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 elaecarpusin are also presented.

1 Introduction

The importance of biaryl-containing medium-sized 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. 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.

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). 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. Organomagnesium and organozinc halides are less reactive than the organolithium precursors that are typically used to generate organocuprates by transmetallation. 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. Conivaptan (3) is a pharmaceutical agent used for the treatment of low serum sodium levels (hyponatremia). Tunephos (4) is a commercially available chiral catalyst.

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. Conivaptan (3) is a pharmaceutical agent used for the treatment of low serum sodium levels (hyponatremia). Tunephos (4) is a commercially available chiral catalyst.

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 antitumor effects. However, the isolation of pure ellagitannins from natural sources has frequently been hindered by cumbersome and low-yielding procedures. 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
Biographical Sketches

**Xianbin Su** obtained his PhD from Cambridge in 2007 for work on organocuprate oxidation methodology and strategies for the synthesis of ellagitannin 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 ellagitannin 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.
The only previous reported synthesis of sanguiin H-5 (6) presents two main challenges. Firstly, the glycosidic link at the anomeric centre needs to be established in a stereochemically 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 atropodiastereoselective 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. Although this key coupling step 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 This key coupling step 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

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 sanguin 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 Sanguin H-5

From a synthetic perspective, the structure of sanguin H-5 (6) presents two main challenges. Firstly, the glycosidic link at the anomeric centre needs to be established in a stereochemically 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 atropodiastereoselective 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.

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The proposed retrosynthesis of sanguiin H-5 (Scheme 2)-atropisomer of the HHDP group with complete diastereoselectivity, free hydroxyl 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 precursor, 

Since the benzyl esters can easily be removed 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. 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 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. Similarly, electrophilic thallation, which was to be followed by treatment with potassium iodide, gave polymeric products. Though iodination of methyl ether proved refractory to electrophilic iodo-lation by a variety of standard methods. In addition, attempts to demethylate the product produced assortments of compounds with evidence of de-iodination. Bromination to furnish 22 and subsequent ester cleavage (Scheme 4). Electrophilic iodination of 19 [via initial protection to give 16, bromination to furnish 22 and subsequent ester cleavage (Scheme 4)]. However, 16 (and the corresponding benzyl-protected acid) proved refractory to electrophilic iodination by a variety of standard methods. In addition, bromide 22 was inert to both mild bromine–magnesium exchange and bromine–zinc exchange 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) gave intractable product mixtures. Fortunately, Swern oxidation 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).

We next turned our attention towards the stereoselective synthesis of β-glucopyranose 11. Using the procedure reported by Murai and co-workers, 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.
(Scheme 5). Conversion of 26 into the (R)-trichloroacetimidate 28 was achieved through treatment with Cl3CCN and DBU.12 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 1H NMR analysis) in an 80% yield. Desilylation using TBAF buffered with acetic acid, followed by column chromatography, allowed the isolation of the desired β-galloylgucose product 11. These desilylation 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-galloylgucose 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·SMe2 and subsequent intramolecular cuprate oxidation furnished benzyl-protected sanguin 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 sanguin 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 sanguin H-5 (6). Gratifyingly, the key biryl 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.28 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 biosynthesis of the molecule simplifies the situation greatly (Scheme 7). Elaeocarpusin (7) is known to come from geranin (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, geranin (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 geranin (31) is the medium-ring biaryl 33. Geranin (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.

![Scheme 7](image)

Scheme 7  Outline of the proposed strategy towards the synthesis of elaeocarpusin (7). Geranin (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

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 acetal protection of the hydroxyl group at the 3-position of the pyranose core was achieved via the intermediate boronate protection of the hydroxyl group at the 3-position of the pyranose core was achieved. Copper-mediated cyclisation of 39 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...
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.24h 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.24h 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
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.

