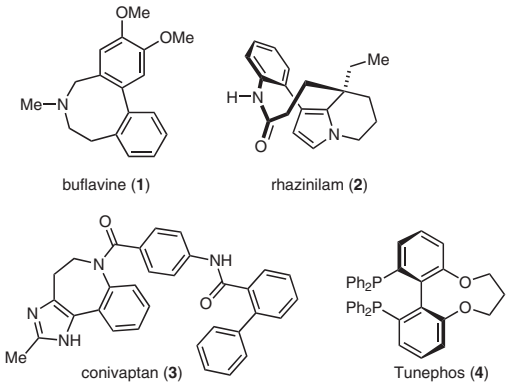

Figure 1 Some examples of compounds containing biaryl medium-ring systems: Buflavine (**1**) and rhazinilam (**2**) are biologically important natural products.[4] Conivaptan (**3**) is a pharmaceutical agent used for the treatment of low serum sodium levels (hyponatremia).[5] Tunephos (**4**) is a commercially available chiral catalyst.[6]

One group of naturally occurring compounds that contain medium (or large) biaryl ring systems are the ellagitannins; a vast family of secondary plant metabolites belonging to the hydrolysable tannin class of natural products.[11,12a,b] The ring systems in question are comprised of an axially chiral biaryl hexahydroxydiphenoyl (HHDP) unit (or oxidized derivative thereof)[12c] attached at two points to a polyhydroxylated core structure, typically D-glucose (Figure 2).[12d–g] This motif is the defining structural characteristic of the ellagitannin class of natural products.

This substance class has attracted considerable interest from the scientific community. In addition to industrial applications, many ellagitannins display biologically useful properties, including antibacterial, antiviral and antitumoral effects.[12b] However, the isolation of pure ellagitannins from natural sources has frequently been hindered by cumbersome and low-yielding procedures.[12b] Therefore, the development of efficient synthetic routes towards the ellagitannins is vital if their therapeutic potential is to be more fully explored and exploited. Indeed, this field has attracted significant interest from the synthetic

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Biographical Sketches

Xianbin Su obtained his PhD from Cambridge in 2007 for work on organocuprate oxidation methodology and strategies for the synthesis of elligitannin natural products under the supervision of Dr. David Spring. He has continued this work as a postdoctoral assistant in the same group.

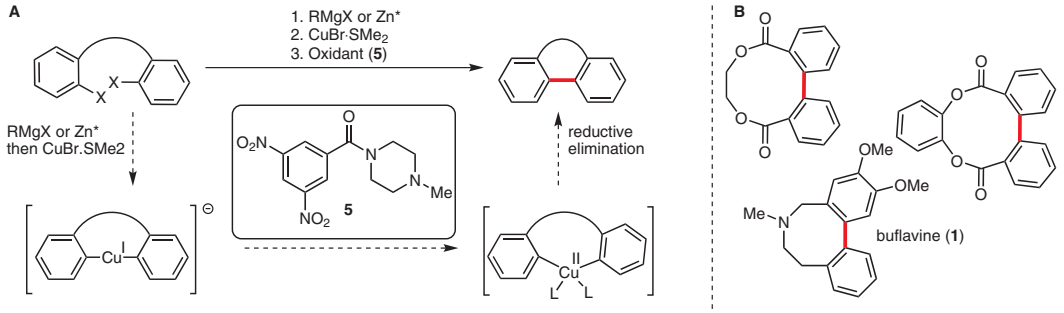
Gemma Thomas obtained her PhD from Cambridge in 2007 for work on the identification of novel antibacterial agents using diversity-oriented synthesis under the supervision of Dr. David Spring. She then spent another year in the Spring group as an EPSRC-funded postdoctoral assistant working on strategies for the synthesis of elligitannin natural products. Gemma is currently working as a medicinal chemist at Forma Therapeutics in Singapore.

Warren Galloway was born in Dundee, Scotland, in 1981 and attended the University of Cambridge for his undergraduate chemistry degree, graduating in 2004. He stayed at Cambridge for his PhD studies, which were funded by the EPSRC and Pfizer. Under the supervision of Dr. David Spring, his doctoral research focused upon the development of strategies for diversity-oriented synthesis. Warren received his PhD in 2008 and is currently a postdoctoral research assistant for Professor Robert Glen and Dr. David Spring at Cambridge, working on the design and synthesis of novel modulators of 5-HT receptors.

David Surry was born in London in 1979 and graduated from the University of Cambridge in 2002. He completed his PhD studies on the oxidation of organocuprates with Dr. David Spring at the same university. Since 2006 he has taken up a Research Fellowship from the Royal Commission for the Exhibition of 1851 in the laboratories of Prof. Steve Buchwald at the Massachusetts Institute of Technology.

Richard Spandl was born in 1982 and brought up near the village of Eye in Suffolk, England. He obtained his MChem in Biological Chemistry from the University of Leicester in 2004 before joining the Spring Group as a PhD student. Richard's PhD, which was funded by the BBSRC and Eli Lilly, focused on the development of strategies for diversity-oriented synthesis.

David Spring is currently an EPSRC Advanced Fellow at the University of Cambridge Chemistry Department. Previous to this appointment he spent two and a half years as a Wellcome Trust Postdoctoral Fellow and Fulbright Scholar at Harvard University with Professor Stuart L. Schreiber. He gained his DPhil for work on the proposed biosynthesis of the manzamine alkaloids at Oxford University under the supervision of Professor Sir Jack E. Baldwin FRS. David's research programme is focused on diversity-oriented synthesis, synthetic methodology and chemical genetics.



Scheme 1 (A) A general illustration of the synthesis of medium-rings through organocuprate oxidation. Organomagnesium or organozinc formation is followed by transmetallation to form the corresponding organocuprate. Oxidation then furnishes the ring-closed product. The oxidant **5** was developed in-house for use in these reactions.[7] Oxidant **5** and oxidant-derived by-products could be removed from the relatively non-polar organic reaction products by an aqueous wash during the work-up or by passage through silica gel. The exact mechanistic details of this process are yet to be fully delineated. The initial organocuprate species is thought to contain a copper(I) atom, which is bonded linearly.[2a,10] Subsequent oxidation then generates a high-energy square-planar or tetrahedral copper(II) intermediate which itself reductively eliminates to form the biaryl C–C bond and regenerate copper(0). The structures of the organometallic reagents and intermediates are simplified as they are most likely to be oligomeric in solution. Zn* = Rieke® zinc; (B) Some examples of biaryl-containing medium-ring systems formed using our copper-based methods.[6] The biaryl C–C bonds formed by oxidative organocuprate coupling are highlighted in red.

community in recent years.[11,12a] Within our own group, research in this area has focused upon the application of our organocuprate-based coupling methodologies to ellagitannin synthesis. These chemistries could allow rapid access to the biaryl-based HHDP cores of a variety of ellagitannins via direct biaryl coupling of functionalized aryl precursors.

Recently, we reported the use of oxidative organocuprate chemistries in the total synthesis of the ellagitannin natural product sanguiin H-5 (**6**; Figure 2).[7c] Herein, we provide a more detailed account of this synthesis. In addition, studies towards the synthesis of another ellagitannin, elaeocarpusin (**7**), using these coupling methodologies are discussed. Taken together, these works provide new insights and conceptual breakthroughs into the scope and utility of organocuprate-mediated biaryl coupling in the context of complex molecule synthesis.

2 Results and Discussion

2.1 Total Synthesis of Sanguiin H-5

From a synthetic perspective, the structure of sanguiin H-5 (**6**) presents two main challenges.[12b,e] Firstly, the glycosidic link at the anomeric centre needs to be established in a sterochemically controlled fashion such that only the β-anomer is formed. Secondly, the HHDP group attached to the 2,3-positions of the D-glucose core needs to be constructed; not only does this need to be achieved in an atropdiastereoselective manner [so as to generate the (*S*)-configuration about the biaryl bond], but the HHDP moiety is also part of a strained medium (10-membered) ring system, further augmenting the synthetic difficulty.

The only previous reported synthesis of sanguiin H-5 (**6**) was achieved by Feldman and Sambandam, and centred around the use of an elegant lead-mediated intramolecular oxidative coupling of pendant gallic acid groups attached to a central pyranose scaffold.[12e] Although this key cou-

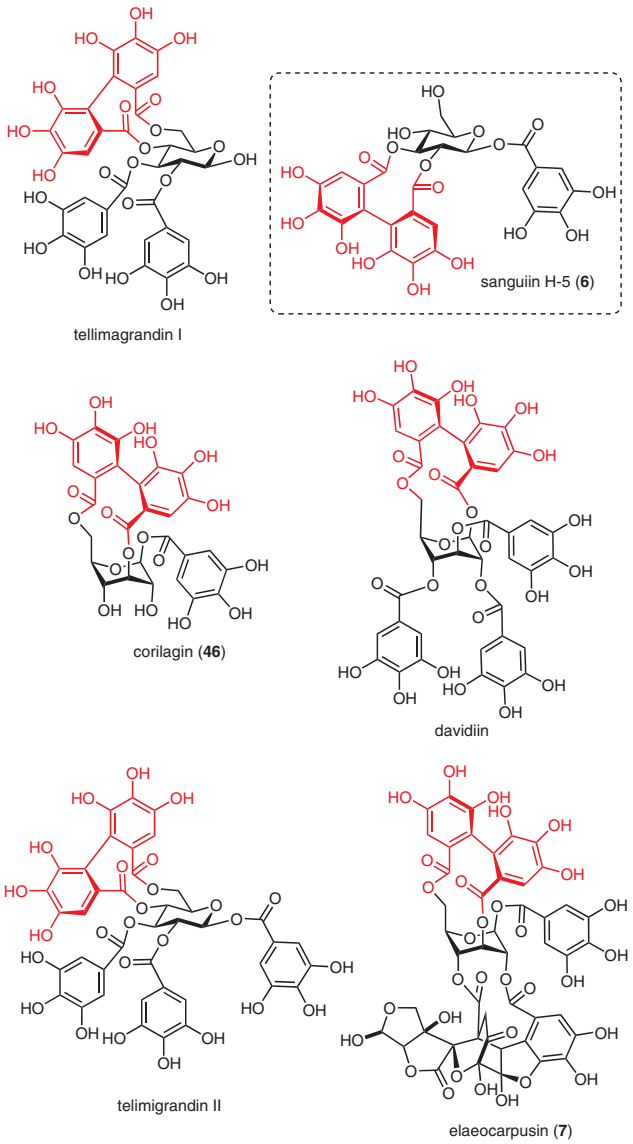
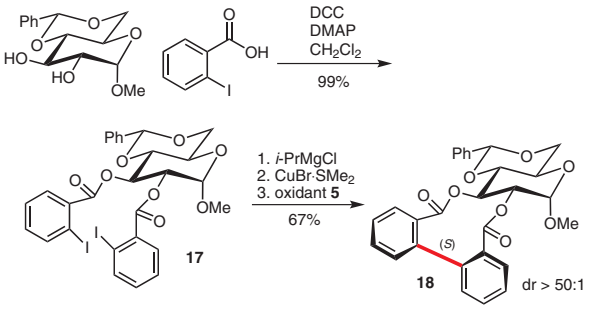


Figure 2 Some examples of ellagitannin natural products. The medium (or large) biaryl-based HHDP core of the molecules are highlighted in red.

pling step generated the desired (*S*)-atropoisomer of the HHDP group with complete diastereoselectivity, free hydroxylic groups in the gallic acid moieties were required in the cyclisation substrate to facilitate reaction; this in turn necessitated the introduction of additional hydroxyl protection/deprotection steps in the synthesis. Overall, the complete reaction pathway suffered from somewhat moderate yields, reflecting the complexity of the target molecule. We therefore sought to develop an alternative synthesis of sanguiin H-5 (**6**).

