CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201200517

Synthetic Studies toward *C*-Glucosidic Ellagitannins: A Biomimetic Total Synthesis of 5-*O*-Desgalloylepipunicacortein A

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Abstract: *C*-glucosidic ellagitannins constitute a subclass of bioactive polyphenolic natural products with strong antioxidant properties, as well as promising antitumoral and antiviral activities that are related to their capacity to interact with both functional and structural proteins. To date, most synthetic efforts toward ellagitannins have concerned glucopyranosic species. The development of a synthetic strategy to access *C*-glucosidic ellagitannins, whose characteristic structural feature includes an atropoisomeric hexahydroxydiphenoyl (HHDP) or a nonahydroxyterphenoyl (NHTP) unit that is linked to an open-chain glucose core by a *C*-aryl glucosidic bond, is described herein. The total synthesis of the biarylic HHDP-containing 5-*O*-desgalloylepipunicacortein A (**1β**) was achieved by either using the natural ellagic acid bis-lactone as a precursor of the requested HHDP unit or by implementing an atroposelective intramolecular oxidative biarylic coupling to forge this HHDP unit. Both routes converged in the penultimate step of this synthesis to enable a biomimetic formation of the key *C*-aryl glucosidic bond in the title compound.

Keywords: biomimetic synthesis · ellagitannins · natural products · oxidative coupling · total synthesis

Introduction

Ellagitannins constitute a family of biologically active plant polyphenols that belong to the hydrolyzable tannin class.[1] Research interest in these plant polyphenols, which are metabolized by dicotyledonous plant species of the *Angiospermea*, initially emerged from the discovery of their occurrence in numerous herbal remedies that are used in traditional Asian medicines and was further fed by the determination of their unusual molecular structures and remarkable biological activities that are related to their antioxidant, antiviral, and host-mediated antitumoral properties.[2] To date, nearly 1000 fully characterized ellagitannins have been isolated from various plant sources, thus constituting by far the largest group of known tannin molecules.[1–3] The existence of these hundreds of different molecular entities is really remarkable when considering that they all plausibly emanate from a single biosynthetic precursor, the penta-*O*-galloyl-β-D-glucopyranose (β-PGG), itself elaborated from two simple building blocks: D-glucopyranose and gallic acid (i.e., 3,4,5-trihydroxybenzoic acid).[4] The defining structural feature of all of the ellagitannins is the 6,6′-dicarbonyl-2,2′,3,3′,4,4′-hexahydroxybiphenyl (bis-ester) moiety, commonly designated by the trivial name hexahydroxydiphenoyl (HHDP), whose hydrolysis releases the bis-lactone ellagic acid from which these natural products are named. Such biarylic HHDP units are formed by oxidative (dehydrogenative) C–C coupling between the phenolic galloyl groups that are attached onto the glucopyranose core. The most common biarylic coupling patterns occur at the 2,3- and/or 4,6-positions of a glucopyranose core in its $^4C_1$-conformation, as exemplified in the structures of tellimagrandin II[5] and pedunculagin[6] (Scheme 1), although biarylic coupling reactions across the 1,6- and 3,6-positions are also known in several structures in which the glucose core adopts its $^1C_4$-conformation.[1] The structural diversity of monomeric ellagitannins emanates not only from the conformational changes in the glucopyranose core and from the variation in the position and number of the HHDP units, but also from the atropoisomerism of their biaryl axis, as well as from the extent of

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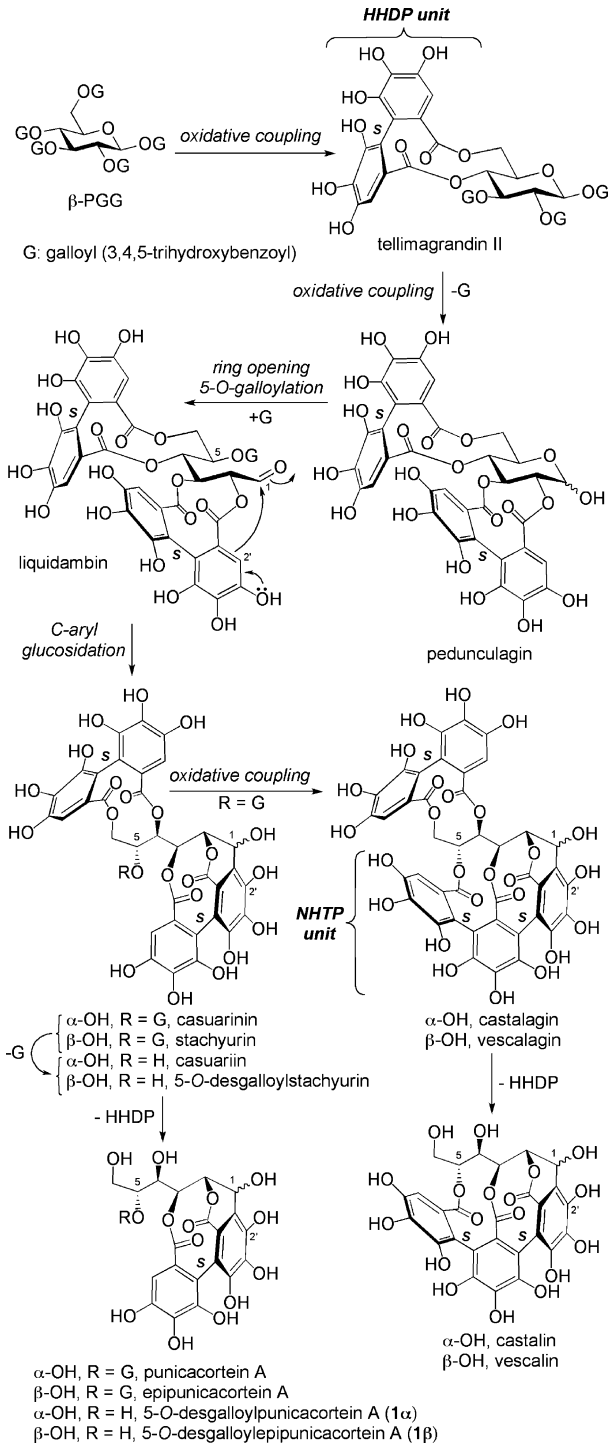
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200517.



Scheme 1. Putative biosynthetic route to *C*-glucosidic ellagitannins.

galloylation and from the anomeric stereochemistry of the glucopyranose core. The *C*-glucosidic ellagitannins constitute yet another subclass of ellagitannins in which a C–C bond links the carbon-1 (anomeric) atom of an "open-chain" glucose core to the carbon-2′ atom of a galloyl-derived unit that has been esterified to the 2-position of the glucose core. Their C-1-linked galloyl-derived unit is either part of a HHDP unit that bridges the 2- and 3-positions of the glucose core, as exemplified in the structures of casuarinin and its C-1 epimer, stachyurin,[6d,7] or part of a terarylic nonahydroxyterphenoyl (NHTP) variant (also known as the flavogallonyl or flavogalloyl group) that is attached through three ester bonds to the 2-, 3-, and 5-positions of the glucose core, as illustrated by the structures of castalagin and vescalagin, which are two ellagitannins that are found in fagaceous woody plants, such as the *Quercus* (oak) species (Scheme 1).[7e,8]