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. CH₂Cl₂, EtOAc, MeOH, n-hexane, MeCN and toluene were distilled from CaH₂. Et₂O was distilled over a mixture of LiAlH₄ and CaH₂. THF was dried over Na wire and distilled from a mixture of LiAlH₄ and CaH₂. 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 \( \lambda_{max} = 254 \text{ nm} \) 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 Kieselgel 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 \( \lambda_{max} \) are reported in wavenumbers \( \text{cm}^{-1} \) 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. \(^1\)H 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 \( \delta \) 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 (\(^1\)H–\(^1\)H 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 \( \delta \) 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 \(^1\)H NMR and \(^{13}\)C NMR spectra. For the sake of clarity the general numbering systems shown in Figure 3 are used for (a) the \( \delta \)-glucose core based of sanguin H-5 and related coupling precursors and (b) the substituted glucose derivatives involved in studies towards the synthesis of laeoiocarpin.

![Figure 3](image-url)

Liquid chromatography mass spectrometry (LC-MS) spectra were recorded on an HP/Agilent MSD LC-MS APOLLO 120-1000 full gradient ACQ; T = 1 min, 1 \mu\text{L}. High resolution mass spectrometry measurements were made by the EPSRC mass spectrometry service (Swansea) or recorded-in-house using a Waters LCT Premier Mass Spectrometer or a Micromass Quadrupole-Time of Flight (Q-ToF) spectrometer. Mass values are reported within the error limits of ±2 ppm mass units. The ionisation technique used is indicated by the following abbreviations: CI = chemical ionisation; EI = electron ionisation; ESI = electrospray ionisation; FAB (LSIMS) = 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 \(10^{-1} \text{ deg cm}^2 \text{ g}^{-1} \) 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 Sanguin 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\(_2\)CO\(_3\) (2.49 g, 18.0 mmol) in anhydrous DMF (100 mL) was stirred at r.t. for 24 h. The solution was then diluted with H\(_2\)O (200 mL) and extracted with Et\(_2\)O (500 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.\(^3\) 98 °C).

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

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\[ \delta = 7.49–7.36 (m, 15 H, aryl CH), 7.31 (s, 2 H, aryl CH), 7.15 (s, 6 H, 3 × CH\(_3\)), 3.92 (s, 3 H, CH\(_3\)). \]

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):

\[ \delta = 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), 124.8 (C), 108.7 (CH), 74.7 (CH\(_2\)), 70.8 (CH\(_3\)), 51.8 (CH\(_3\)). \]

HRMS (ESI\(^+\)): \([M + H]^+\) calcd for [C\(_{11}H_{12}O_5]^+: 245.1858; found: 245.1860.

The data are consistent with those previously reported.\(^\text{31}\)

**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\(_2\)O (200 mL) and extracted with Et\(_2\)O (500 mL). The organic layer was separated, washed with H\(_2\)O (4 × 200 mL), brine (200 mL), dried (Na\(_2\)SO\(_4\)) 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, 699 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\[ \delta = 7.54 (dd, J = 7.5, 1.5 \text{ Hz}, 2 \text{ 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\(_3\)):

\[ \delta = 166.4 (C), 151.8 (C), 151.0 (C), 145.9 (C), 136.8 (C), 136.7 (C), 136.1 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 112.18 (C), 110.4 (CH), 75.8 (CH\(_2\)), 75.5 (CH\(_3\)), 71.4 (CH\(_3\)), 52.6 (CH\(_3\)). \]

Anal. Calcd for C\(_{29}\)H\(_{27}\)Br\(_2\)O\(_5\): 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.\cite{16} A mixture of methyl 3,4,5-tris(benzyloxy)-2-bromobenzoate (22; 10.03 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 H2O, and the organic layer was extracted with EtOAc, then sequentially with aqueous HCl solution (approx. 3 M) and brine, dried (MgSO4) 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): 3320 (br, O-H), 1438, 1373, 1120, 1069, 732, 694 cm–1.

1H NMR (500 MHz, CDCl3): 6 = 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 × CH2), 5.08 (s, 2 H, CH2).

13C NMR (125 MHz, CDCl3): 6 = 138.7 (C), 138.5 (C), 138.4 (C), 138.3 (C), 138.2 (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 (CH2), 75.3 (CH2), 71.2 (CH2), 69.5 (CH3).

Anal. Calcd for C23H19BO4: C, 70.3; H, 4.3. Found: C, 70.2; H, 4.2.