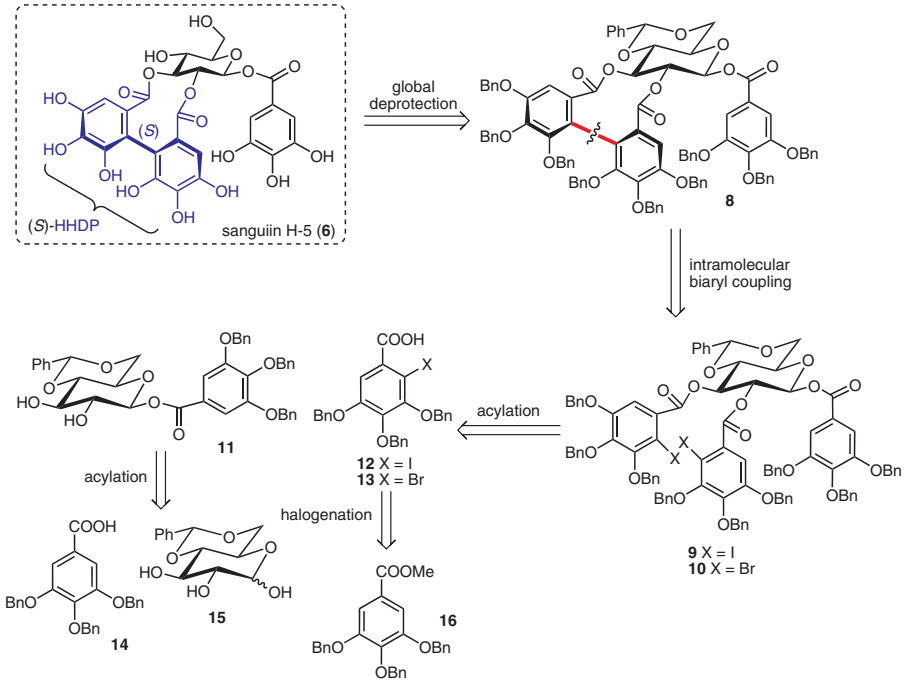
We envisaged that our functional-group tolerant organocuprate oxidation protocols could be exploited to forge the medium-ring biaryl HHDP core of the natural product by direct C–C bond coupling. Traditional oxidative organocuprate coupling strategies, which typically require the use of organolithium intermediates as the cuprate precursors, would not be suitable in this case due to the presence of ester groups in the target compound.[9] Our strategy assumed that benzyl-protected sanguiin H-5 precursor **8** could be accessed via an atropdiastereoselective intramolecular biaryl coupling from the appropriate diaryl halide **9** or **10** (Scheme 2). The decision to use benzyl protecting groups for the phenolic hydroxyl functionalities was based on the results of previous published studies on structurally related compounds; these have established that methyl esters cannot be cleaved without degradation of the gross ellagitannin framework.[11b] Thus, the use of benzyl-protected gallic acid derivatives is generally preferred since the benzyl esters can easily be removed hydrogenolytically in the final step of the synthesis without substrate decomposition.[12b] We planned to obtain precursors **9** and **10** by di-acylation of diol **11** with the gallic acid derivatives **12** or **13**. It was anticipated that **11** could be synthesized with a β-configuration at the anomeric centre (from acid **14** and sugar derivative **15**) and that the halogenation of **16** was possible. Therefore compounds **14**, **15**, and **16** would serve as readily available starting materials.

In order to investigate the validity of our approach towards the synthesis of sanguiin H-5 (**6**), a model system study was deemed appropriate. Towards this end, compound **17** was prepared from commercially available materials (Scheme 3). Pleasingly, application of our previously established organomagnesium-based cuprate coupling protocol allowed the synthesis of **18**, a structural mimic of the highly strained medium-ring core of sanguiin H-5 (**6**), in a good yield and with complete diastereoselectivity in favour of the desired (*S*)-atropisomer.[7a] Given this very promising result, we were encouraged to apply this methodology to the total synthesis of sanguiin H-5 (**6**) itself, which is a more sterically hindered and demanding target.



Scheme 3 Synthesis of **18**; a model for the strained medium-ring biaryl core of sanguiin H-5[7a]

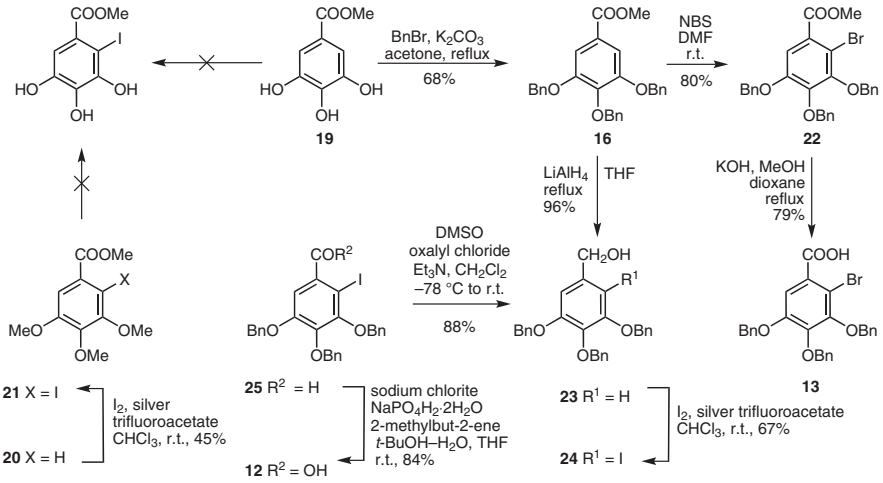
Initial studies focused upon the use of the magnesium-based protocols, which require the use of aryl iodides to facilitate transmetallation. Thus, the iodo-gallic acid de-



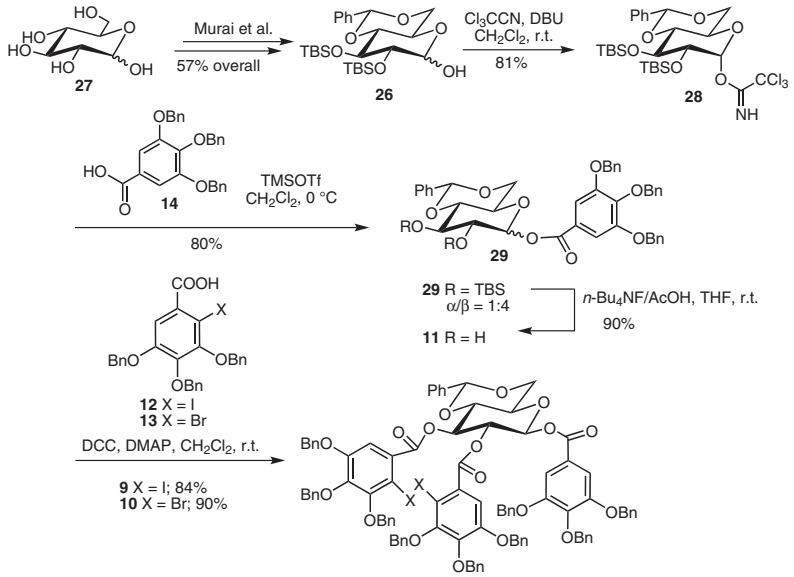
Scheme 2 The proposed retrosynthesis of sanguiin H-5 (**6**)

rivative **12** was required. Intriguingly, no method of making **12** has previously been disclosed and so the synthesis of this molecule constituted an important initial goal. This proved to be non-trivial and is worthy of discussion (Scheme 4). Electrophilic iodination of **19** with iodine and silver trifluoroacetate led only to the formation of high molecular weight compounds, presumably as a result of competitive oxidation of the highly electron-rich aromatic ring.[13] Similarly, electrophilic thallation, which was to be followed by treatment with potassium iodide,[14] gave polymeric products. Though iodination of methyl ether **20** could be achieved under standard literature conditions,[15] attempts to demethylate the product **21** produced assortments of compounds with evidence of de-iodination. Bromide **13** could be accessed in a straightforward manner from methyl gallate **19** [*via* initial protection to give **16**, bromination to furnish **22** and subsequent ester cleavage (Scheme 4)].[16] However, **16** (and the corresponding benzyl-protected acid) proved refractory to electrophilic iodination by a variety of standard methods.[17] In addition, bromide **22** was inert to both mild bromine–magnesium exchange[18] and bromine–zinc exchange[19] reactions (with the intention of quenching the organometallic intermediate with iodine). Ultimately, a stepwise approach from **16** was found to be productive. Reduction of **16** using lithium aluminium hydride generated alcohol **23**. Iodination of **23** could be achieved by treatment with iodine and silver trifluoroacetate to give **24** (Scheme 4). Direct oxidation of the alcohol **24** to the benzoic acid **12** with tetrabutylammonium permanganate (conditions which are reported to be suitable for such iodinated benzyl alcohols[20]) gave intractable product mixtures. Fortunately, Swern oxidation[21] of **24** to the aldehyde **25** could be carried out without difficulty. This aldehyde was then oxidised to the carboxylic acid **12** with sodium chlorite under the conditions of Pinnick (Scheme 4).[22]

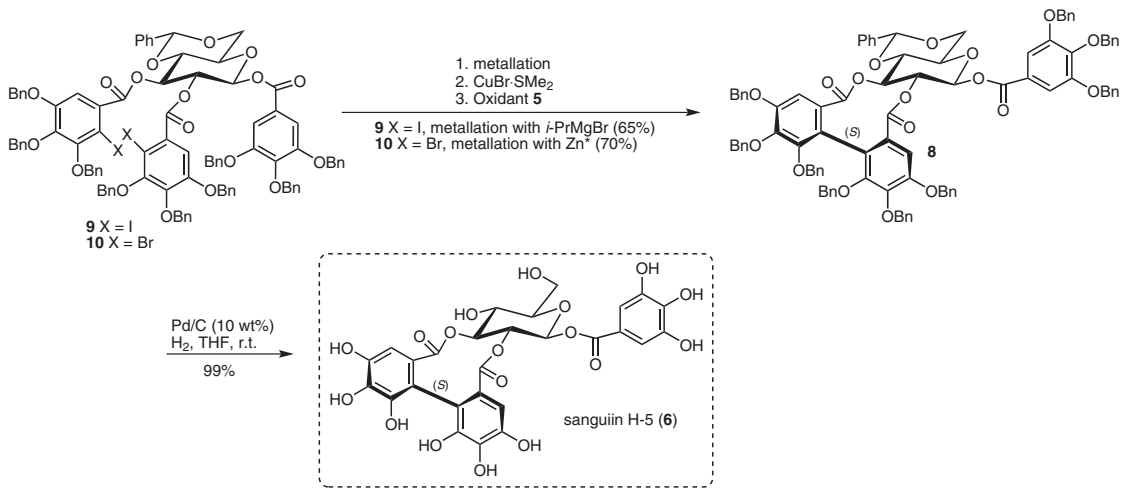
We next turned our attention towards the stereoselective synthesis of β-glucopyranose **11**. Using the procedure reported by Murai and co-workers,[23] alcohol **26** was generated from D-glucose (**27**) by a five-step sequence



Scheme 4 Synthesis of benzoic acids **12** and **13**



Scheme 5 Synthesis of the substrates for the intramolecular oxidative biaryl coupling. The conversion of **27** into **26** was carried out according to the procedure of Murai et al.[23]



Scheme 6 Completion of the total synthesis of sanguiin H-5 (**6**) using both magnesium- and zinc-based oxidative cuprate coupling protocols

(Scheme 5). Conversion of **26** into the (*R*)-trichloroacetimidate **28** was achieved through treatment with Cl_3CCN and DBU.[12g] Reaction of **28** with protected gallic acid **14** furnished the ester **29** as a mixture of α- and β-anomers (α:β = 1:4 by ^{1}H NMR analysis) in an 80% yield. Desilylation using TBAF buffered with acetic acid, followed by column chromatography, allowed the isolation of the desired β-galloylglucose product **11**. These disilylation conditions were found to be crucial for maintaining the integrity of the sensitive dehydrogallyl ester bonds. Other common desilylation protocols (unbuffered TBAF, TASF, HF, HF·pyridine) led to partial or complete anomeric ester hydrolysis. Finally, DCC/DMAP-mediated double esterification of β-galloylglucose **11** with benzoic acid **12** led to the formation of the cyclization precursor **9**.

With compound **9** in hand, we were ready to attempt the key organocuprate oxidative intramolecular biaryl bond-forming reaction (Scheme 6). Treatment of **9** with isopropylmagnesium chloride, followed by transmetallation with $CuBr{\cdot}SMe_2$ and subsequent intramolecular cuprate oxidation furnished benzyl-protected sanguiin H-5 (**8**) in a good isolated yield (65%). The reaction proceeded with complete diastereoselectivity for the desired (*S*)-atropisomer; pleasingly, no dimer side products were observed and high-dilution reaction conditions were not required.[24a] The diastereoselectivity observed in the copper-catalysed oxidative biaryl coupling process is thought to be controlled by the conformational preferences of the chiral galloylated sugar core, as has been discussed previously by Schmidt and Haslam.[25] Our efforts to determine whether this selectivity was as a result of kinetic or thermodynamic effects were unsuccessful; heating the biaryl **8** led to decomposition, and isomerization was not observed.