The biosynthetic steps that lead to glucopyranosic ellagitannins from their precursor, β-PGG, are just today starting to be elucidated, essentially thanks to the work initiated by Gross and co-workers.[4] Of most significance was the observation of a β-PGG-oxidizing (phenol oxidase) enzyme that promotes the formation of the 4,6-HHDP-containing tellimagrandin II.[9] The biochemical event that mediates the passage from the glucopyranosic ellagitannin class to the open-chain *C*-glucosidic class still remains a matter of speculation, but a biogenetic filiation has nevertheless been inferred from a phytochemical study on *Liquidambar formosana* (Hamamelidaceae), in which members of the two classes coexist.[10] Thus, the proposed biosynthetic pathway starts from tellimagrandin II to furnish pedunculagin through an oxidative C–C coupling reaction between the 2- and 3-galloyl groups and a 1-*O*-desgalloylation step (Scheme 1). Opening the pedunculagin glucopyranose ring, which would be biochemically driven by an enzymatic 5-*O*-galloylation reaction, is the first key event that opens the door to the *C*-glucosidic ellagitannins. This step leads to the open-chain aldehyde liquidambin, which was first isolated in 1987 by Okuda et al.[11] It is then reasonable to suggest that the electrophilic aldehyde function hence unveiled could be exposed to an intramolecular aldol-type attack by the phenolic 2,3-HHDP unit to forge the characteristic *C*-glucosidic bond of the casuarinin and stachyurin epimers. Their 5-*O*-desgalloylation would give rise to casuariin and 5-*O*-desgalloylstachyurin,[6d,7b–e] whereas oxidative coupling between their 5-galloyl and 2,3-HHDP groups would furnish castalagin and vescalagin.[1b,12] Other related examples of *C*-glucosidic ellagitannins are castalin and vescalin,[7e,8a,13] both of which lack the 4,6-HHDP unit, as well as the (epi)punicacorteins A[14] and their 5-*O*-desgalloylated analogues, compounds **1α/β**[14b,c] (Scheme 1).

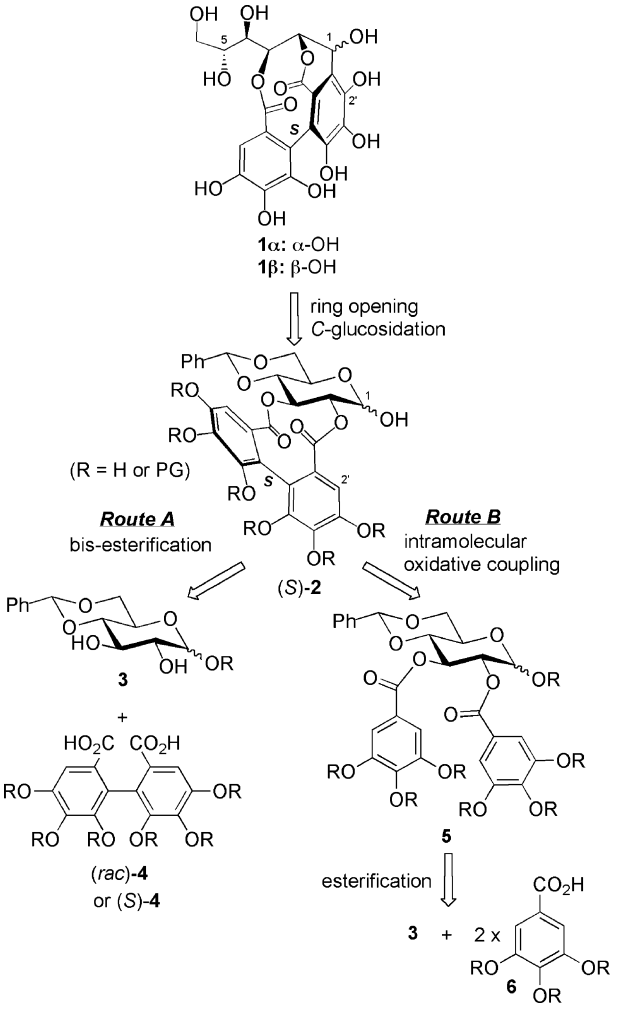
Our previous investigations on the occurrence and chemical transformations of *C*-glucosidic ellagitannins in wines, as a result of their aging in oak-made barrels,[15] and our continuing interest in the remarkable biological activities of some of these polyphenols, notably through their interactions with tumor- or virus-related proteins,[15d,e,16] led us to contemplate their total synthesis. Furthermore, although several ellagitannins of the glucopyranosic class have been successfully synthesized,[17] the fact that no ellagitannin of the *C*-glucosidic type had been generated by total synthesis provided us with extra impetus to tackle the unprecedented synthetic challenge posed by these structurally unique natural products.

Herein, we report our work on the exploration of methodological tactics for the development of a biomimetic strategy toward *C*-glucosidic ellagitannins that led to the first total synthesis of a first member of this ellagitannin class, 5-*O*-desgalloylepipunicacortein A (**1β**).[18]

Results and Discussion

Besides the challenge of the fact that no member of the *C*-glucosidic ellagitannin class had yet succumbed to total synthesis efforts, the main incentive to undertake this work was to test the chemical plausibility of the glucopyranosic to *C*-glucosidic ellagitannins route that has been proposed for their biosynthesis (Scheme 1). Thus, we selected the two 5-*O*-desgalloylated (epi)punicacorteins A (**1α/β**) as targets for this endeavor. Both compounds are likely to be metabolized by ellagitannin-producing plant species, but so far only **1α** has been identified as a naturally occurring compound that was first isolated from *Obseckia Chinensis* L. (Melastomataceae),[14b] whereas **1β** was biochemically produced by the hydrolytic action of a tannase on epipunicacortein A, which was isolated from the leaves of the oak tree species *Quercus aliena* BLUME (Fagaceae).[14c]. These two compounds (**1α/β**) can be viewed as the simplest members of the *C*-glucosidic ellagitannin class, but they constitute ideal, yet challenging, targets to validate biomimetic chemical means that are capable of forming their *C*-aryl open-chain glucosidic bond from a glucopyranosic precursor. Therefore, our retrosynthetic plan (Scheme 2) reflected the aim of developing a biomimetic route to these HHDP-bearing *C*-glucosidic ellagitannins with an opening of a glucopyranosic sugar core and a concomitant formation of the *C*-glucosidic bond that were deferred until the end of the synthesis. The 4,6-*O*-benzylidene-2,3-(*S*)-HHDP-D-glucopyranose derivative (**2**, Scheme 2) was elected as a synthetic surrogate of the natural glucopyranosic precursor pedunculagin (Scheme 1). This key advanced intermediate, which contained the requisite biarylic *S* atropoisomer, was elaborated by using two conceptually different strategies.