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Adapted from the method of Molander et al.\cite{15} A solution of iodine (146.8 g, 560 mmol) in CH2Cl2 (135 mL) was added to a stirred solution of oxalyl chloride (2.72 mL, 3.96 g, 131 mmol) in CH2Cl2 (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 CH2Cl2 (190 mL) was added slowly. The solution was maintained at –78 °C for a further 20 min before addition of Et2N (18.9 mL). The reaction mixture was allowed to warm to r.t. and then H2O (95 mL) was added and the organic layer separated. The aqueous layer was washed with CH2Cl2 (100 mL), the combined organic layers washed with brine, dried (MgSO4) 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, 759, 746, 699 cm–1.

1H NMR (500 MHz, CDCl3): 6 = 7.58–7.32 (m, 16 H, aryl CH), 5.20 (s, 4 H, CH2), 5.12 (s, 2 H, CH2).

13C NMR (125 MHz, CDCl3): 6 = 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 (CH2), 75.5 (CH2), 71.2 (CH2).


3,4,5-Tris(benzyloxy)-2-iodobenzoic Acid (12)
Adapted from the method of Bal et al.\cite{22} A solution of sodium chlorite (208.8 g, 808.8 mmol) and sodium dihydrogen phosphate dihydrate (24.79 g, 158.9 mmol) in H2O (100 mL) was added over 10 min to a stirred solution of 3,4,5-tris(benzyloxy)benzaldehyde (25; 12.5 g, 22.7 mmol) and 2-methylbut-2-ene (100 mL, 66.0 g, 940 mmol) in r-BuOH (500 mL), H2O (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 CH2Cl2 (400 mL), washed with H2O (200 mL), dried (MgSO4) and concentrated under reduced pressure to give the title compound 26 (10.84 g, 84%) as a solid.

Mp 177–179 °C (MeOH).

IR (neat): 1687, 1318, 1087, 759, 746, 699 cm–1.

1H NMR (500 MHz, CDCl3): 6 = 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, CH2), 5.10 (s, 2 H, CH2), 5.04 (s, 2 H, CH2).

13C NMR (125 MHz, CDCl3): 6 = 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), 128.29 (CH), 127.7 (CH), 113.4 (CH), 86.0 (C), 75.7 (CH2), 75.5 (CH2), 71.2 (CH2).


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Preparation of β-Glucopyranose 11

1-O-(3,4,5-Tribenzylgalloyl)-4,6-benzylidene-2,3-bis(2,2-di-
butylmethylene)-β-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 CHCl₃ (50 mL) at 0 °C, was added Me₃SiOTf (0.25 g, 1.13 mmol). The mixture was stirred for 2 h at 0 °C, then the reaction was quenched with Et₃N (50 mL) and the resulting suspension filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO₂; 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 1H NMR).

Mp 39–41 °C (EtOAc–hexane); [α]D²⁵ –26.7 (∞ 0.45, CHCl₃); Rf = 0.25 (SiO₂; EtOAc–hexanes, 1:8).

IR (neat): 1733, 1588, 1499, 1456, 1428, 1333, 1074, 771 cm⁻¹.

β- Anomer

Anomeric position designated C(1).

1H NMR (500 MHz, CDCl₃); δ = 7.50–7.46 (m, 2 H, aryl CH), 7.44–7.40 (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, CH₃), 4.34 [dd, J = 10.0, 4.5 Hz, 1 H, C(6)H], 3.92–3.75 (m, 3 H, CH₃), 3.72–3.63 (m, 2 H, CH₂), 0.83 (s, 9 H, CH₃), 0.78 (s, 9 H, CH₃), 0.11 (s, 3 H, CH₃), 0.09 (s, 3 H, CH₃), 0.03 (s, 3 H, CH₃), 0.01 (s, 3 H, CH₃).

13C NMR (125 MHz, CDCl₃); 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 (C), 81.7 (CH), 75.8 (CH), 75.1 (CH), 75.0 (CH), 71.3 (CH), 69.1 (CH), 65.7 (CH), 26.0 (CH₂), 25.8 (CH₂), 18.2 (CH), 18.0 (CH), –3.5 (CH₃), –3.6 (CH₃), –3.8 (CH₃), –4.0 (CH₃).