After demonstrating the effectiveness of the above methodology, the copper-catalysed oxidative organozinc biaryl coupling was examined. Organozinc compounds are less reactive nucleophiles than the corresponding organomagnesium halides. Consequently, electrophilic functional groups such as esters can be tolerated without the need for low reaction temperatures; organozinc formation can be carried out at room temperature, allowing the use of less reactive but generally more readily available aryl bromide substrates. Thus, we targeted **10** as the coupling precursor for the key C–C bond-forming step. Pleasingly, compound **10** could be readily accessed from bromobenzoic acid **13** and β-glucopyranose **11** in good yield (Scheme 5). Treatment of **10** with Rieke® zinc (Zn*) followed by transmetallation, and oxidation (as before) generated the cyclized product **8** in an optimised 70% isolated yield (Scheme 6). The reaction was highly sensitive to moisture and rigorously anhydrous reaction conditions were required in order to minimize the formation of the debrominated by-product.

The globally protected compound **8** could thus be accessed via either the magnesium- or zinc-based cuprate oxidative coupling protocols discussed above. Simple hydrogenolytic deprotection using Pd/C followed by filtration through Celite® furnished the desired natural product sanguiin H-5 (**6**; Scheme 6).[26] Pleasingly, the spectroscopic data obtained matched those reported previously for the natural product.[12e]

The use of oxidative organocuprate biaryl coupling thus facilitated the concise and efficient total syntheses of ellagitannin sanguiin H-5 (**6**). Gratifyingly, the key biaryl C–C bond forming reaction was found to proceed smoothly on a sterically congested and complex functionalized substrate, allowing direct access to the strained HHDP core of the natural product through concomitant and diastereoselective biaryl bond and medium-ring formation. Thus, these methodologies represent a significant advance that will complement existing biaryl-coupling strategies. Furthermore, this study raises the possibility that oxidative organocuprate biaryl coupling may constitute a robust procedure of broad synthetic utility that is suitable for the construction of related strained medium-ring biaryl motifs found in many other natural products. Towards this end we are currently investigating the application of this chemistry in the total synthesis of several other ellagitannins, including elaeocarpusin (**7**).

2.2 Studies towards the Synthesis of Elaeocarpusin

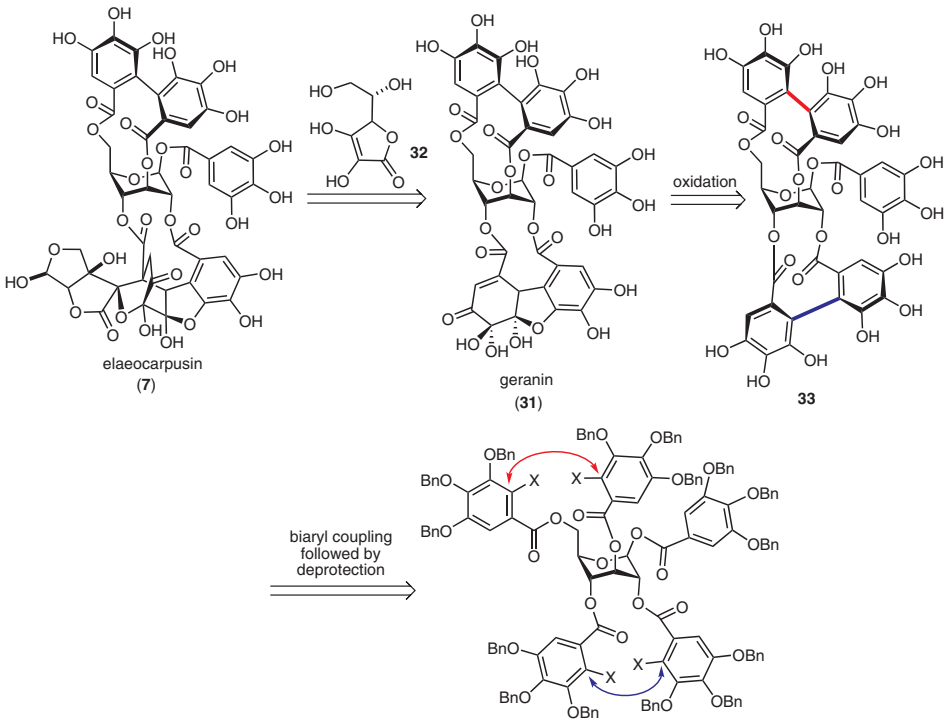
Elaeocarpusin (**7**; Scheme 7) was isolated from the leaves of *Elaeocarpus sylvestris* and has yet to yield to total synthesis.[27] Structurally, one can consider the molecule as being composed of two different ring systems attached to a central glucose core. The upper portion of the molecule contains the HHDP motif common to all ellagitannins which, in the case of elaeocarpusin, is comprised of an axially-chiral 13-membered biaryl ring system. The lower portion of the molecule consists of a complex fused ring system which, at first glance, presents a daunting synthetic challenge. However, consideration of the likely biogenesis of the molecule simplifies the situation greatly (Scheme 7). Elaeocarpusin (**7**) is known to come from geraniin (**31**). In fact, treatment of **31** with L-ascorbic acid (**32**) has been shown to produce elaeocarpusin (**7**).[27b] As a member of the ellagitannin family of natural products, geraniin (**31**) must be biosynthesised by the phenolic oxidative coupling of gallic acid units acylated on D-glucose.[11b] Therefore, we hypothesize that the biosynthetic precursor of geraniin (**31**) is the medium-ring biaryl **33**. Geraniin (**31**) can thus be derived from biaryl **33** through selective oxidation of the lower ring system.[28] The most direct synthesis of compound **33** is by the closure of the medium rings with concomitant and diastereoselective formation of the biaryl C–C bonds, which we envisaged could be affected via two oxidative organocuprate-mediated biaryl couplings.

2.2.1 Towards Elaeocarpusin: Organocuprate Oxidation

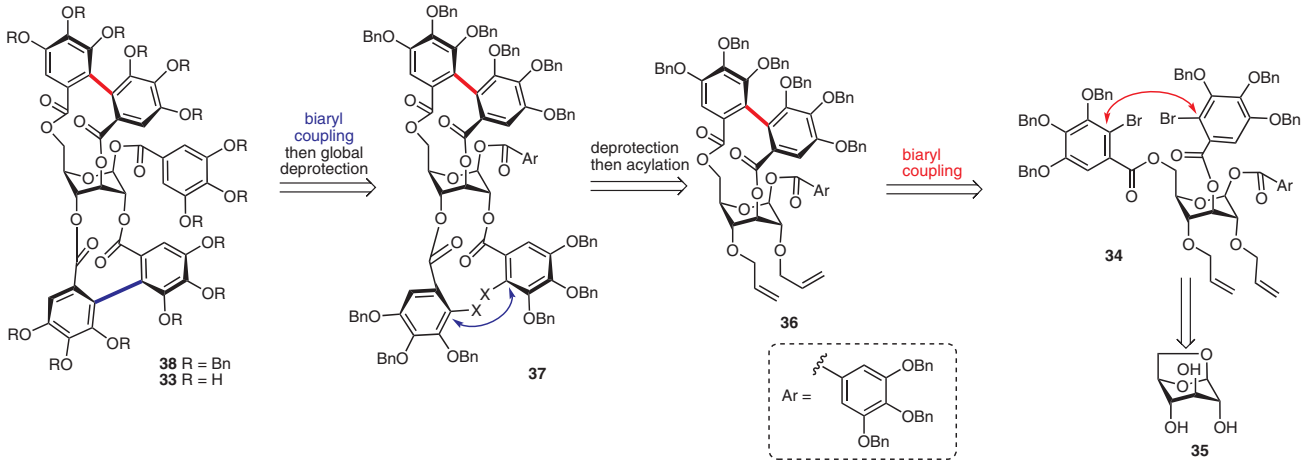
Our initial synthetic strategy towards compound **33** is outlined in Scheme 8. It was envisaged that compound **34** could be generated from 1,6-anhydro-β-D-glucopyranose (laevoglucosan, **35**) via ring-opening followed by a series of protecting group manipulations (*vide infra*). Copper-mediated cyclisation of **34** would afford **36**; subsequent deprotection and esterification of the resulting diol would furnish **37** and a second oxidative biaryl coupling would lead to compound **38**. Global deprotection would then generate **33**.

Before embarking upon the synthesis of **33**, a model system study was deemed appropriate. Towards this end, we chose the methyl-ether derivative **39** as our cyclization precursor (Scheme 9). Compound **39** was synthesised in a four-step sequence from laevoglucosan (**35**). Selective acetate protection of the hydroxyl group at the 3-position of the pyranose core was achieved via the intermediate boronate derivative **40** to give compound **41**.[29] Reaction with allyl iodide in the presence of silver triflate generated the bis-alkylated product **42**.[30] Ring-opening to give **43** was followed by acetate hydrolysis and selective methylation of the anomeric alcohol to furnish diol **44**; esterification with 3,4,5-tris(benzyloxy)-2-bromobenzoic acid (**13**) led to the formation of the desired cyclization substrate **39**.

Unfortunately, preliminary attempts to convert **39** into the medium-ring biaryl system **45** using our zinc-based oxidative cuprate methodology have proven unsuccessful. In all cases, only debrominated material could be isolated. Presumably, this material results from a zinc insertion into the carbon–bromine bonds of **39** followed by protonation



Scheme 7 Outline of the proposed strategy towards the synthesis of elaeocarpusin (**7**). Geraniin (**31**) contains an electrophilic α,β-unsaturated ketone. Conjugate addition of L-ascorbic acid (**32**) to **31** followed by hemiacetal formation has been shown to yield elaeocarpusin (**7**).[27b]



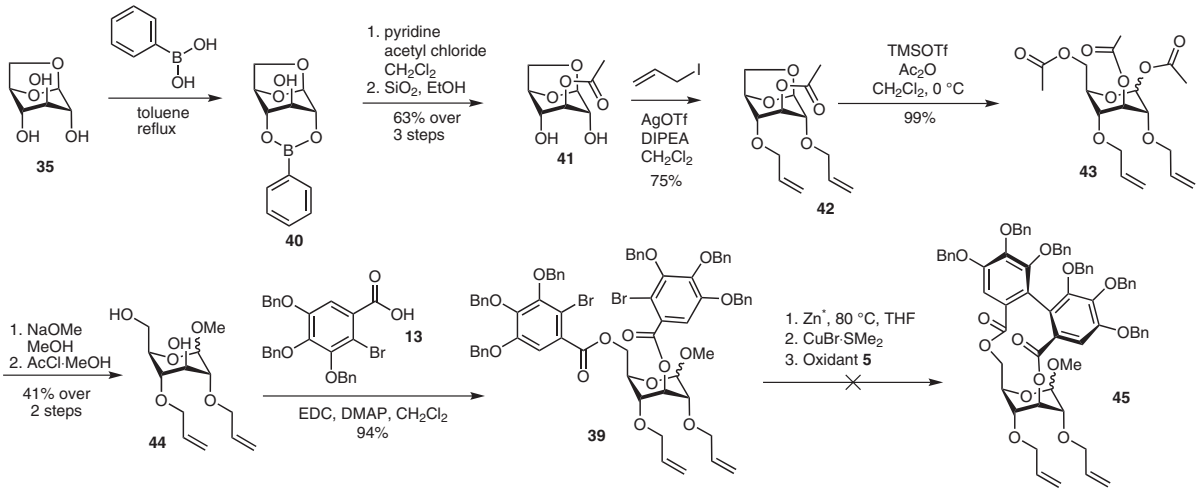
Scheme 8 Outline of the strategy towards medium-ring biaryl **33**

upon work-up. The inability to form the biaryl-coupled product could be due to problems associated with the transmetallation reaction of the aryl zinc species with copper to form the desired biaryl-linked organocuprate species or problems with the behaviour of such a species if formed; e.g. the organocuprate may be unstable under the reaction conditions. Further investigations into this step are ongoing. Recently, Yamada et al. reported a total synthesis of the ellagitannin corilagin (**46**), which is structurally identical to elaeocarpusin, except that the complex lower ring system is no longer present (Figure 2).[12h] The synthesis was based around an elegant copper-mediated Ullman coupling to generate the key HHDP group; however, the coupling was carried out on an acyclic substrate, generated by the ring-opening of the central pyranose unit. Reconstruction of the pyranose ring was carried out *after* HHDP formation. It may be the case that a similar strategy will prove fruitful for the synthesis of the upper-ring system of elaeocarpusin using oxidative organocuprate coupling. In addition, alternative non-cuprate-based synthetic strategies are under consideration. For example, we are currently exploring an esterification-based approach towards the synthesis of **33** (Scheme 10).