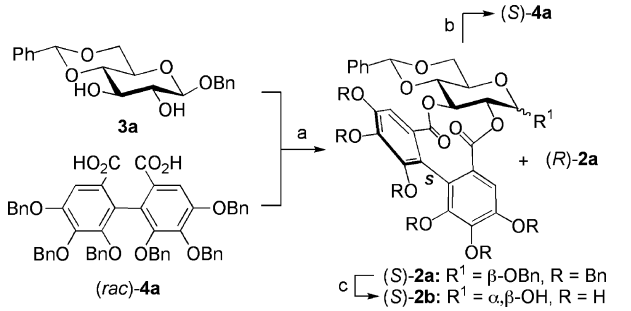
The first approach (route A) relied on a bis-esterification reaction between a 4,6-*O*-benzylidene-D-glucopyranoside (**3**) and an adequately protected version of the (*S*)-atropoisomer or racemate of hexahydroxydiphenic acid (**4**, Scheme 2). This strategy was first introduced by Nelson and Meyers[19] and was largely developed thereafter by Khanbabaee et al. in a series of total syntheses of glucopyranosic ellagitannins.[17,20] Alternatively, compound (*S*)-**2** can be generated by a strategy that is analogous to the biosynthetic construction of HHDP through an intramolecular and atroposelective oxidative-coupling reaction (Scheme 1). This biomimetic strategy, first developed by Feldman et al.,[21] has also enabled them and a few other research groups to achieve the chemical synthesis of various glucopyranosic ellagitannins and their derivatives by using different tactics.[17,22] Although this strategy imposes the installation of two adequately protected galloyl groups on a glucopyranose species, it takes



Scheme 2. Retrosynthetic analysis of the epimers of 5-*O*-desgalloyl-(epi)punicacortein A (**1α** and **1β**).

full advantage of the efficient and correct induction of asymmetry that is brought by the chiral glucopyranose core to the HHDP atropoisomer. Our implementation of this second approach to compound (*S*)-**2** (route B) resulted in the double acylation of compound **3** into oxidative-coupling precursor **5** by using two suitably protected gallic acids (**6**, Scheme 2).

Synthesis of compound (*S*)-2 by route A: Although this route has no biomimetic features and, thus, might be seen as being less elegant than the alternative route (route B), it nevertheless allows a rapid access to the key, late intermediate of our planned synthesis, (*S*)-**2**. Our first synthesis of compound (*S*)-**2** by using this approach involved the bis-acylation of benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**3a**) with racemic hexabenzyloxydiphenic acid (**4a**, Scheme 3). Sugar **3a** was synthesized in three steps from the commercially available 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide by using known procedures.[18,23] Hexabenzyloxydiphenic acid ((*rac*)-**4a**) was prepared in 27% overall



Scheme 3. Synthesis of the 2,3-HHDP-4,6-*O*-benzylidene-D-glucopyranose derivative (*S*)-**2b** by route A. a) DCC, DMAP, CH_2Cl_2, RT, 18 h (35%); b) KO*t*Bu, H_2O (approx. 6 equiv.),THF, RT, 12 h (quant.); c) H_2, Pd/C, THF, RT, 48 h (quant.).

yield by the Schmidt three-step alkaline benzylation of the commercially available ellagic acid bis-lactone.[24]

The bis-esterification of (*rac*)-**4a** with 1-*O*-benzyl-β-D-glucopyranoside **3a** was accomplished under Steglich conditions by using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). No diastereoinduction from the most-proximal glucose C-2 and/or C-3 stereocenters was observed in this reaction; the two diastereoisomers, (*S*)-**2a** and (*R*)-**2a**, were observed in a ratio that was very close to 1:1 by ^{1}H NMR analysis of the crude reaction mixture. This lack of diastereoselectivity has previously been observed by Khanbabaee et al. in the similar 2,3-*O*-bis-acylation of glucose derivatives, whereas the related 4,6-*O*-bis-acylation reactions that use compound (*rac*)-**4a** surprisingly do express a significant level of atropodiastereoselectivity.[20] Thus, we had to rely on column chromatography on silica gel to separate the two diastereoisomers of **2a**, with some difficulties. In fact, we could not purify the (*R*)-**2a** atropoisomer, which remained embedded in a fraction that was contaminated with what we assumed to be some oligomeric materials.[18] Fortunately, the *S*-configured atropoisomer that was required for the continuation of the synthesis was isolated with a satisfactory level of purity in 35% yield. Verification of the absolute configuration of this first HHDP-containing intermediate, compound (*S*)-**2a**, was initially attempted by following the procedure developed by Khanbabaee et al.[20] This procedure involves subjecting the compound to hydrolysis under Gassman conditions (i.e., KO*t*Bu in dry THF plus a trace of water)[25] to compare the specific optical rotation of the resulting hexabenzyloxydiphenic acid (**4a**) to those reported for individual compounds (*S*)-(+)-**4a** and (*R*)-(−)-**4a**.[20a,26] Unfortunately, despite the observation by circular dichroism (CD) spectroscopy of a strong positive Cotton effect near 235 nm, which is characteristic of an *S*-configured biaryl unit,[27] the diphenic acid that was hydrolytically released from our presumed compound (*S*)-**2a** was measured to be levogyre ($[\alpha]_D^{22} = -30.3$; $c = 1.0$, CH_2Cl_2). This unexpected and confusing observation led us to rely on vibrational circular dichroism (VCD)[28] to determine the absolute configuration of compound **4a**. The VCD spectrum of compound **4a** was recorded in $CDCl_3$ and then compared with the predicted VCD spectra of both atropoisomers, which were calculated by using density functional theory (DFT) at the B3PW91/6-31G* level (for details, see the Supporting Information). These comparisons unambiguously established that the axial chirality of our levogyre diphenic acid (**4a**) was *S* and, therefore, also that of the 2,3-HHDP-bearing glucopyranose derivative (**2a**) from which it was derived (Figure 1).

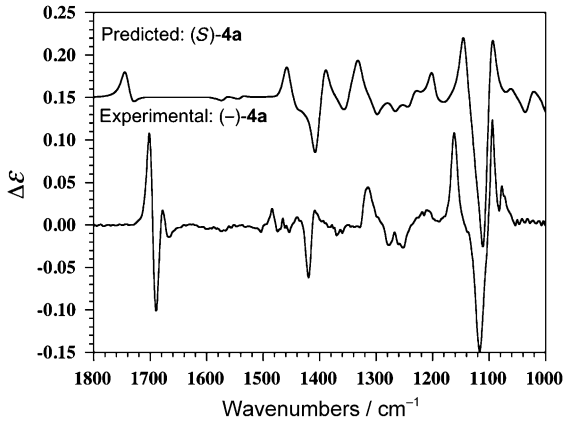
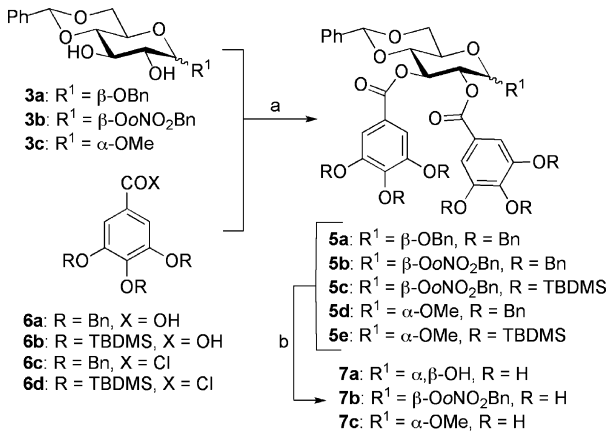


Figure 1. Comparison of the experimental VCD spectrum for compound (−)-**4a** in $CDCl_3$ (33 mM, path length: 200 mm) with the predicted VCD spectrum of compound (*S*)-**4a**.

Pure atropoisomer (*S*)-**2a** was then submitted to standard hydrogenolysis conditions that, gratifyingly, did not affect the benzylidene acetal protecting group, even after 24 h. Thus, the desired heptahydroxylated compound, (*S*)-**2b**, was obtained in quantitative yield as a 1:1 (α/β) anomeric mixture (Scheme 3).