HRMS (ESI⁺); m/z [M + Na⁺] calcd for [C₉₇H₈₀NaO₁₈]⁺: 1809.3361; found: 1809.3326.

1-0-(3,4,5-Tribenzylgalloyl)-4,6-benzylidene-β-D-glucopyra-
noside (11)

Adapted from the method of Feldman et al. A solution of 29 (1.33 g, 1.45 mmol) in THF (10 mL) at rt was treated with AcOH (0.3 mL, 5 mmol) and TBAF (1 M in THF, 1.5 mL, 5 mmol). The resulting yellow-green reaction mixture was stirred for 7 h and then diluted with EtOAc (50 mL) before being poured over H₂PO₄ (1 M, 30 mL). The organic phase was washed sequentially with H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (SiO₂; EtOAc–hexane, 1:3) to give the title compound 11 (0.9 g, 90%) as a white solid.

Mp 165–167 °C (EtOAc–hexane); [α]D²⁵ –15.6 (∞ 0.95, CHCl₃); Rf = 0.30 (SiO₂; EtOAc–hexane, 1:3).

IR (neat): 3478, 1736, 1586, 1499, 1451, 1335, 1199, 1079, 731 cm⁻¹.

1H NMR (500 MHz, CDCl₃); 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, CH₂), 5.12 (s, 2 H, CH₂), 5.11 (s, 2 H, CH₂), 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).

13C NMR (125 MHz, CDCl₃); 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), 68.4 (CH₂), 67.0 (CH).
136.52 (C), 136.50 (C), 135.89 (C), 135.84 (C), 129.2 (CH), 128.66 (CH), 127.80 (CH), 127.6 (CH), 127.0 (C), 126.16 (C), 126.14 (CH), 128.27 (CH), 128.21 (CH), 128.0 (CH), 127.9 (CH), 127.86 (CH), 127.60 (CH), 127.52 (CH), 126.4 (CH), 123.20 (C), 122.21 (C), 109.3 (CH), 107.2 (CH), 106.9 (CH), 101.16 (CH), 91.9 (CH), 77.18 (CH), 77.12 (CH), 75.7 (CH), 75.54 (CH), 75.50 (CH), 75.3 (CH), 75.25 (CH), 75.20 (CH), 75.0 (CH), 71.34 (CH), 71.31 (CH), 71.0 (CH), 68.3 (CH), 67.7 (CH).


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 (4.1 mg, 0.02 mmol), which was subsequently converted into the complex (8 mg, 0.04 mmol) dissolved in THF (2 mL) and stirred for 15 min.

1H NMR (500 MHz, CDCl3): δ = 7.56–7.18 (m, 42 H, aryli CH), 7.12–7.06 (m, 6 H, aryl CH2), 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 (m, 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, CH2), 4.82 (t, J = 11.5 Hz, 2 H, CH2), 4.66 (dd, J = 11.0, 9.0 Hz, 2 H, CH3), 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].

(b) By Copper-Mediated Oxidation of Organocarbonylic Iodides 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 stirred for 10 min. The reaction mixture was then filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO2; EtOAc–hexanes, 1:3) to give the title compound 8 (19.9 g, 65%) as an amorphous solid.

Mp 102–104 °C (EtOAc–hexanes); [α]D25 –66.5 (c 0.8, CHCl3);


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

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1,2,3,12,13,14-Hexakis(benzilxyloxy)-7,8-dihydrodibenzo-...
1,2,3,13,14,15-Hexakis(benzylxylo)-8,9-dihydro-5H-dibenzo[5,1][1,5]dioxacycloundecine-5,11(7H)-dione (53)

To a solution of the diacid rac-30 (200 mg, 0.23 mmol) in CH₂Cl₂ (10 mL) under nitrogen at r.t., was added Et₃N (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 CH₂Cl₂ (2.5 mL). Both solutions were added dropwise to a solution of TBAI (1 g, 5.07 mmol) followed by propylene glycol (0.02 mL, 0.23 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) under nitrogen at r.t., was added Et₃N (0.045 mL, 0.32 mmol) and stirred for 12 h. Then the reaction mixture was filtered through Celite®, washing with H₂O–MeCN (1:1) until the washings ran clear. The solvent was removed in vacuo to yield the title compound 53 as a purple solid (21 mg, 10%).