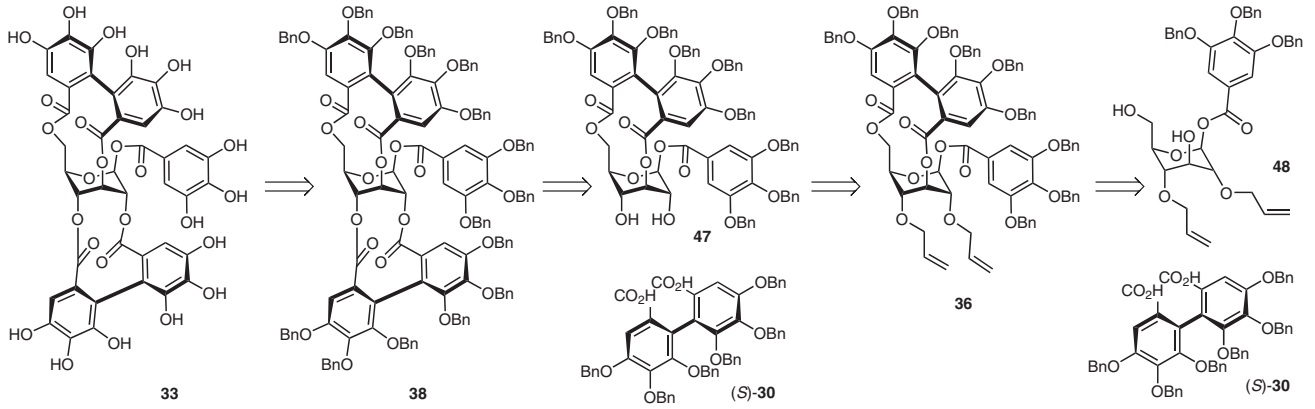
2.2.2 Towards Elaeocarpusin: A Double Esterification Approach

In this proposed route it is envisaged that **33** can be derived from globally benzyl-protected derivative **38** (Scheme 10). The lower 11-membered biaryl-based ring system of **38** could conceivably be derived from a double esterification reaction of axially chiral diol **47** and the diacid (*S*)-**30**. Diol **47** could potentially be obtained from **36** via protecting group manipulations. Diacid (*S*)-**30** can be obtained from ellagic acid via literature procedures.[24b] The 12-membered biaryl ring system present in **36** would again be generated by a double esterification reaction between diol **48** and diacid (*S*)-**30**.

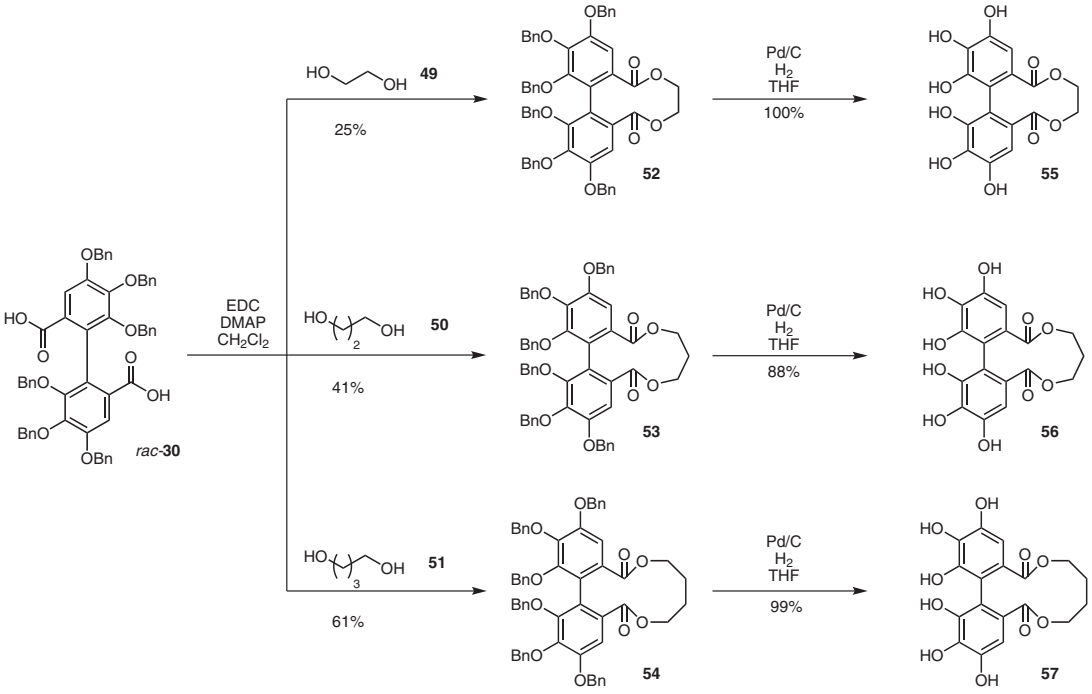
The feasibility of this synthetic approach towards the biaryl medium-ring systems of **33** was investigated using a series of model systems. Racemic benzyl-protected diacid *rac*-**30** was synthesised from ellagic acid.[24b] *rac*-**30** was then reacted with various length acyclic diols **49**–**51** in an attempt to generate 11-, 12- and 13-membered biaryl-containing medium-ring systems **52**–**54**, respectively, by a double esterification process (Scheme 11). Pleasingly, after global benzyl deprotection, the desired products **55**–**57**



Scheme 9 A model system study for the formation of the 13-membered biaryl ring system of elaeocarpusin



Scheme 10 Proposed retrosynthesis of key compound **33** using a double esterification approach



Scheme 11 Synthesis of model biaryl medium-ring systems

could be obtained, suggesting that this approach towards the upper (11-membered) and lower (13-membered) biaryl-based ring systems of key intermediate **33** is feasible. In addition, this method may provide an alternative strategy towards the HHDP cores of other ellagitannin natural products.

3 Conclusions

A concise and efficient total synthesis of the ellagitannin sanguiin H-5 has been achieved, which was based around an oxidative organocuprate biaryl coupling as the key synthetic step. This result provides a clear illustration of the usefulness of these copper-mediated coupling methodologies in complex molecule synthesis. However, preliminary attempts to construct the core of the ellagitannin elaeocarpusin using this chemistry were unsuccessful. Further work in this area is ongoing. Thus, although our copper-based methods have proven to be synthetically valuable in a variety of situations, there remains considerable scope for further exploration and development, particularly in the context of natural product synthesis.

Reactions were performed using oven-dried glassware under an atmosphere of nitrogen with anhydrous, freshly distilled solvents unless otherwise stated. CH_2Cl_2, EtOAc, MeOH, *n*-hexane, MeCN and toluene were distilled from CaH_2. Et_2O was distilled over a mixture of $LiAlH_4$ and CaH_2. THF was dried over Na wire and distilled from a mixture of $LiAlH_4$ and CaH_2. Petroleum ether (PE) was distilled before use and refers to the fraction boiling between 30–40 °C. All other solvents and reagents were used as obtained from commercial sources. Room temperature (r.t.) refers to ambient temperature. Temperatures of 0 °C were maintained using an ice–water bath and temperatures below 0 °C were maintained using an acetone–cardice bath. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Were possible,

reactions were monitored by thin layer chromatography (TLC) performed on commercially prepared glass plates precoated with Merck silica gel 60 F254 or aluminium oxide 60 F254. Visualisation was by the quenching of UV fluorescence (λ_{max} = 254 nm) or by staining with ceric ammonium molybdate, potassium permanganate or Dragendorff 's reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3M aq. AcOH). Retention factors (R_f) are quoted to 0.01. All flash chromatography was carried out using slurry-packed Merck 9325 Keiselgel 60 silica gel unless otherwise stated. Infrared spectra were recorded neat (unless otherwise stated) on a Perkin–Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima (λ_{max}) are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; st, strong; br, broad. Melting points were obtained using a Reichert hot plate microscope with a digital thermometer attachment and are uncorrected. ^1H NMR were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker Avance 500 BB ATM (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δ) are quoted in ppm, to the nearest 0.01 ppm, and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. Data are reported as follows: chemical shift, multiplicity (app. = apparent, br = broad; v br = very broad; s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; sext = sextet; m = multiplet), coupling constant(s), integration and assignment. Proton assignments were determined either on the basis of unambiguous chemical shift or coupling pattern, by patterns observed in 2D experiments (^1H–^1H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds. Diastereotopic protons are assigned as H and H′. ^{13}C NMR were recorded by broadband proton-spin-decoupling at ambient probe temperatures (unless otherwise stated) using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz), Bruker Avance 500 BB ATM (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δ) are quoted in ppm, to the nearest 0.1 ppm, and are referenced to the residual non-deuterated solvent peak. Where appropriate, coupling constants are reported in Hertz to the nearest 0.5 Hz and data are reported as for proton magnetic resonance spectra without integration. Assignments were supported by DEPT editing and determined either on the basis of unambiguous chemical shift or coupling pattern, by patterns observed in 2D experiments (HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds. Any numbering in selected spectral data does not follow the IUPAC naming system and is used for the assignment of the ^1H NMR and ^{13}C NMR spectra. For the sake of clarity the general numbering systems shown in Figure 3 are used for (a) the D-glucose based core of sanguiin H-5 and related coupling precursors and (b) the substituted glucose derivatives involved in studies towards the synthesis of elaeocarpusin.

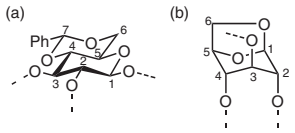


Figure 3

Liquid chromatography mass spectrometry (LC-MS) spectra were recorded on an HP/Agilent MSD LC-MS APCI 120-1000 full gradient ACq; T = 1 min, 1μL. High resolution mass spectroscopy measurements were made by the EPSRC mass spectrometry service (Swansea) or recorded in-house using a Waters LCT Premier Mass Spectrometer or a Micromass Quadrapole-Time of Flight (Q-ToF) spectrometer. Mass values are reported within the error limits of ±5 ppm mass units. The ionisation technique used is indicated by the following abbreviations: CI = chemical ionisation; EI = electron ionisation; ESI = electrospray ionisation; FAB (LSIMIS) = fast atom bombardment (liquid secondary ion mass spectrometry); MALDI = matrix-assisted laser desorption/ionisation. Microanalyses were performed by the Cambridge Microanalytical Laboratory in the Department of Chemistry and are quoted to the nearest 0.1% for all elements except hydrogen, which is reported to the nearest 0.05%. Reported atomic percentages are the averages of two determinations (where possible) and are within the error limits of ±0.4% compared to the theoretical value. Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. $[\alpha]_D^{25}$ values are reported in 10^{-1} deg cm^2 g^{-1} at 589 nm, concentration (*c*) is given in $g(100mL)^{-1}$.

Full spectral data for all novel compounds are given below, all previously characterized compounds gave spectra consistent with the literature.

Total Synthesis of Sanguiin H-5; Synthesis of Coupling Precursors

Methyl 3,4,5-Tris(benzyloxy)benzoate (16)

A mixture of methyl gallate **19** (1.00 g, 5.50 mmol), benzyl bromide (2.14 mL, 3.08 g, 18.0 mmol) and K_2CO_3 (2.49 g, 18.0 mmol) in acetone (50 mL) was heated at reflux for 9 h, allowed to cool to r.t., poured into H_2O and extracted with Et_2O (2 × 40 mL). The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was recrystallised (hexane) to give the title compound **16** (1.55 g, 68%) as a solid.

Mp 99–100 °C (hexane) (Lit.[31] 98 °C).

IR (neat): 1714, 1212, 1124, 754, 740, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.36 (m, 15 H, aryl CH), 7.31 (s, 2 H, aryl CH), 5.17 (s, 6 H, 3 × CH_2), 3.92 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2 (C), 152.2 (C), 142.0 (C), 137.1 (C), 136.3 (C), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 124.8 (C), 108.7 (CH), 74.7 (CH_2), 70.8 (CH_2), 51.8 (CH_3).

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $[C_{29}H_{27}O_5]^+$: 455.1858; found: 455.1860.