Synthesis of compound (*S*)-2 by route B: The most-appealing aspects of this route are that it is conducted in an intramolecular, atroposelective, and thus biomimetic fashion (Scheme 2). However, previously reported ellagitannin syntheses that took advantage of this route usually implied a constraining selective functionalization of the phenolic hydroxy groups of the galloyl units to be coupled. For example, the pioneering method reported by Feldman and coworkers[1d,17,21] involves the intramolecular oxidative phenolic coupling of diphenylmethylene-protected glucopyranosyl gallates. Their preparation requires orthogonal-protection/deprotection steps and their lead tetraacetate-mediated oxidative coupling generates mixtures of regioisomers that fortunately easily converge to a single product upon cleavage of their diphenyl ketal units. Thus, we wanted to examine the possibility of biomimetically forming the HHDP unit of (*S*)-**2** by using chemical oxidative-coupling methods still in an intramolecular fashion but from unprotected, instead of partially protected, galloyl groups.

To evaluate the feasibility of such a route to compound (*S*)-**2**, we prepared several 2,3-*O*-bis-galloylated sugar derivatives of type **7**, as shown in Scheme 4. For the bis-galloyl-



Scheme 4. Synthesis of 2,3-*O*-bis-galloylated glucopyranose derivatives of type **7**. a) esterification and b) deprotection (Table 1 and Table 2).

ations of 4,6-*O*-benzylidene-D-glucopyranosides of type **3**, four different galloylating reaction partners (**6a–6d**), which were protected with either benzyl (Bn) or *tert*-butyldimethylsilyl (TBDMS) groups and used as either the free carboxylic acids or as acyl-chloride entities, were prepared according to literature procedures.[29] In addition to compound **3a**, we also utilized two other glucosides that contained either a photocleavable *ortho*-nitrobenzyl group (**3b**) or a simple methyl group at the anomeric position (**3c**, commercially available).

The 2,3-*O*-bis-galloylated glucopyranosides of type **5** were then generated according to three different procedures: a standard Steglich esterification reaction (conditions i),[30a] its modified version (conditions ii)[30b] with gallic acid derivatives **6a** or **6b**, or an esterification reaction with acyl chlorides **6c** or **6d** (conditions iii). The results are summarized in Table 1. Although the use of acyl chlorides adds one step onto the synthesis, it turned out to be beneficial when using the silylated galloylating compounds because bis-galloylated products **5c** and **5e** were obtained in much-higher yields (Table 1, entries 3 and 4 and entries 7 and 8). Next, all of the resulting bis-galloylated sugar products (**5a–5e**) were submitted to either hydrogenolysis (R = Bn) or desilylation (R = TBDMS) to afford the desired oxidative-coupling precursors (**7a–7c**) in excellent yields (Table 2). The only notable exception was the case of 1-*O*-nitrobenzylated compound **5b**, which led to an intractable mixture of products upon hydrogenolysis (Table 2, entry 2). The *ortho*-nitrobenzyl group probably did not resist these reaction conditions but we were unable to even pinpoint any product that contained a free anomeric hydroxy group on the ^{1}H NMR spectrum of the reaction mixture. However, we were pleased to observe that the 4,6-*O*-benzylidene acetal protecting group again resisted hydrogenolysis (Table 2, entries 1 and 4).

The next objective was to identify oxidative conditions to efficiently and atroposelectively couple the galloyl groups of these 2,3-*O*-bis-galloylated glucopyranosides (**7**). To this end, we initially selected the most-readily available compound (**7c**) and made the choice of staying away from the use of any highly toxic heavy-metal-based oxidant. Our interest in the development of the chemistry of hypervalent iodine reagents[31] led us first to try some of their commercially available versions, such as $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$, which have been reported to mediate the biaryl coupling reactions of oxygenated arenes,[32] including phenolic species.[32b] Unfortunately, our attempts to couple the galloyl groups of compound **7c** by using these iodanes afforded complex mixtures from which we could not isolate any product. These failures led us to contemplate the use of the organic oxidant *ortho*-chloranil, which has previously been reported to mediate the intermolecular coupling of methyl gallate in Et_2O into a dehydrogenated HHDP unit through dimerization of the α-hydroxy *ortho*-quinone that was initially produced by the oxidation of methyl gallate by *ortho*-chloranil. The reduction of this dehydrogenated HHDP species by using sodium dithionite ($Na_2S_2O_4$) afforded dimethyl hexahydroxydiphenoate in 79%.[33] The complete lack of solubility of compound **7c** in Et_2O obliged us to modify the reaction conditions. After extensive variation of the reaction parameters (solvent, temperature, and duration), the reaction was finally performed in MeCN by using 2 equivalents of *ortho*-chloranil at a temperature that was increased from 0 °C to room temperature over 2 h, followed by reductive treatment of the reaction mixture with aqueous

Table 1. Bis-galloylation of 4,6-*O*-benzylidene-D-glucopyranosides (**3**).

Entry	Glucoside **3** (R^1)	Galloylating unit **6** (R, X)	Conditions[a]	Product	Yield [%][b]
1	**3a** (β-OBn)	**6a** (Bn, OH)	i	**5a**	76
2	**3b** (β-O*o*NO_2Bn)	**6a** (Bn, OH)	ii	**5b**	100
3	**3b** (β-O*o*NO_2Bn)	**6b** (TBDMS, OH)	ii	**5c**	35
4	**3b** (β-O*o*NO_2Bn)	**6d** (TBDMS, Cl)	iii	**5c**	59
5	**3c** (α-OMe)	**6a** (Bn, OH)	ii	**5d**	97
6	**3c** (α-OMe)	**6c** (Bn, Cl)	iii	**5d**	80
7	**3c** (α-OMe)	**6b** (TBDMS, OH)	ii	**5e**	57
8	**3c** (α-OMe)	**6d** (TBDMS, Cl)	iii	**5e**	80

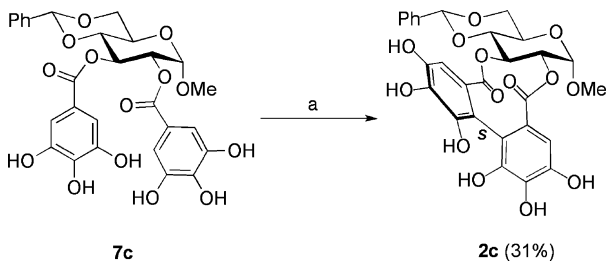
[a] (i) Compound **6** (2.2 equiv), DCC (4.4 equiv), DMAP (2.2 equiv), CH_2Cl_2, RT; (ii) compound **6** (2.2 equiv), DCC (2.2 equiv), DMAP (0.5 equiv), DMAP·HCl (0.5 equiv), CH_2Cl_2, reflux; (iii) compound **6** (2.4 equiv), DMAP (3.3 equiv), CH_2Cl_2, RT. [b] Isolated by column chromatography.

Table 2. Selective deprotection of 2,3-*O*-bis-galloylated 4,6-*O*-benzylidene-D-glucopyranosides (**5**).

Entry	Compound **5**	R^1	R	Conditions[a]	Product	Yield [%][b]
1	**5a**	β-OBn	Bn	i	**7a**[c]	100
2	**5b**	β-O*o*NO_2Bn	Bn	i	**7b**[d]	0
3	**5c**	β-O*o*NO_2Bn	TBDMS	ii	**7b**	97
4	**5d**	α-OMe	Bn	i	**7c**	100
5	**5e**	α-OMe	TBDMS	ii	**7c**	100

[a] (i) H_2, Pd/C, THF, RT, 24 h; (ii) TBAF, THF, RT, 45 min–2 h. [b] Isolated by column chromatography. [c] R^1 = α,β-OH. [d] Complex mixture.