Mp 300 °C (dec).

IR (neat): 3119, 1686, 1614, 1514, 1317, 1215, 1180, 1126, 1033 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆): 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, OCH₂CH₂CH₂O), 3.92–3.88 (m, 2 H, OCH₂CH₂CH₂O), 1.97–1.92 (m, 2 H, OCH₂CH₂CH₂O).

13C NMR (125 MHz, DMSO-d₆): δ = 168.3 (C), 144.8 (C), 144.2 (C), 134.8 (C), 124.5 (C), 115.2 (C), 105.6 (CH), 60.1 (CH₂), 25.3 (CH₃).


1,2,3,14,15,16-Hexa-(benzyloxy)-7,8,9,10-tetrahydrodibenzo[3,4][1,6]dioxacyclocadecine,5,12-dione (54)

To a solution of the diacid rac-30 (200 mg, 0.23 mmol) in CH₂Cl₂ (10 mL) under nitrogen at r.t., was added Et₃N (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 CH₂Cl₂ (2.5 mL). Meanwhile, butane-1,4-diol glycol (0.02 mL, 0.23 mmol) was dissolved in anhydrous CH₂Cl₂ (2.5 mL) and the solution was added dropwise to a solution of TBAI (1 mg, 1 mol%) and anhydrous K₂CO₃ (31 mg, 0.23 mmol) in CH₂Cl₂ (25 mL) under nitrogen. The reaction was stirred for 12 h, then the solvent was removed in vacuo and the product was purified by column chromatography (SiO₂; hexane–EtOAc, 7:3) to yield the title compound 54 as a colourless oil (54 mg, 41%).

Rᵣ = 0.23 (SiO₂; hexane–EtOAc, 7:3).

IR (neat): 3031, 2927, 1737 (ester), 1592, 1497, 1454, 1367, 1327, 1192, 1095 cm⁻¹.

1H NMR (500 MHz, CDCl₃): 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), 6.97–6.91 (m, 6 H, aryl H), 5.15 (d, J = 11.5 Hz, 2 H, OCH₂Ph), 4.99–4.95 (m, 2 H, OCH₂Ph), 4.92 (d, J = 11.5 Hz, 2 H, OCH₂Ph), 4.86–4.87 (m, 4 H, OCH₂Ph, OCH₂CH₂CH₂OH), 4.10 (dt, J = 11.5, 5.0 Hz, 2 H, OCH₂CH₂CH₂O), 2.22–2.17 (m, 2 H, OCH₂CH₂CH₂O).

13C NMR (125 MHz, CDCl₃): δ = 168.2 (C), 152.4 (C), 152.4 (C), 135.3 (C), 123.1 (C), 115.0 (C), 105.5 (CH), 64.5 (CH₂), 60.6 (CH₂).


1,2,3,12,13,14-Hexahydroxy-7,8-dihydrodibenzo[5,6][1,1]dioxacyclododecine-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 H₂O–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, 10%).

Mp 300 °C (dec).

IR (neat): 3119, 1686, 1614, 1514, 1317, 1215, 1180, 1126, 1033 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆): 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, OCH₂CH₂CH₂O), 3.92–3.88 (m, 2 H, OCH₂CH₂CH₂O), 1.97–1.92 (m, 2 H, OCH₂CH₂CH₂O).

13C NMR (125 MHz, DMSO-d₆): δ = 168.3 (C), 144.8 (C), 144.2 (C), 134.8 (C), 124.5 (C), 115.2 (C), 105.6 (CH), 60.1 (CH₂), 25.3 (CH₃).


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1^H NMR (500 MHz, CDCl3): 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], 3.60 [dd, J = 7.5, 5.5 Hz, 2 H, C(1)H, C(2)H], 1.95 [br t, J = 5.3 Hz, 2 H, OH], 1.11 (s, 3 H, CH3).

1^3C NMR (125 MHz, CDCl3): δ = 170.4 (C), 101.3 (CH), 75.9 (CH), 73.8 (CH), 68.8 (CH), 67.9 (CH), 65.0 (CH2), 21.1 (CH3).