The data are consistent with those previously reported.[31]

Methyl 3,4,5-Tris(benzyloxy)-2-bromobenzoate (22)

A mixture of methyl 3,4,5-tris(benzyloxy)benzoate (**16**; 12.31 g, 27.10 mmol) and NBS (5.31 g, 29.8 mmol) in anhydrous DMF (100 mL) was stirred at r.t. for 24 h. The solution was then diluted with H_2O (200 mL) and extracted with Et_2O (500 mL). The organic layer was separated, washed with H_2O (4 × 200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallised (hexane) to give the title compound **22** (11.54 g, 80%) as needles.

Mp 91–93 °C (hexane).

IR (neat): 1717, 1332, 1094, 961, 738, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (dd, *J* = 7.5, 1.5 Hz, 2 H, aryl CH), 7.47–7.31 (m, 14 H, aryl CH), 5.13 (s, 4 H, 2 × CH_2), 5.08 (s, 2 H, CH_2), 3.96 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (C), 151.8 (C), 151.0 (C), 145.9 (C), 136.8 (C), 136.7 (C), 136.1 (C), 128.8 (CH), 128.70 (CH), 128.68 (CH), 128.5 (CH), 128.4 (CH), 128.33 (CH), 128.30 (CH), 127.8 (C), 127.7 (CH), 112.18 (C), 110.4 (CH), 75.8 (CH_2), 75.5 (CH_2), 71.4 (CH_2), 52.6 (CH_3).

Anal. Calcd for $C_{29}H_{25}BrO_5$: C, 65.3; H, 4.7. Found: C, 65.1; H, 4.5.

3,4,5-Tris(benzyloxy)-2-bromobenzoic Acid (13)

Adapted from the method of Feldman.[16] A mixture of methyl 3,4,5-tris(benzyloxy)-2-bromobenzoate (**22**; 10.034 g, 18.8 mmol), KOH (10.55 g, 188 mmol), MeOH (210 mL) and dioxane (210 mL) was heated at reflux for 30 min. The solvent was removed, the residue dissolved in H_2O, and the organic layer was extracted with EtOAc, then sequentially with aqueous HCl solution (approx. 3 M) and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The product was recrystallised (MeOH) to give the title compound **13** (7.67 g, 79%) as a white solid.

Mp 158–160 °C (MeOH).

IR (neat): 3028, 2944, 1697, 1359, 1324, 1098, 732, 683 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 3 H, aryl CH), 7.48–7.38 (m, 10 H, aryl CH), 7.35–7.32 (m, 3 H, aryl CH), 5.17 (s, 4 H, 2 × CH_2), 5.08 (s, 2 H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5 (C), 151.7 (C), 151.2 (C), 146.8 (C), 136.7 (C), 136.6 (C), 136.0 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 113.3 (CH), 111.7 (C), 75.8 (CH_2), 75.5 (CH_2), 71.4 (CH_2).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for [$C_{28}H_{24}BrO_5$]$^+$: 519.0807; found: 519.0803.

[3,4,5-Tris(benzyloxy)phenyl]methanol (23)

A solution of methyl 3,4,5-tris(benzyloxy)benzoate (**16**; 5.598 g, 12.32 mmol) in THF (60 mL) was added to a stirred suspension of $LiAlH_4$ (0.565 g, 14.9 mmol) in THF (35 mL) at r.t. over 1 h. The mixture was then heated at reflux for 2 h and subsequently cooled to 0 °C before addition of H_2O (0.35 mL), aq NaOH (15% w/w, 0.6 mL) and H_2O (1.7 mL). The mixture was filtered and the solid residue was suspended in Et_2O (200 mL) and heated at reflux for 30 min. The slurry was filtered, and the two filtrates were combined and then concentrated under reduced pressure. The residue was recrystallised (MeOH) to give the title compound **23** (5.06 g, 96%) as a solid.

Mp 109–110 °C (MeOH) (Lit.[33] 111 °C).

IR (neat): 3320 (br, O-H), 1438, 1373, 1120, 1069, 732, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.29 (m, 15 H, aryl CH), 6.70 (s, 2 H, aryl CH), 5.13 (s, 4 H, CHCOCH_2), 5.09 (s, 2 H, CHC[O]COCH_2), 4.48 (d, *J* = 6.0 Hz, 2 H, CH_2OH), 1.91 (t, *J* = 6.0 Hz, 1 H, CH_2O*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.0 (C), 137.9 (C), 137.8 (C), 137.2 (C), 136.8 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 106.5 (CH), 75.3 (CH_2), 71.2 (CH_2), 65.3 (CH_2).

The data are consistent with those previously reported.[32]

[3,4,5-Tris(benzyloxy)-2-iodophenyl]methanol (24)

Adapted from the method of Molander et al.[15] A solution of iodine (10.32 g, 40.70 mmol) in $CHCl_3$ (1.5 L) was added dropwise to a stirred suspension of [3,4,5-tris(benzyloxy)phenyl]methanol (**23**; 17.35 g, 40.70 mmol) and silver trifluoroacetate (8.99 g, 40.7 mmol) in $CHCl_3$ (170 mL). After the addition was complete, the mixture was washed with aq $NaHSO_3$ (10% w/w, 200 mL), the organic layer dried ($MgSO_4$), and the resulting suspension filtered through Celite®. Concentration under reduced pressure gave the title compound **24** (15.0 g, 67%) as a solid.

Mp 134 °C (MeOH).

IR (neat): 3308, 3033, 1373, 1096, 1077, 743, 649 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 8.0, 1.5 Hz, 2 H, aryl CH), 7.47–7.30 (m, 14 H, aryl CH), 5.15 (s, 2 H, CH_2OC), 5.09 (s, 2 H, CH_2OC), 5.07 (s, 2 H, CH_2OC), 4.68 (s, 2 H, CH_2OH), 2.11 (s, 1 H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.5 (C), 152.4 (C), 141.3 (C), 138.7 (C), 137.2 (C), 136.9 (C), 136.6 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 110.0 (CH), 85.6 (C), 75.8 (CH_2), 75.3 (CH_2), 71.2 (CH_2), 69.5 (CH_2).

Anal. Calcd for $C_{28}H_{25}IO_4$: C, 60.9; H, 4.6. Found: C, 60.8; H, 4.5.

3,4,5-Tris(benzyloxy)-2-iodobenzaldehyde (25)

Adapted from the method of Leopold et al.[21] A solution of DMSO (4.63 mL, 5.09 g, 65.0 mmol) in CH_2Cl_2 (13.5 mL) was added rapid dropwise to a stirred solution of oxalyl chloride (2.72 mL, 3.96 g, 131 mmol) in CH_2Cl_2 (67.5 mL) at –78 °C. After 5 min, a solution of [3,4,5-tris(benzyloxy)-2-iodophenyl]methanol (**24**; 15.0 g, 27.0 mmol) in CH_2Cl_2 (190 mL) was added slowly. The solution was maintained at –78 °C for a further 20 min before addition of Et_3N (18.9 mL). The reaction mixture was allowed to warm to r.t. and then H_2O (95 mL) was added and the organic layer separated. The aqueous layer was washed with CH_2Cl_2 (100 mL), the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **25** (13.1 g, 88%) as a fluffy solid.

Mp 115–116 °C (95% EtOH).

IR (neat): 1687, 1318, 1087, 956, 759, 746, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.11 (s, 1 H, CHO), 7.58–7.32 (m, 16 H, aryl CH), 5.20 (s, 4 H, CH_2), 5.12 (s, 2 H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.2 (CH), 153.5 (C), 152.5 (C), 147.5 (C), 136.6 (C), 136.4 (C), 135.9 (C), 130.9 (C), 128.9 (CH), 128.73 (CH), 128.71 (CH), 128.51 (CH), 128.47 (CH), 128.4 (CH), 127.8 (CH), 110.4 (CH), 92.2 (C), 75.8 (CH_2), 75.5 (CH_2), 71.2 (CH_2).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for [$C_{28}H_{24}IO_4$]$^+$: 551.0714; found: 551.0716.

3,4,5-Tris(benzyloxy)-2-iodobenzoic Acid (12)

Adapted from the method of Bal et al.[22] A solution of sodium chlorite (18.88 g, 208.8 mmol) and sodium dihydrogen phosphate dihydrate (24.79 g, 158.9 mmol) in H_2O (100 mL) was added over 10 min to a stirred solution of 3,4,5-tris(benzyloxy)-2-iodobenzaldehyde (**25**; 12.5 g, 22.7 mmol) and 2-methylbut-2-ene (100 mL, 66.0 g, 940 mmol) in *t*-BuOH (500 mL), H_2O (100 mL) and THF (400 mL) at r.t. After a further 15 min, the volatile components were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (400 mL), washed with H_2O (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallised (MeOH) to give the title compound **12** (10.84 g, 84%) as a solid.

Mp 177–179 °C (MeOH).

IR (neat): 3034, 2900, 1694, 1363, 1319, 1093, 735, 683 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.52 (m, 3 H, aryl CH), 7.44–7.34 (m, 9 H, aryl CH), 7.29–7.26 (m, 4 H, aryl CH), 5.13 (s, 2 H, CH_2), 5.10 (s, 2 H, CH_2), 5.04 (s, 2 H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9 (O), 153.5 (C), 152.7 (C), 145.5 (C), 136.7 (C), 136.5 (C), 135.9 (C), 128.9 (CH), 128.69 (CH), 128.66 (CH), 128.40 (CH), 128.37 (CH), 128.33 (CH), 128.32 (CH), 128.29 (CH), 127.7 (CH), 113.4 (CH), 86.0 (C), 75.7 (CH_2), 75.2 (CH_2), 71.2 (CH_2).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for [$C_{28}H_{24}IO_5$]$^+$: 567.0663; found: 567.0661.

Anal. Calcd for $C_{28}H_{23}IO_5$: C, 59.4; H, 4.1. Found: C, 59.3; H, 4.1.

Preparation of β-Glucopyranose 11

1-*O*-(3,4,5-Tribenzylgalloyl)-4,6-benzylidene-2,3-bis(*tert*-butyldimethylsilyl)-D-glucopyranoside (29)

To a mixture of **28** (2 g, 3.13 mmol), tribenzylgallic acid **14** (1.4 g, 3.18 mmol), activated 4 Å molecular sieve and anhydrous CH_2Cl_2 (50 mL) at 0 °C, was added Me_3SiOTf (0.25 g, 1.13 mmol). The mixture was stirred for 2 h at 0 °C, then the reaction was quenched with Et_3N (50 mL) and the resulting suspension filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; EtOAc–hexanes, 1:8) to give the title compound **29** (2.3 g, 80%) as an inseparable mixture of α- and β-anomers (α/β = 1:4 from ^{1}H NMR).

Mp 39–41 °C (EtOAc–hexane); $[\alpha]_D^{25}$ –26.7 (*c* 0.45, $CHCl_3$); R_f = 0.25 (SiO_2; EtOAc–hexanes, 1:8).

IR (neat): 1733, 1588, 1499, 1456, 1428, 1333, 1074, 771 cm^{-1}.

β-Anomer

Anomeric position designated C(1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.46 (m, 2 H, aryl CH), 7.44–7.30 (m, 18 H, aryl CH), 7.28–7.25 (m, 2 H, aryl CH), 5.96 [d, *J* = 5.8 Hz, 1 H, C(1)H], 5.44 [s, 1 H, C(7)H], 5.13 (s, 6 H, CH_2), 4.34 [dd, *J* = 10.0, 4.5 Hz, 1 H, C(6)H], 3.92–3.75 (m, 3 H, CH), 3.72–3.63 (m, 2 H, CH), 0.83 (s, 9 H, CH_3), 0.78 (s, 9 H, CH_3), 0.11 (s, 3 H, CH_3), 0.09 (s, 3 H, CH_3), 0.03 (s, 3 H, CH_3), 0.01 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.7 (C), 152.5 (C), 142.9 (C), 137.2 (C), 137.1 (C), 136.5 (C), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 126.4 (CH), 126.1 (CH), 124.4 (C), 109.7 (CH), 102.1 (CH), 95.4 (CH), 81.7 (CH), 75.8 (CH), 75.1 (CH_2), 75.0 (CH), 71.3 (CH_2), 69.1 (CH_2), 65.7 (CH), 26.0 (CH_3), 25.8 (CH_3), 18.2 (CH), 18.0 (CH), –3.5 (CH_3), –3.6 (CH_3), –3.8 (CH_3), –4.0 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $[C_{53}H_{66}NaO_{10}Si_2]^+$: 941.4116; found: 941.4088.