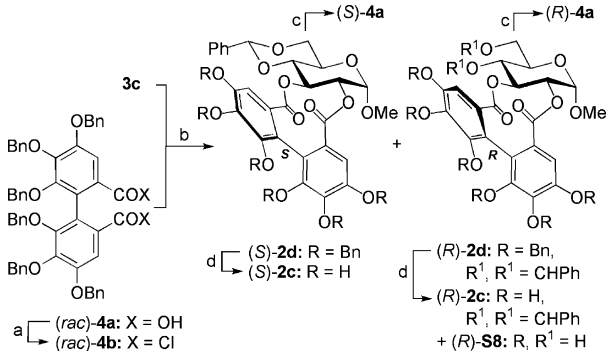
$Na_2S_2O_4$ over 15 h (for the HPLC profile of reaction mixture, see the Supporting Information, Figure S1). The mixture was then filtered through Celite, the filtrate was evaporated, and the residue was triturated with Et_2O to remove the reduced form of *ortho*-chloranil (i.e., tetrachlorocatechol). Thus, the expected coupled product (**2c**) was obtained in 31% yield (Scheme 5). Considering the susceptibility of



Scheme 5. Intramolecular *ortho*-chloranil-mediated bigalloyl coupling reaction (route B). a) (i) *ortho*-chloranil (2 equiv), CH_3CN, 0 °C to RT, 2 h; (ii) aq. $Na_2S_2O_4$, RT, 15 h.

pyrogallol systems toward oxidative transformations, often leading to complex oligomerized materials, we were quite satisfied by this yield of compound **2c**, which was, gratifyingly, solely obtained as its *S*-atropoisomer.

To confirm the absolute configuration of compound **2c**, we also prepared it by route A. To this end, we relied on the conditions reported by Itoh et al.[34a] to achieve a bis-esterification reaction between commercially available sugar derivative **3c** and the racemic hexabenzyloxydiphenoyl chloride **4b**[24] by using 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (Scheme 6). Separation of the product mixture by column chromatography on silica gel afforded atropoisomers (*S*)-**2d** and (*R*)-**2d** in 24% and 4% yield, respectively, thus indicating a significant level of diastereoselectivity in this reaction, in contrast to what was observed by Itoh and co-workers who used a permethylated diphenoyl chloride instead of the perbenzylated variant (**4b**).[34] The two compounds were



Scheme 6. Synthesis of the two atropoisomers (*S*)-**2c** and (*R*)-**2c** by route A. a) Oxalyl chloride, DMF (cat.), benzene, reflux, 12 h (91%). b) DMAP, CH_2Cl_2, RT, 12 h (*S*: 24%, *R*: 4%). c) KO*t*Bu, H_2O (approx. 6 equiv.), THF, RT, 12 h (quant.). d) H_2, Pd/C, THF, RT, 36 h ((*S*)-**2c**: quant., (*R*)-**2c**: 4%, (*R*)-**S8**: 36%).

then separately subjected to hydrolysis by using anhydrous potassium hydroxide and the absolute axial configuration of the resulting diphenic acids, (*S*)-**4a** and (*R*)-**4a**, was unambiguously determined by VCD measurements (for VCD spectra of the two enantiomers, see the Supporting Information, Figure S2). The two compounds, (*S*)-**2d** and (*R*)-**2d**, were also finally debenzylated in THF under standard hydrogenolysis conditions to afford compounds (*S*)-**2c** and (*R*)-**2c**, respectively (Scheme 6). Surprisingly, in the case of the *R*-atropoisomer, hydrogenolysis also affected the 4,6-*O*-benzylidene acetal group and the fully deprotected compound **S8** was isolated in 36% yield (see the Supporting Information). The reasons for this dramatic change in reactivity between the two atropoisomers of compound **2d** are unclear, but one could perhaps argue that the *R*-configured 2,3-HHDP biaryl axis imposes a deleterious level of strain in this methyl α-D-glucopyranoside. This developing strain would probably also interfere with the formation of the *R*-configured 2,3-HHDP unit, as can be inferred from the lower yield of compound (*R*)-**2d** compared to that of (*S*)-**2d** (4% versus 24%, Scheme 6). Thus, it is reasonable to suggest that the hydrogenolysis of the benzyl acetal in compound (*R*)-**2d** would then, at least in part, relieve this strain by offering extra conformational flexibility to the glucopyranoside core. The expected debenzylated product, (*R*)-**2c**, was isolated in only 4% yield. Nevertheless, the corresponding amount of material was sufficient to obtain a ^{1}H NMR spectrum of compound (*R*)-**2c** for comparison with that of compound (*S*)-**2c**.

A clear difference between these two diastereoisomers can be observed in the aromatic region of their ^{1}H NMR spectra (Figure 2). The two aromatic protons of the 2,3-HHDP unit appear as sharp singlets in the case of the *S*-atropoisomer, but as slightly downfield-shifted, low-intensity, broad singlets in the case of the *R*-atropoisomer. This

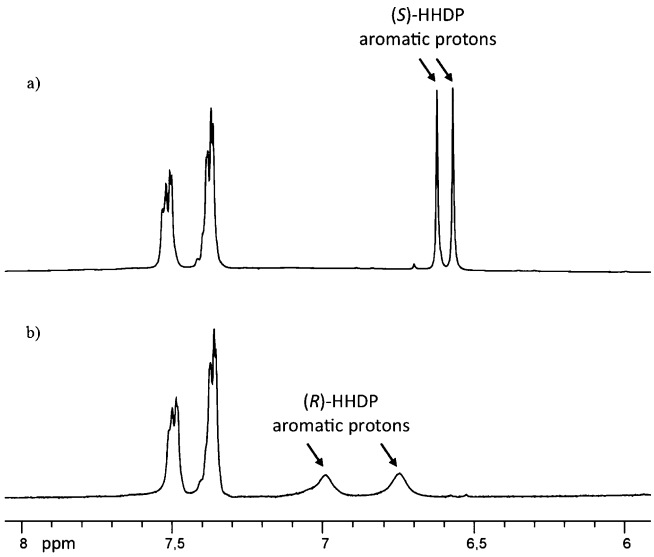
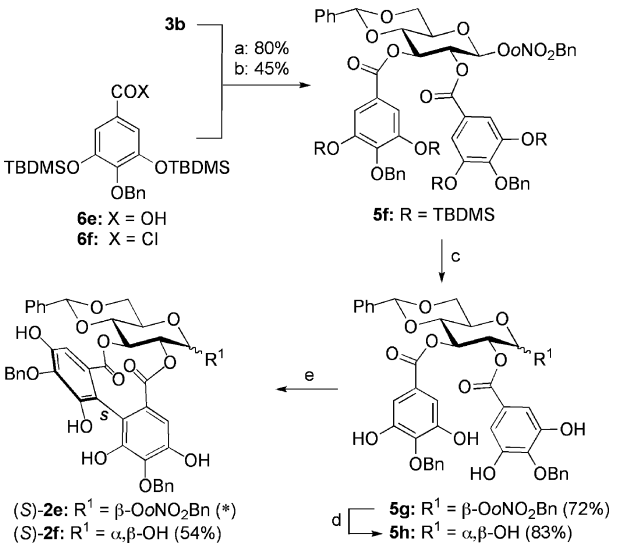


Figure 2. Diagnostic aromatic region of the ^{1}H NMR spectra of atropoisomers (*S*)-**2c** (a) and (*R*)-**2c** (b).

line-broadening attests to the existence of some (ring) strain in this non-natural 2,3-HHDP-coupled product ((*R*)-**2c**). Similarly, sharp singlets were also observed in the aromatic region of compound (*S*)-**2b** for the signals of their 2,3-HHDP units.[18] Therefore, these diagnostic differences in the shape of ^{1}H NMR resonances could likely be relied upon to rapidly determine the configuration of the biaryl axis in 2,3-HHDP-containing compounds without having to perform any chemical degradation.