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

To a solution of 2,4-bis(allyloxy)-6,8-dioxabicyclo[3.2.1]octan-3-yl acetate (41) in MeOH (50 mL) and silica (5 g) was added. The reaction was stirred at 40 °C for 3 d under nitrogen, then the reaction was quenched with sat. aq NaHCO3 (30 mL). The solvent was removed in vacuo and the crude material was purified by column chromatography (SiO2; hexane–EtOAc, 5:3) to yield the title compound 43 as a colourless oil (1.9 g, 91%). The yield 1H NMR (500 MHz, CDCl3): δ = 5.30 (s, 1 H, CH3), 4.84 (m, 4 H, CH2), 3.65 (dd, J = 7.5, 5.5 Hz, 2 H, C(1)H, C(2)H), 3.60 (d, J = 10.1 Hz, 1 H, C(4)H), 1.96 (t, J = 6.0 Hz, 1 H, OH), 1.06 (s, 3 H, CH3).

IR (neat): 2935, 2923, 1731, 1578, 1562, 1475, 1453, 1361, 1329, 1191, 1096 cm–1.

(3R,5S,6R)-3,5-Bis allyloxy-2-hydroxy-4,6-dimethyl-2H-pyran-4-ol (44)

To a solution of 3(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 2 h and neutralised (acidic MeOH prepared by dropping acetyl chloride into MeOH). The solvent was removed in vacuo and the crude material was purified by column chromatography (SiO2; hexane–EtOAc, 6:4) to yield the desired product 44 as a mixture of anomers (470 mg, 45%).

IR (neat): 2978, 2900, 1737 (ester), 1464, 1372, 1230, 1095 cm–1.

(3R,5S,6R)-3,5-Bis(allyloxy)-2-hydroxy-4,6-dimethyl-2H-pyran-4-ol (44)

To a solution of 3(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 2 h and neutralised (acidic MeOH prepared by dropping acetyl chloride into MeOH). The solvent was removed in vacuo and the crude material was purified by column chromatography (SiO2; hexane–EtOAc, 6:4) to yield the desired product 44 as a mixture of anomers (470 mg, 45%).

IR (neat): 2978, 2900, 1737 (ester), 1464, 1372, 1230, 1095 cm–1.
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, OCH3), 3.45–3.41 [m, 1 H, C(2)H]

13C NMR (125 MHz, CDCl3): 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.

References

(6) (a) First isolation of rhazinilam, see: Banerji, A.; Majumder, Hline, S. S.; Pham, P.-T. T.; Pham, P.-T. T.; Aung, M. H.; Lei, A.; Wu, S.; He, M.; Zhang, X.
(8) It is not entirely obvious why the oxidative coupling of organocuprates should be so effective at forming medium-ring biaryl systems, especially given the difficulties associated with the use of more conventional palladium-mediated methods.
(9) (a) First isolation of rhazinilam, see: Banerji, A.; Majumder, Hline, S. S.; Pham, P.-T. T.; Pham, P.-T. T.; Aung, M. H.; Lei, A.; Wu, S.; He, M.; Zhang, X.
(12) (a) First isolation of rhazinilam, see: Banerji, A.; Majumder, Hline, S. S.; Pham, P.-T. T.; Pham, P.-T. T.; Aung, M. H.; Lei, A.; Wu, S.; He, M.; Zhang, X.

(28) Conformational analysis of the 11-membered medium-ring in 33 reveals that it does not have a low-energy conformation where both esters’ groups are capable of obtaining their preferred U-shape (s-cis) simultaneously (unlike the northern-hemisphere 12-membered ring). The crystal structure of geraniin (31) shows that the strain in the 11-membered ring is relieved somewhat, since both esters’ groups can form a lower energy s-trans conformation. We hypothesize that the internal strain inherent in this medium-ring may make this system more susceptible to oxidation, and be the reason why the 2,4-bridging biaryl group has never been observed as such in ellagitannin natural products (see ref. 11b).

(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 benzyol group (by reaction with benzoyl chloride) also met with failure.

(30) Treatment of laevoglucosan (35) with allyl bromide or iodide in the presence of sodium hydride generated fully alkylated product rather than the desired 2,4-allyl protected derivative. Silver triflate was found to be essential for the generation of 42 from 41.