1-*O*-(3,4,5-Tribenzylgalloyl)-4,6-benzylidene-β-D-glucopyranoside (11)

Adapted from the method of Feldman et al.[12e] A solution of **29** (1.33 g, 1.45 mmol) in THF (10 mL) at r.t. was treated with AcOH (0.3 mL, 5 mmol) and TBAF (1 M in THF, 5 mL, 5 mmol). The resulting light-yellow reaction mixture was stirred at r.t. for 7 h and then diluted with EtOAc (50 mL) before being poured over H_3PO_4 (1 M, 30 mL). The organic phase was washed sequentially with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexane, 1:3) to give the title compound **11** (0.9 g, 90%) as a white solid.

Mp 165–167 °C (EtOAc–hexane); $[\alpha]_D^{25}$ –15.6 (*c* 0.95, $CHCl_3$); R_f = 0.30 (SiO_2; EtOAc–hexane, 1:3).

IR (neat): 3478, 1736, 1586, 1499, 1451, 1335, 1199, 1079, 731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2 H, aryl CH), 7.46–7.30 (m, 17 H, aryl CH), 7.28–7.20 (m, 3 H, aryl CH), 5.82 [d, *J* = 8.0 Hz, 1 H, C(1)H], 5.54 [s, 1 H, C(7)H], 5.13 (s, 2 H, CH_2), 5.12 (s, 2 H, CH_2), 5.11 (s, 2 H, CH_2), 4.37 [dd, *J* = 10.0, 4.5 Hz, 1 H, C(6)H], 3.90 [t, *J* = 9.0 Hz, 1 H, CH), 3.79 (t, *J* = 8.0 Hz, 1 H, CH), 3.76 [t, *J* = 10.0 Hz, 1 H, C(6)H], 3.64 [m, 1 H, C(5)H], 3.60 (t, *J* = 9.0 Hz, 1 H, C(4)H].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4 (C), 152.6 (C), 143.1 (C), 137.2 (C), 136.7 (C), 136.5 (C), 129.4 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.2 (CH), 123.6 (C), 109.7 (CH), 102.0 (CH), 94.6 (CH), 80.1 (CH), 75.1 (CH2), 73.6 (CH), 73.5 (CH), 71.3 (CH_2), 68.4 (CH_2), 67.0 (CH).

HRMS (ESI)$^+$: *m*/*z* [M + Na]$^+$ calcd for $[C_{41}H_{38}NaO_{10}]^+$: 713.2357; found: 713.2357.

Synthesis of the Coupling Precursors 9 and 10

1-*O*-(3,4,5-Tribenzylgalloyl)-4,6-benzylidene-2,3-bis(2,2′-diiodo-3,3′4,4′,5,5′-hexabenzylgalloyl)-β-D-glucopyranoside (9)

Adapted from the method of Feldman et al.[12e] A mixture of the benzoic acid **12** (228 mg, 0.4 mmol), the diol **11** (138 mg, 0.2 mmol), DCC (82.4 mg, 0.4 mmol), DMAP (6 mg, 0.05 mmol) and CH_2Cl_2 (15 mL) was stirred at r.t. for 18 h. The resulting slurry was filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexane, 1:3) to give the title compound **9** (300 mg, 84%) as an amorphous solid.

Mp 60–62 °C (EtOAc–hexane); $[\alpha]_D^{25}$ –33.6 (*c* 0.3, $CHCl_3$); R_f = 0.28 (SiO_2; EtOAc–hexane, 1:3).

IR (neat): 1736, 1586, 1497, 1454, 1329, 1182, 1094, 734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.20 (m, 54 H, aryl CH), 6.18 [d, *J* = 8.0 Hz, 1 H, C(1)H], 5.95 [t, *J* = 9.5 Hz, 1 H, C(3)H], 5.83 [dd, *J* = 9.5, 8.0 Hz, 1 H, C(2)H], 5.61 [s, 1 H, C(7)H], 5.20–4.90 (m, 18 H, 9 × CH_2), 4.53 [dd, *J* = 9.0, 3.5 Hz, 1 H, C(6)H], 4.03 [t, *J* = 9.5 Hz, 1 H, C(4)H], 3.94 [m, 2 H, C(5)H and C(6)H].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (C), 164.9 (C), 164.1 (C), 153.3 (C), 153.3 (C), 152.8 (C), 152.7 (C), 152.6 (C), 145.1 (C), 145.0 (C), 143.2 (C), 137.2 (C), 136.7 (C), 136.6 (C), 136.5 (C), 136.4 (C), 130.5 (C), 129.4 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.65 (CH), 128.61 (CH), 128.59 (CH), 128.56 (CH), 128.4 (CH), 128.39 (CH), 128.37 (CH), 128.36 (CH), 128.35 (CH), 128.29 (CH), 128.27 (CH), 128.25 (CH), 128.22 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.88 (CH), 127.81 (CH), 127.63 (CH), 127.61 (CH), 127.58 (CH), 126.1 (CH), 123.0 (C), 112.7 (CH), 112.6 (CH), 109.7 (CH), 101.5 (CH), 93.1 (CH), 85.2 (C), 84.9 (C), 78.3 (CH), 75.76 (CH_2), 75.72 (CH_2), 75.2 (CH_2), 75.1 (CH_2), 75.0 (CH_2), 72.6 (CH), 72.0 (CH), 71.2 (CH_2), 71.2 (CH_2), 71.1 (CH_2), 68.3 (CH_2), 67.3 (CH).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $[C_{97}H_{80}I_2NaO_{18}]^+$: 1809.3361; found: 1809.3326.

1-*O*-(3,4,5-Tribenzylgalloyl)-4,6-benzylidene-2,3-bis(2,2′-dibromo-3,3′4,4′,5,5′-hexabenzylgalloyl)-β-D-glucopyranoside (10)

Adapted from the method of Feldman et al.[12e] A mixture of benzoic acid **13** (208 mg, 0.4 mmol), diol **11** (138 mg, 0.2 mmol), DCC (82.4 mg, 0.4 mmol), DMAP (6 mg, 0.05 mmol) and CH_2Cl_2 (15 mL) was stirred at r.t. for 18 h. The resulting slurry was filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexanes, 1:3) to give the title compound **10** (305 mg, 90%) as an amorphous solid.

Mp 62–64 °C (EtOAc–hexanes); $[\alpha]_D^{25}$ –38.5 (*c* 0.2, $CHCl_3$); R_f = 0.28 (SiO_2; EtOAc–hexanes, 1:3).

IR (neat): 1732, 1586, 1498, 1454, 1331, 1193, 1095, 1016, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.22 (m, 54 H, aryl CH), 6.17 [d, *J* = 8.0 Hz, 1 H, C(1)H], 5.95 [t, *J* = 9.5 Hz, 1 H, C(3)H], 5.83 [dd, *J* = 9.5, 8.0 Hz, 1 H, C(2)H], 5.62 [s, 1 H, C(7)H], 5.20–4.90 (m, 18 H, CH_2), 4.54 [dd, *J* = 9.0, 3.5 Hz, 1 H, C(6)H], 4.04 [t, *J* = 9.5 Hz, 1 H, C(4)H], 3.93 [m, 2 H, C(5)H and C(6)H].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1 (C), 164.4 (C), 164.1 (C), 152.6 (C), 151.8 (C), 151.8 (C), 151.07 (C), 151.01 (C), 146.2 (C), 146.1 (C), 143.2 (C), 137.3 (C), 136.7 (C), 136.6 (C), 136.55 (C),

136.52 (C), 136.50 (C), 135.89 (C), 135.84 (C), 129.2 (CH), 128.66 (CH), 128.64 (CH), 128.61 (CH), 128.58 (CH), 128.56 (CH), 128.5 (CH), 128.44 (CH), 128.40 (CH), 128.37 (CH), 128.30 (CH), 128.27 (CH), 128.21 (CH), 128.0 (CH), 127.9 (CH), 127.86 (CH), 127.80 (CH), 127.6 (CH), 127.0 (C), 126.16 (C), 126.14 (CH), 123.0 (C), 112.1 (CH), 110.5 (C), 110.3 (C), 109.6 (CH), 101.6 (CH), 93.1 (CH), 78.3 (CH), 75.8 (CH_2), 75.7 (CH_2), 75.5 (CH_2), 75.4 (CH_2), 75.1 (CH_2), 72.5 (CH), 71.9 (CH), 71.2 (CH), 71.1 (CH_2), 71.1 (CH_2), 68.39 (CH_2), 67.38 (CH).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $[C_{97}H_{80}Br_2NaO_{18}]^+$: 1713.3494; found: 1713.3606.

Intramolecular Coupling Reactions

Benzyl Ether-Protected Sanguiin H-5 (8)

*(a) By Copper-Mediated Oxidation of Organomagnesium Iodides from **9***: A flame-dried round-bottom flask containing the iodide **9** (35.7 mg, 0.02 mmol) and anhydrous THF (2 mL) at –20 °C was charged with *iso*-propylmagnesium chloride (2 M in anhydrous THF, 0.02 mL, 0.04 mmol) and the reaction mixture was stirred for 15 min. The reaction mixture was then transferred via cannula into a second round-bottom flask containing the copper(I) bromide-dimethyl sulfide complex (4.1 mg, 0.02 mmol), which was subsequently charged with the oxidant **5** (12 mg, 0.04 mmol) dissolved in anhydrous THF (2 mL) and stirred at r.t. for 1 h. The reaction mixture was filtered through a plug of silica, washed with EtOAc–hexane (1:1), and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexanes, 1:3) to give the title compound **8** (19.9 g, 65%) as an amorphous solid.

*(b) By Copper-Mediated Oxidation of Organozinc Bromides from **10***: A flame-dried round-bottom flask containing the bromide **10** (68.7 mg, 0.04 mmol) and anhydrous THF (2 mL) under argon was charged with Rieke® zinc (1 mL, 5 g/100 mL in THF) and the reaction mixture was heated at 80 °C for 3 h. The suspension was allowed to settle and the resultant supernatant was transferred via cannula onto copper(I) bromide dimethyl sulfide complex (8.2 mg, 0.04 mmol) contained in a second round-bottom flask. The oxidant **5** (24 mg, 0.08 mmol) dissolved in anhydrous THF (2 mL) was then added and the solution was stirred at r.t. for 1 h. The reaction mixture was filtered through a plug of silica, washed with EtOAc–hexanes (1:1), and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexanes, 1:3) to give the title compound **8** (42.9 mg, 70%) as an amorphous solid.

Mp 102–104 °C (EtOAc–hexanes); $[\alpha]_D^{25}$ –66.5 (*c* 0.8, $CHCl_3$); R_f = 0.35 (SiO_2; EtOAc–hexanes, 1:3).

IR (neat): 1754, 1585, 1497, 1451, 1330, 1075 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.18 (m, 42 H, aryl CH), 7.12–7.06 (m, 6 H, aryl CH), 7.02 (s, 1 H, aryl CH), 6.98–6.93 (m, 4 H, aryl CH), 6.78 (s, 1 H, aryl CH), 6.18 [d, *J* = 8.5 Hz, 1 H, C(1)H], 5.62 [s, 1 H, C(7)H], 5.55 [t, *J* = 9.5 Hz, 1 H, C(3)H], 5.39 [t, *J* = 8.5 Hz, 1 H, C(2)H], 5.22–4.94 (m, 14 H, CH_2), 4.82 (t, *J* = 11.5 Hz, 2 H, CH_2), 4.66 (dd, *J* = 11.0, 9.0 Hz, 2 H, CH_2), 4.45 [dd, *J* = 10.0, 4.5 Hz, 1 H, C(6)H], 3.98 [t, *J* = 9.5 Hz, 1 H, C(4)H], 3.88 [t, *J* = 10.0 Hz, 1 H, C(6)H], 3.80 [m, 1 H, C(5)H].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9 (C), 167.7 (C), 164.0 (C), 152.8 (C), 152.7 (C), 152.5 (C), 152.4 (C), 144.54 (C), 144.50 (C), 143.2 (C), 137.54 (C), 137.51 (C), 137.4 (C), 137.2 (C), 136.5 (C), 136.3 (C), 136.2 (C), 129.4 (C), 128.8 (CH), 128.55 (CH), 128.54 (CH), 128.52 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.19 (CH), 128.14 (CH), 128.02 (CH), 128.00 (CH), 127.9 (CH), 127.89 (CH), 127.85 (CH), 127.6 (CH), 127.5 (CH), 126.4 (CH), 123.20 (C), 122.21 (C), 109.3 (CH), 107.2 (CH), 106.9 (CH), 101.8 (CH), 91.9 (CH), 77.18 (CH), 77.12 (CH), 75.7 (CH), 75.54 (CH_2), 75.50 (CH_2), 75.3 (CH_2), 75.25 (CH), 75.20 (CH_2), 75.0 (CH_2), 71.34 (CH_2), 71.31 (CH_2), 71.0 (CH_2), 68.3 (CH_2), 67.7 (CH).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $[C_{97}H_{80}NaO_{18}]^+$: 1555.5277; found: 1555.5237.