The NMR spectrum of compound (*S*)-**2c** was identical to that generated by route B, thereby confirming the 2,3-HHDP *S*-configuration of the latter product. Thus, in spite of a relatively low-yielding production of compound (*S*)-**2c** (31%, Scheme 5), the *ortho*-chloranil-mediated oxidative coupling of compound **7c** occurred with the same sense of diastereoselectivity as that followed in the biosynthesis of ellagitannins. Thus, this stereochemical outcome is also in full agreement with the Haslam–Schmidt hypothesis[1d,3g,35] that states that stereocontrol in the coupling reactions of ellagitannin galloyl units is induced by the chirality of the sugar core rather than owing to the action of some stereodirigent oxidase enzymes. To the best of our knowledge, this conversion of compound **7c** into compound (*S*)-**2c** is the first example of intramolecular atroposelective oxidative coupling of galloyl units that was successfully achieved in a protecting-group-free manner.

Unfortunately, this oxidative-coupling methodology was ineffective on both the *ortho*-nitrobenzyl β-D-glucopyranoside (**7b**) and the hemiacetal (**7a**), which only gave rise to intractable mixtures of products. These disappointing results forced us to consider other oxidants, among which more-traditional metal-based reagents that are known for their capacity to promote the coupling reactions of phenolic biaryls, such as iron(III) and copper(II)–amine-complex species, were tried.[36] Various attempts all resulted in either the complete recovery of the starting digalloylated sugars (**7a**–**7c**) or the cleavage of their 4,6-*O*-benzylidene acetal group without any observation of biaryl-coupling products. Thus, we had to resign ourselves to construct the 2,3-HHDP bridge by relying on the use of phenol protecting groups on the galloyl units to direct their reactivity toward the desired coupling transformation. We opted for the methodology that has recently been developed by Yamada and co-workers,[22a,37] which makes use of 4-*O*-benzylgallates that are oxidatively coupled by using copper(II)–amine complexes.[36b] Yamada and co-workers successfully applied this elegant oxidative-phenolic-coupling tactic in the total synthesis of corilagin, a $^1C_4$-glucopyranosic ellagitannin that contains a 3,6-(*R*)-HHDP unit.[22a] Our adaptation of this methodology to the synthesis of 2,3-HHDP-bearing $^4C_1$-glucopyranosic entities began with the preparation of the orthogonally protected gallic acid derivatives (**6e** and **6f**, respectively, 4 and 5 steps from methyl gallate; for details, see the Supporting Information), which were then mounted onto *ortho*-nitrobenzyl β-D-glucopyranoside **3b** to furnish compound **5f**. The highest yield of compound **5f** (80%, Scheme 7) was obtained from compound **6e** under Steglich-type esterification



Scheme 7. Synthesis of 2,3-HHDP-4,6-*O*-benzylidene-D-glucopyranose derivative (*S*)-**2f** by using Yamada's copper(II)–amine-complex methodology (route B). a) Compound **6e**, EDCI, DMAP, CH_2Cl_2, RT, 18 h; b) compound **6f**, DMAP, CH_2Cl_2, RT, 16–22 h; c) TBAF, THF, RT, 2.5 h; d) hν (365 nm), THF/EtOH/H_2O (30:10:1), RT, 36 h; e) $CuCl_2$, *n*$BuNH_2$, MeOH, 45 min. *Incomplete reaction: an inseparable 5:2 mixture of compounds **2e** and **5g** (for details, see the text and the Supporting Information).

conditions by using DMAP and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) in CH_2Cl_2.

After cleavage of the four *tert*-butyldimethylsilyl ether protecting groups, a first attempt at bigalloyl coupling was performed on the resulting compound (**5g**) by using $CuCl_2$ (5 equiv) and *n*-butylamine (20 equiv) in MeOH, according to the experimental conditions reported by Yamada et al.[22a] Monitoring the reaction by ^{1}H NMR spectroscopy indicated partial conversion of compound **5g** into the desired coupling product ((*S*)-**2e**) after 30 min. After this time, a 5:2 mixture of compounds (*S*)-**2e** and **5g** had been generated, but extending the reaction time to 45 min led to extensive degradation of the reaction mixture. We envisaged processing the reaction mixture after only 30 min, but we could not identify appropriate conditions to separate the mixture by column chromatography, because both compounds had the same retention time in all of the solvent systems that we tested. The same oxidative-coupling conditions were then applied to compound **5h**, which was conveniently generated by the photolysis of compound **5g**. We hoped that this removal of the *ortho*-nitrobenzyl group would allow chromatographic separation of the reaction mixture, even though we feared the possible incompatibility of the anomeric hemiacetal group of compound **5h** with the oxidative reaction conditions used. Thus, we were extremely pleased to observe the complete consumption of compound **5h** after only 45 min and to isolate the product (**2f**), once again as the correct *S*-atropoisomer, in 54% yield after rapid flash chromatography of the reaction mixture.

At this stage, we had obtained two advanced intermediates, compounds (*S*)-**2b** (route A) and (*S*)-**2f** (route B), which were ready to be used in the key *C*-arylglucosidation step of our planned synthesis of 5-*O*-desgalloyl-(epi)punicacorteins A (**1α** and/or **1β**).

The biomimetic *C*-arylglucosidation step: This step implies the opening of the glucopyranosyl ring with the concomitant formation of the *C*-arylglucosidic bond. This route from a glucopyranosic system to an open-chain *C*-glucosidic entity had not been previously investigated in the total synthesis of ellagitannins,[18] but a related hemisynthesis precedent was reported in the work of Tanaka et al.[38] They managed to convert pedunculagin into the *C*-glucosidic ellagitannins casuariin and its β-epimer, 5-*O*-desgalloylstachyurin (Scheme 1), in 6% and 34% yield, respectively, by simply heating a solution of pedunculagin in potassium phosphate buffer (pH 7.5) at 70°C. This enlightening precedent gave us the confidence we needed to pursue our objective, because, at first, we were not totally convinced of the preparative feasibility of the intended C–C bond formation during the conversion of compounds (*S*)-**2b** or (*S*)-**2f** into the ultimate intermediates of our planned synthesis (**9a** or **9b**, Scheme 8). Indeed, putting such a synthetic transformation in perspective with what probably occurs in the biosynthetic pathway to *C*-glucosidic ellagitannins underlines the fact that the inconvenience of having to go through transient open-chain aldehyde precursors that are prone to fast re-closing, such as our proposed synthetic intermediates **8a** and **8b**, has perhaps been solved in planta by the mobilization of an even faster 5-*O*-galloyltransferase (Scheme 1 and Scheme 8).

The above concerns notwithstanding, we explored the reaction conditions reported by Tanaka et al., and variations thereof, to treat compounds (*S*)-**2b** and (*S*)-**2f**. In the case of free bipyrogallolic compound (*S*)-**2b**, the close-to-neutral conditions (pH 7.5) were not suitable and consistently provoked significant degradation of the starting material. Fine-tuning of the reaction conditions (pH 5.3, 65°C, 48 h) enabled a partial, yet effective, conversion of compound (*S*)-**2b** into compound **9a** as a 14:1 (β/α) epimeric mixture. Purification of the reaction mixture by preparative reverse-phase HPLC led to the isolation of the major *C*-arylglucoside product (β-**9a**) in 32% yield (the minor α-**9a** epimer could not be isolated), together with a 1:1 anomeric mixture of glucopyranose derivative **10a** (23%, Figure 3), which resulted from hydrolytic cleavage of the benzylidene acetal group of compound (*S*)-**2b**, which was itself recovered in 27% yield. At a slightly higher pH value (i.e., pH 6.4), intensive degradation of compound (*S*)-**2b** occurred, whereas slightly more acidic conditions (i.e., pH 4) systematically led to compound **10a** being the major product. Interestingly, this compound resisted the conditions of *C*-arylglucosidation (see below). Starting with bis-*p*-benzyloxylated compound (*S*)-**2f**, the addition of MeOH was necessary for improved solubility. In a MeOH/phosphate-buffer (pH 5.3) mixture (1:1), the *C*-arylglucosidation reaction was rather ineffective, thereby leading only to a small amount of an epimeric mixture of compound **9b** after 48 h at 65°C. The highest conversion of compound (*S*)-**2f** was observed by increasing the pH value of the phosphate buffer to 7.5. In such a reaction medium, compound (*S*)-**2f** did not suffer from any extensive degradation, as observed for compound (*S*)-**2b** in pure phosphate buffer solvent system (pH 7.5), and led, after only 2.5 h at 65°C, to compound β-**9b**, which was isolated in 25% yield after purification by preparative HPLC. The formation of small amounts of compound α-**9b** was also observed, but again we could not separate this C-1 epimer in a pure state from the reaction mixture.

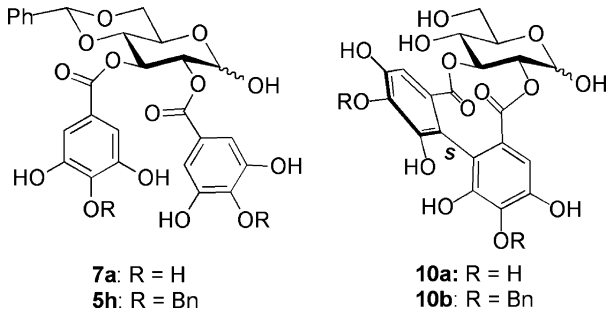
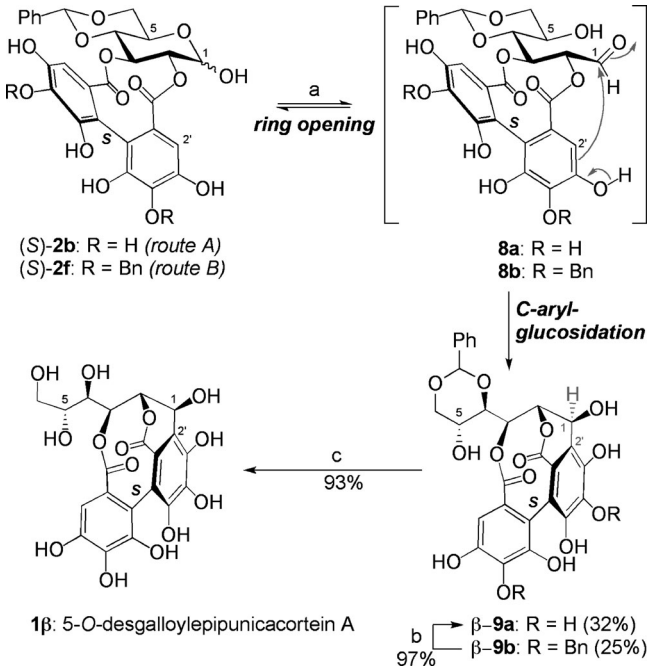


Figure 3. 2-*O*-Galloylated glucopyranosic compounds that could not be converted into *C*-glucosidic species under the biomimetic *C*-arylglucosidation conditions used.



Scheme 8. Completion of the total synthesis of compound **1β**. a) Phosphate buffer (0.2 M), 65°C, pH 5.3 for compound (*S*)-**2b** and 0.2 M phosphate buffer/MeOH (1:1), 65°C, pH 7.5 for compound (*S*)-**2f**; b) H_2, $Pd(OH)_2$/C, THF, RT, 24 h; c) H_2, $Pd(OH)_2$/C, THF, RT, 5 days.

Evidence for the formation of the *C*-arylglucosidic bond was obtained by the observation of a two-bond correlation

between the H-1 and C-2′ atoms in the HMBC NMR data map of either compounds β-**9a** or β-**9b** (see the Supporting Information, Figure S9). In addition, their ^{1}H NMR spectra showed one singlet at $\delta \approx 6.45$ ppm, which integrated to one proton and was assigned to the sole remaining aromatic proton on the C-1-linked HHDP unit. Furthermore, the values of the coupling constants between the H-1, H-2, and H-3 atoms were only about 2–3 Hz, which are characteristic for the open-chain glucose core of *C*-glucosidic ellagitannins. The configuration of the C-1 center for both compounds was deduced from either the value of the coupling constant between the H-1 and H-2 atoms (i.e., 1.7 Hz for β-**9a**, and 2.1 Hz for β-**9b**) or by selective NOE experiments that showed through-space correlations between the H-1 and H-3 atoms (see the Supporting Information). These NMR data and their interpretation are in accordance with the results of Nishioka and co-workers,[7e] who, after accumulating data on related *C*-glucosidic ellagitannins, concluded that a small coupling constant between the H-1 and H-2 atoms (about 0–2 Hz) is indicative of a β-orientation of the sugar C-1-OH bond, whereas a larger coupling constant (about 5 Hz) indicates an α-orientation of the same bond. Even though we could not purify the α-epimeric products, analysis of the ^{1}H NMR spectra of the crude reaction mixtures clearly indicated H-1/H-2 coupling constants with values that were expected for an α-orientation of their C-1-OH bond (i.e., 4.6 Hz for α-**9a** and 4.7 Hz for α-**9b**; see the Supporting Information).

At this stage, we also conducted additional experiments on some of our synthetic intermediates and by-products to further examine the structural requirements of the *C*-arylglucosidation reaction with regards to the hypotheses on the biosynthesis of *C*-glucosidic ellagitannins (Scheme 1). In particular, similar *C*-arylglucosidation reactions on non-coupled intermediates **7a** and **5h**, as well as on coupled compounds (*S*)-**10a** and (*S*)-**10b**, which lacked the 4,6-*O*-benzylidene moiety, were all non-operational (Figure 3). These failures are quite instructive, because they indicate that a free galloyl group at the O-2 position does not seem to be capable of trapping a transient aldehyde function at the C-1 position and that the absence of the cyclic benzylidene protecting group at the O-4/O-6 positions (which can be viewed as a surrogate of the 4,6-HHDP unit in pedunculagin; Scheme 1) still prevents the formation of the *C*-arylglucosidic bond, even though the O-2-galloyl group is part of a 2,3-HHDP unit. All together, these observations suggest that some level of conformational constraint is required for enabling the *C*-arylglucosidation event. In other words, both the 4,6-*O*-benzylidene and the 2,3-HHDP ring systems mutually contribute to maintain the sugar core and the O-2-galloyl group in a conformational status that is propitious for the intramolecular *C*-arylglucosidation reaction.