Sanguiin H-5 (6)

A round-bottom flask containing a solution of **8** (31 mg, 0.02 mmol) and anhydrous THF (2 mL) was charged with 10% Pd/C (25 mg, 10 wt% of starting material). The system was purged several times with hydrogen and stirred under a balloon of hydrogen for 15 h. The reaction mixture was then filtered through Celite® and the filtrate was concentrated under reduced pressure to give the title compound sanguiin H-5 (12 mg, 99%) as a brown amorphous powder. The crude compound was partially purified using reverse-phase column chromatography (stationary phase: KP-C_{18}-HS, 60 Å, solution phase: MeOH–H_2O, 1:1).

$[\alpha]_D^{25}$ –12.5 (*c* 0.1, MeOH).

IR (neat): 3280, 1718, 1611, 1445, 1311, 1179, 1040 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.08 (s, 2 H, aryl CH), 6.67 (s, 1 H, aryl CH), 6.39 (s, 1 H, aryl CH), 6.07 [d, *J* = 9.0 Hz, 1 H, C(1)H], 5.18 [t, *J* = 9.5 Hz, 1 H, C(3)H], 5.06 [t, *J* = 9.0 Hz, 1 H, C(2)H], 3.96–3.56 [m, 4 H, C(4)H, C(5)H and 2 × C(6)H].

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $[C_{27}H_{22}O_{18}Na]^+$: 657.0806; found: 657.0821.

The data are consistent with those previously reported.[12e,34]

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1,2,3,12,13,14-Hexakis(benzyloxy)-7,8-dihydrodibenzo[*f*,*h*][1,4]dioxecine-5,10-dione (52)

To a solution of the diacid *rac*-**30** (200 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) under nitrogen at r.t., was added Et_3N (0.045 mL, 0.32 mmol) followed by thionyl chloride (0.22 mL, 3.2 mmol). The reaction was stirred at 50 °C for 2 h then the solvent was removed in vacuo. The crude brown solid (210 mg, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL). Meanwhile ethylene glycol (0.013 mL, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) and both solutions were added dropwise to a solution of TBAI (1 mg, 1 mol%) and anhydrous K_2CO_3 (31 mg, 0.23 mmol) in CH_2Cl_2 (25 mL) under nitrogen. The reaction was stirred for 12 d, then the solvent was removed in vacuo and the product was purified by column chromatography (SiO_2; hexane–EtOAc, 7:3) to yield the title compound **52** as a colourless oil (52 mg, 25%).

R_f = 0.18 (SiO_2; hexane–EtOAc, 7:3).

IR (neat): 3031, 2928, 1748 (ester), 1592, 1497, 1454, 1410, 1366, 1188, 1094 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.36 (m, 14 H, aryl H), 7.31–7.26 (m, 6 H, aryl H), 7.18–7.12 (m, 6 H, aryl H), 7.03–6.99 (m, 4 H, aryl H), 6.98 (s, 2 H, aryl H), 5.24 (d, *J* = 11.5 Hz, 2 H, OC*H*$_2$Ph), 5.15 (d, *J* = 11.5 Hz, 2 H, OC*H*$_2$Ph), 5.04–7.96 (m, 6 H, 2 × OC*H*$_2$Ph and OC*H*$_2$CH$_2$O), 4.88 (d, *J* = 11.0 Hz, 2 H, OC*H*$_2$Ph), 4.70 (d, *J* = 11.0 Hz, 2 H, OC*H*$_2$Ph), 4.15 (d, *J* = 9.0 Hz, 2 H, OCH$_2$C*H*$_2$O).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5 (C), 152.6 (C), 152.5 (C), 144.4 (C), 137.7 (C), 137.6 (C), 136.5 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.15 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 122.5 (C), 107.4 (CH), 75.5 (CH_2), 75.3 (CH_2), 71.1 (CH_2), 64.5 (CH_2).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{58}H_{49}O_{10}$: 905.3326; found: 905.3325.

1,2,3,13,14,15-Hexakis(benzyloxy)-8,9-dihydro-5*H*-dibenzo[*g*,*i*][1,5]dioxacycloundecine-5,11(7*H*)-dione (53)

To a solution of the diacid *rac*-**30** (200 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) under nitrogen at r.t., was added Et_3N (0.045 mL, 0.32 mmol) followed by thionyl chloride (0.22 mL, 3.2 mmol). The reaction was stirred at 50 °C for 2 h and then the solvent was removed in vacuo. The crude brown solid (210 mg, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL). Meanwhile propylene glycol (0.016 mL, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL). Both solutions were added dropwise to a solution of TBAI (1 mg, 1 mol%) and anhydrous K_2CO_3 (31 mg, 0.23 mmol) in CH_2Cl_2 (25 mL) under nitrogen. The reaction was stirred for 12 d, then the solvent was removed in vacuo and the product was purified by column chromatography (SiO_2; hexane–EtOAc, 7:3) to yield the title compound **53** as a colourless oil (54 mg, 41%).

R_f = 0.23 (SiO_2; hexane–EtOAc, 7:3).

IR (neat): 3031, 2927, 1737 (ester), 1952, 1497, 1454, 1367, 1327, 1192, 1095 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.36 (m, 14 H, aryl H), 7.30–7.25 (m, 6 H, aryl H), 7.17–7.12 (m, 6 H, aryl H), 7.04–6.99 (m, 6 H, aryl H), 5.23 (d, *J* = 11.5 Hz, 2 H, OC*H*$_2$Ph), 5.15 (d, *J* = 11.5 Hz, 2 H, OC*H*$_2$Ph), 5.05 (d, *J* = 4.5 Hz, 2 H, OC*H*$_2$Ph), 5.02 (d, *J* = 4.5 Hz, 2 H, OC*H*$_2$Ph), 4.92 (d, *J* = 11.0 Hz, 2 H, OC*H*$_2$Ph), 4.86–4.78 (m, 4 H, OC*H*$_2$Ph, OC*H*H′CH$_2$C*H*H′O), 4.10 (dt, *J* = 11.5, 5.0 Hz, 2 H, OCH*H*′CH$_2$CH*H*′O), 2.22–2.17 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$O).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2 (C), 152.4 (C), 152.4 (C), 144.4 (C), 137.9 (C), 137.6 (C), 136.6 (C), 129.0 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.96 (CH), 127.94 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 123.6 (C), 108.1 (CH), 75.5 (CH$_2$), 75.0 (CH$_2$), 71.2 (CH$_2$), 60.4 (CH$_2$), 25.6 (CH$_2$).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{59}H_{51}O_{10}$: 919.3482; found: 919.3481.

1,2,3,14,15,16-Hexakis(benzyloxy)-7,8,9,10-tetrahydrodibenzo[*h*,*j*][1,6]dioxacyclododecine-5,12-dione (54)

To a solution of the diacid *rac*-**30** (200 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) under nitrogen at r.t., was added Et_3N (0.045 mL, 0.32 mmol) followed by thionyl chloride (0.22 ml, 3.2 mmol). The reaction was stirred at 50 °C for 2 h and then the solvent was removed in vacuo. The crude brown solid (210 mg, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL). Meanwhile, butane-1,4-diol glycol (0.02 mL, 0.23 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) and both solutions were added dropwise to a solution of TBAI (1 mg, 1 mol%) and anhydrous K_2CO_3 (31 mg, 0.23 mmol) in CH_2Cl_2 (25 mL) under nitrogen. The reaction was stirred for 12 d, then the solvent was removed in vacuo and the product was purified by column chromatography (SiO_2; hexane–EtOAc, 7:3) to yield the title compound **54** as a colourless oil (55 mg, 61%).

R_f = 0.27 (SiO_2; hexane–EtOAc, 7:3).

IR (neat): 3031, 1732 (ester), 1592, 1497, 1454, 1366, 1329, 1194, 1095 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 4 H, aryl H), 7.46–7.36 (m, 10 H, aryl H), 7.30–7.24 (m, 6 H, aryl H), 7.17–7.10 (m, 8 H, aryl H), 7.02–6.98 (m, 4 H, aryl H), 5.24 (d, *J* = 11.5 Hz, 2 H, OC*H*$_2$Ph), 5.15 (d, *J* = 11.5 Hz, 2 H, OC*H*$_2$Ph), 5.06 (d, *J* = 3.0 Hz, 2 H, OC*H*$_2$Ph), 5.06 (d, *J* = 3.0 Hz, 2 H, OC*H*$_2$Ph), 4.94 (d, *J* = 11.0 Hz, 2 H, OC*H*$_2$Ph), 4.82 (d, *J* = 11.0 Hz, 2 H, OC*H*$_2$Ph), 4.51 (br t, *J* = 9.5 Hz, 2 H, OC*H*H′CH$_2$CH$_2$C*H*H′O), 4.14 (br dd, *J* = 11.0, 5.0 Hz, 2 H, OCH*H*′CH$_2$CH$_2$CH*H*′O), 2.08–2.01 (m, 2 H, OCH$_2$CH$_2$C*H*$_2$CH$_2$O), 1.91–1.82 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$CH$_2$O).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8 (C), 152.3 (C), 152.1 (C), 144.6 (C), 138.0 (C), 137.6 (C), 136.7 (C), 128.8 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 124.2 (C), 109.0 (CH), 75.5 (CH$_2$), 74.8 (CH$_2$), 71.2 (CH$_2$), 65.4 (CH$_2$), 25.9 (CH$_2$).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ cacld for $C_{60}H_{52}O_{10}Na$: 955.3458; found: 955.3459.

1,2,3,12,13,14-Hexahydroxy-7,8-dihydrodibenzo[*f*,*h*][1,4]dioxecine-5,10-dione (55)

To a solution of **52** (50 mg, 55 μmol) in THF (6 mL) at r.t., was added Pd/C (107 mg) and the reaction was placed under a hydrogen atmosphere (balloon). The reaction was stirred overnight and then filtered through Celite®, washing with H_2O–MeCN (1:1) until the washings ran clear. The solvent was removed in vacuo to yield the title compound **55** as a pink solid (20 mg, 100%).

Mp 300 °C (dec).

IR (neat): 3132, 1696 (ester), 1614, 1514, 1437, 1315, 1227, 1180, 1126, 1033 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.18 (br s, 6 H, OH), 6.40 (s, 2 H, aryl H), 4.53 (d, *J* = 9.0 Hz, 2 H, OC*H*$_2$CH$_2$O), 4.23 (d, *J* = 9.0 Hz, 2 H, OCH$_2$C*H*$_2$O).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 206.6 (C), 169.2 (C), 162.3 (C), 145.4 (C), 144.0 (C), 135.3 (C), 123.1 (C), 115.0 (C), 105.5 (CH), 64.5 (CH$_2$), 60.6 (CH$_2$).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}O_{10}$: 365.0509; found: 365.0522.

1,2,3,13,14,15-Hexahydroxy-8,9-dihydro-5*H*-dibenzo[*g*,*i*][1,5]dioxacycloundecine-5,11(7*H*)-dione (56)

To a solution of **53** (50 mg, 54 μmol) in THF (6 mL), was added Pd/C (107 mg) and the reaction was placed under a hydrogen atmosphere (balloon). The reaction was stirred overnight and then filtered through Celite® washing with H_2O–MeCN (1:1) until the washings ran clear. The solvent was removed in vacuo to yield the title compound **56** as a purple solid (18 mg, 88%).

Mp 300 °C (dec).

IR (neat): 3119, 1686, 1614, 1514, 1398, 1340, 1247, 1188, 1041 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.23 (br s, 1 H, OH), 8.70 (br s, 1 H, OH), 8.02 (br s, 1 H, OH), 7.01 (br s, 3 H, OH), 6.37 (s, 2 H, aryl H), 4.57–4.40 (m, 2 H, OC*H*$_2$CH$_2$CH$_2$O), 3.92–3.88 (m, 2 H, OCH$_2$CH$_2$C*H*$_2$O), 1.97–1.92 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$O).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.3 (C), 144.8 (C), 144.2 (C), 134.8 (C), 124.5 (C), 115.2 (C), 105.6 (CH), 60.1 (CH$_2$), 25.3 (CH$_2$).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}O_{10}$: 379.0665; found: 379.0658.

1,2,3,14,15,16-Hexahydroxy-7,8,9,10-tetrahydrodibenzo[*h*,*j*][1,6]dioxacyclododecine-5,12-dione (57)

To a solution of **54** (50 mg, 54 μmol) in THF (6 mL), was added Pd/C (107 mg) and the reaction was placed under a hydrogen atmosphere (balloon). The reaction was stirred overnight and then filtered through Celite®, washing with H_2O–MeCN (1:1) until the washings ran clear. The solvent was removed in vacuo to yield the title compound **57** as a purple solid (21 mg, 99%).

Mp 300 °C (dec).

IR (neat): 3213, 1674, 1674, 1606, 1463, 1430, 1393, 1340, 1248, 1199, 1084, 1048 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 6.41 (s, 2 H, aryl H), 4.22–4.19 (m, 2 H, OC*H*$_2$CH$_2$CH$_2$CH$_2$O), 3.88–3.86 (m, 2 H, OC*H*$_2$CH$_2$CH$_2$CH$_2$O), 3.50–3.00 (br s, 6 H, OH), 1.89–1.83 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$CH$_2$O), 1.65–1.63 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$CH$_2$O).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.9 (C), 145.0 (C), 143.7 (C), 134.9 (C), 124.6 (C), 115.6 (C), 105.2 (CH), 66.1 (CH_2), 31.5 (CH_2), 25.5 (CH_2).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}O_{10}$: 393.0822; found: 393.0820.

2,4-Dihydroxy-6,8-dioxabicyclo[3.2.1]octan-3-yl Acetate (41)

A solution of laevoglucosan (**35**; 15.00 g, 0.09 mol) and phenyl boronic acid (15.80 g, 0.09 mol) in toluene (500 mL), was heated to reflux under Dean–Stark conditions until no further water was observed (~4 h). The reaction was cooled and the solvent removed in vacuo to yield **40** as a white solid (22.30 g, 0.09 mol), which was used directly in the next reaction.

Compound **40** (22.00 g, 89 mmol) was dissolved in CH_2Cl_2 (440 mL) and pyridine (15.7 mL, 195 mmol) was added. Acetyl chloride (6.9 mL, 97 mmol) was added dropwise and the reaction was stirred for 48 h. Cyclohexane was added in order to precipitate out the pyridine HCl salt, which was removed by filtration. The solvent was removed in vacuo and the crude product was dissolved in EtOH (200 mL) and silica (5 g) was added. The reaction was heated to 45 °C for 12 h and then concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; EtOAc) to yield the title compound **41** as a yellow oil (11.6 g, 63% over three steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.46 [s, 1 H, C(1)H], 4.77 [br t, *J* = 1.5 Hz, 1 H, C(3)H], 4.60 [br d, *J* = 5.5 Hz, 1 H, C(5)H], 4.06 [d, *J* = 7.5 Hz, 1 H, C(6)H], 3.81 [dd, *J* = 7.5, 5.5 Hz, 1 H, C(6)H′], 3.63 [d, *J* = 1.0 Hz, 1 H, C(4)H], 3.55 [d, *J* = 1.0 Hz, 1 H, C(2)H], 3.37 (br s, 2 H, OH), 2.11 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (C), 101.3 (CH), 75.9 (CH), 73.8 (CH), 68.8 (CH), 67.9 (CH), 65.0 (CH_2), 21.1 (CH_3).

2,4-Bis(allyloxy)-6,8-dioxabicyclo[3.2.1]octan-3-yl Acetate (42)

To a solution of 2,4-dihydroxy-6,8-dioxabicyclo[3.2.1]octan-3-yl acetate (**41**; 2.00 g, 9.8 mmol) and silver triflate (10.00 g, 39 mmol) in CH_2Cl_2 (100 mL) under a nitrogen atmosphere at 0 °C, was added diisopropylethylamine (10.2 mL, 59 mmol) dropwise followed by allyl iodide (3.36 mL, 39 mmol), dropwise. The reaction was stirred at 0 °C until TLC analysis indicated complete consumption of starting material **41**. The yellow/brown reaction mixture was then filtered through Celite®, washing with CH_2Cl_2 until the washings ran clear. The solvent was removed in vacuo and the red product was purified by column chromatography (SiO_2; hexane–EtOAc, 7:3) to isolate the title compound **42** as a yellow oil (2.1 g, 75%).

R_f = 0.28 (SiO_2; hexane–EtOAc, 7:3).

IR (neat): 2978, 2900, 1737 (ester), 1646, 1372, 1230, 1095 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.97–5.87 (m, 2 H, C*H*=CH_2), 5.47 [s, 1 H, C(1)H], 5.31 (app. dddd, *J* = 17.0, 7.5, 3.0, 1.5 Hz, 2 H, CH=CH_2), 5.22 (app. dddd, *J* = 10.5, 7.5, 2.5, 1.5 Hz, 2 H, CH=CH_2), 4.95 [t, *J* = 1.5 Hz, 1 H, C(3)H], 4.63 [d, *J* = 5.0 Hz, 1 H, C(5)H], 4.26–4.11 (m, 4 H, CH_2CH=CH_2), 3.97 [dd, *J* = 7.5, 1.0 Hz, 1 H, C(6)H], 3.77 [d, *J* = 7.5, 6.0 Hz, 1 H, C(6)H′], 3.27 (d, *J* = 1.0 Hz, 1 H, C(4)H], 3.22 [d, *J* = 1.0 Hz, 1 H, C(2)H], 2.11 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C), 134.8 (CH), 134.3 (CH), 117.8 (CH_2), 117.7 (CH_2), 100.3 (CH), 75.2 (CH), 74.3 (CH), 74.1 (CH), 71.1 (CH_2), 70.5 (CH_2), 69.00 (CH), 65.9 (CH_2), 21.2 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_6Na$: 307.1158; found: 307.1172.

(3*R*,4*S*,5*R*,6*R*)-6-(Acetoxymethyl)-3,5-bis(allyloxy)tetrahydro-2*H*-pyran-2,4-diyl Diacetate (43)

To a solution of 2,4-bis(allyloxy)-6,8-dioxabicyclo[3.2.1]octan-3-yl acetate (**42**; 2.1 g, 7.4 mmol) in a solution of CH_2Cl_2 (30 mL) and Ac_2O (10 mL) at 0 °C, was added one drop of TMSOTf. The yellow reaction was stirred at 0 °C until complete by TLC analysis (~1 h). The reaction was quenched with sat. aq $NaHCO_3$ (30 mL). The organic layer was separated and the solvent removed in vacuo to furnish the title compound **43** as a colourless oil (3.0 g, 99%).

R_f = 0.34 (SiO_2; hexane–EtOAc, 7:3).

IR (neat): 2918, 1742, 1647, 1428, 1372, 1216, 1076 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.31 [d, *J* = 3.5 Hz, 1 H, C(1)H], 5.84–5.76 (m, 2 H, C*H*=CH_2), 5.41 [t, *J* = 10.0 Hz, 1 H, C(3)H], 5.27–5.15 (m, 4 H, CH=CH_2), 4.28 [d, *J* = 3.5 Hz, 2 H, C(6)H_2], 4.11–3.95 [m, 5 H, C(5)H and 2 × CH_2CH=CH_2], 3.51 [dd, *J* = 10.0, 3.5 Hz, 1 H, C(2)H], 3.47 [t, *J* = 10.0 Hz, 1 H, C(4)H], 2.16 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6 (C), 169.8 (C), 169.3 (C), 134.0 (CH), 133.9 (CH), 117.9 (CH_2), 117.7 (CH_2), 89.3 (CH), 75.9 (CH), 75.4 (CH), 73.5 (CH_2), 73.1 (CH_2), 71.9 (CH), 70.9 (CH), 62.6 (CH_2), 21.1 (CH_3), 21.0 (CH_3), 20.8 (CH_3).

(2*R*,3*S*,4*S*,5*R*)-3,5-Bis(allyloxy)-2-(hydroxymethyl)-6-methoxytetrahydro-2*H*-pyran-4-ol (44)

To a solution of **43** (3.1 g, 8.0 mmol) in MeOH (20 mL) under nitrogen, was added MeONa (4.0 g, 80 mmol). The reaction was stirred at r.t. for 12 h and neutralised (acidic MeOH prepared by dropping acetyl chloride into MeOH). The solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2; EtOAc, R_f = 0.31) to yield the triol (3*R*,4*S*,5*S*,6*R*)-3,5-bis(allyloxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2,4-diol as a colourless oil (1.9 g, 91%). This triol (1.0 g, 3.8 mmol) was dissolved in MeOH (50 mL) and a few drops of acidic MeOH were added. The reaction was stirred at 40 °C for 3 d under nitrogen, then the reaction was quenched with sat. aq Na_2CO_3 and the crude material was purified by column chromatography (SiO_2; hexane–EtOAc, 6:4) to yield the desired product **44** as a mixture of anomers (470 mg, 45%).

R_f = 0.38 (SiO_2; hexane–EtOAc, 6:4).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.92–5.81 (m, 2 H, C*H*=CH_2), 5.25–5.10 (m, 4 H, CH=CH_2), 4.36–4.25 (m, 2 H), 4.21 [d, *J* = 8.0 Hz, 1 H, C(1)H], 4.15–4.04 (m, 2 H), 3.83 (ddd, *J* = 12.0, 5.5, 3.0 Hz, 1 H), 3.72–3.65 (m, 1 H), 3.59 (dd, *J* = 8.5, 1.5 Hz, 1 H), 3.47 (s, 3 H, CH_3), 3.42 (br d, *J* = 4.0 Hz, 1 H, OH), 3.25–3.35 (m, 2 H), 3.04 (dd, *J* = 9.5, 8.0 Hz, 1 H), 2.49 (br d, *J* = 4.0 Hz, 1 H, OH).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}O_6Na$: 297.1314; found: 297.1327.

(3*R*,4*S*,5*R*,6*R*)-3,5-Bis(allyloxy)-2-methoxy-6-{[3,4,5-tris(benzyloxy)-2-bromobenzoyloxy]methyl}tetrahydro-2*H*-pyran-4-yl 3,4,5-Tris(benzyloxy)-2-bromobenzoate (39)

To a solution of the diol **44** (25 mg, 0.09 mmol) in CH_2Cl_2 (10 mL) under nitrogen, was added 3,4,5-tris(benzyloxy)-2-bromobenzoic acid (**13**; 92mg, 0.18 mmol), DMAP (20 mg, 0.45 mmol) and EDC (15 mg, 0.23 mmol). The reaction was stirred at 50 °C for 48 h, then the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2; hexane–EtOAc, 6.5:3.5) to yield the title compound **39** as an off-white foam (110 mg, 94%).

R_f = 0.28 (SiO_2; hexane–EtOAc, 6.5:3.5).

IR (neat): 3032, 2944, 2879, 1731, 1578, 1562, 1475, 1453, 1361, 1329, 1191, 1096 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.28 (m, 32 H, aryl H), 5.85–5.79 (m, 2 H, C*H*=CH_2), 5.48 [t, *J* = 9.0 Hz, 1 H, C(3)H], 5.27–5.06 (m, 16 H, 2 × CH=CH_2 and 6 × OCH_2Ph), 4.71 [dd, *J* = 12.0, 2.5 Hz, 1 H, C(6)H], 4.55 [dd, *J* = 12.0, 5.5 Hz, 1 H, C(6)H′], 4.45 [d, *J* = 7.5 Hz, 1 H, C(1)H], 4.41–4.37 (m, 1 H, C*H*H′CH=CH_2), 4.16–4.06 (m, 3 H, CH_2CH=CH_2 and CH*H*′CH=CH_2), 3.78 [ddd, *J* = 9.5,

5.5, 2.0 Hz, 1 H, C(5)H], 3.69 [t, *J* = 9.5 Hz, 1 H, C(4)H], 3.59 (s, 3 H, OCH_3), 3.45–3.41 [m, 1 H, C(2)H].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 164.9, 151.8, 151.0, 146.0, 136.7, 136.6, 135.9, 134.6, 133.9, 128.7, 128.7, 128.4, 128.4, 128.3, 127.6, 127.5,117.8, 116.9, 112.5, 112.4, 110.4, 104.3, 79.3, 76.4, 75.8, 75.5, 73.4, 73.1, 72.8, 71.3, 64.3, 57.3, 56.3.

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(29) Attempts to protect the 3-hydroxyl group of **35** with the silane protecting groups TBS and TMS were unsuccessful. In addition, attempts to protect this hydroxyl group with a benzoyl group (by reaction with benzoyl chloride) also met with failure.

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