Next, theoretical calculations were performed at the semi-empirical RM1 level by using the simulated annealing method[39,40] to characterize the conformers of transient aldehyde intermediates (*S*)-**8a**, (*S*)-**11**, and **12** that would have presumably been derived from compounds (*S*)-**2b**, (*S*)-**10a**, and **7a**, respectively (Figure 4; for details on these calculations, see the Supporting Information). The results of these calculations provided us with some evidence that both the 4,6-*O*-benzylidene and the 2,3-HHDP ring systems lend support to the establishment of a potentially reactive conformer. A shortest distance of 2.8 Å was found between the pyrogallolic C-2′ and the aldehydic C-1 centers for one of the conformers of compound (*S*)-**8a**. The same distance was also calculated for compound (*S*)-**11**, but for a more transient conformer with a smaller energy gap relative to the lowest-energy conformer (6 kcal mol^{-1} versus 14 kcal mol^{-1} in the case of **8a**). For the 2,3-*O*-bis-galloylated species (**12**), all of its more-flexible conformers exhibited longer distances of between 3.2 and 5.9 Å. Moreover, calculations that were performed on both epimers of *C*-glucosidic product **9a** indicated that the β-epimer was more stable than the α-epimer by about 20 kcal mol^{-1}, which was in accordance with the preferred formation of compounds β-**9a** and β-**9b** over that of their corresponding α-epimers (Scheme 8). However, we could not pinpoint any structural feature that could underlie this preference, neither by comparing the calculated conformers of compounds β-**9a** and α-**9a** with the aim of rationalizing the difference between their thermodynamic stabilities, nor by scrutinizing the positioning of the pyrogallolic C-2′ nucleophilic center with respect to the orientation of the electrophilic carbonyl group at the C-1 position in the conformers of compound (*S*)-**8a** with the aim of rationalizing any difference in the kinetic lability of such an intermediate.

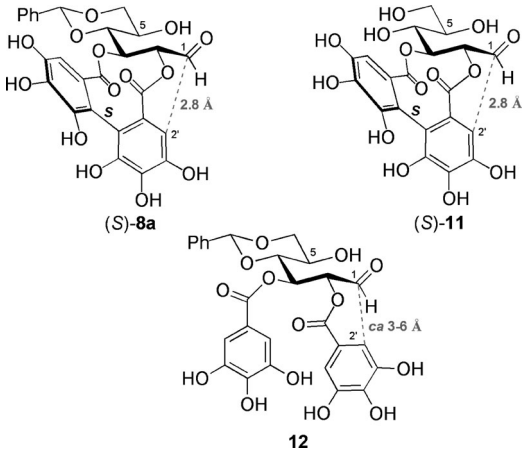


Figure 4. Structures of the presumed aldehyde intermediates (*S*)-**8a**, (*S*)-**11**, and **12**.

Nevertheless, the above experimental and theoretical results are in agreement with the currently held hypothesis on the biosynthesis of *C*-glucosidic ellagitannins that they could all conceivably be derived from a single glucopyranosic ellagitannin precursor that contains HHDP units at both its 2,3- and 4,6-positions, that is, pedunculagin (Scheme 1).[1b,7c,10–12] Numerous plant species do contain *C*-glucosidic ellagitannins, but certain species, such as those of the *Hamamelidae*, *Rosidae*, and *Dilleniidae* subclasses, that are

particularly rich in *C*-glucosidic ellagitannins might have evolved to systematically anabolize these metabolites.[3a] As alluded to above, such plant species would have solved the inconvenience of the fleeting nature of an open-chain aldehyde form of pedunculagin by the action of a 5-*O*-galloyltransferase, as can be inferred from the occurrence of liquidambin in *Liquidambar formosana* (Hamamelidaceae),[11] as well as from the existence of several liquidambin-derived 5-*O*-galloylated and 2,3,5-NHTP-bearing *C*-glucosidic ellagitannins, such as those shown in Scheme 1. Hence, the absence of a 5-galloyl unit, as well as that of a 4,6-HHDP unit, in *C*-glucosidic ellagitannins, such as the epimeric pair **1α**/**1β**, should logically be due to hydrolytic transformations that occur after the *C*-arylglucosidation event.

The total synthesis of 5-*O*-desgalloylepipunicacortein A (**1β**) was completed by hydrogenolysis of either main epimer β-**9a** or β-**9b**. However, this last, supposedly simple step gave us cause for concern because we had to screen many reaction conditions (i.e., the nature of the catalyst, solvent, duration of the reaction, and type of workup/purification procedure) before reaching success. The two ether groups of compound β-**9b** could be efficiently cleaved after 24 h in dry THF under H_2 in the presence of Pearlman's $Pd(OH)_2$/C to furnish β-**9a** in 97% yield. The hydrogenolytic cleavage of the 4,6-*O*-benzylidene group of compound β-**9a** required a much longer reaction time and the daily addition of $Pd(OH)_2$/C for 5 days at room temperature (for details, see the Supporting Information). This procedure furnished compound **1β** as a yellowish amorphous solid in 93% yield (Scheme 8). This material was dissolved in water, passed through a Sephadex LH-20 column, and lyophilized before analysis. The spectroscopic data and the specific rotation of this synthetic compound **1β** ($[\alpha]_D^{25} = -38.9$, $c = 0.18$, MeOH) were in agreement with those reported for the isolated compound ($[\alpha]_D^{22} = -37.5$; $c = 1.0$, MeOH).[14c]

Conclusion

Two strategies have been implemented to open up synthetic accesses to *C*-glucosidic ellagitannins; herein, both were successfully put to use in the first chemical syntheses of a member of this class of natural products: 5-*O*-desgalloylepipunicacortein A (**1β**). This ellagitannin was synthesized by route A in 4 steps with an overall yield of 10% from glucoside **3a** and racemic hexabenzyloxydiphenic acid (**4a**) and by route B in 7 steps with an overall yield of 6% from glucoside **3b** and the protected gallic acid (**6e**). The focal step of both of these syntheses is an intramolecular *C*-arylglucosidation of a reducing glucopyranose derivative into an open-chain *C*-glucosidic system in a manner that parallels the current hypothesis on the biosynthesis of these natural products. The observations that we made and the limitations that we had to face during the implementation of this synthetic step, which exclusively relied on the inherent chemical reactivity of the starting glucopyranosic hemiacetal, shed some light on the structural features and chemical transformations that are likely to be required for the efficient biosynthesis of *C*-glucosidic ellagitannins, and hence on their biogenetic filiation. Therefore, this synthesis work should provide biochemists with useful pointers towards the elucidation of the biogenesis of these unique natural products. Furthermore, we believe that these syntheses of 5-*O*-desgalloylepipunicacortein A (**1β**) represent an important step toward the chemical preparations of other *C*-glucosidic ellagitannins because extensions of this work should lead to the total synthesis of more-complex NHTP-bearing members of this class of plant polyphenols, such as vescalin and vescalagin.

Acknowledgements

This work was financially supported by the Agence Nationale de la Recherche (ANR-06-BLAN-0139, project EllagInnov). We also thank the French Ministry of Research, as well as Università Italo-Francese and the Italian Ministry of Education and Research (PRIN, Grant No.: 20082L3NFT-003) for research assistantships to G.M. and A.N., respectively. We also thank the CDCH-Universidad Central de Venezuela for having enabled our colleague Prof. Jaime Charris to join our group during the academic year 2006–2007.

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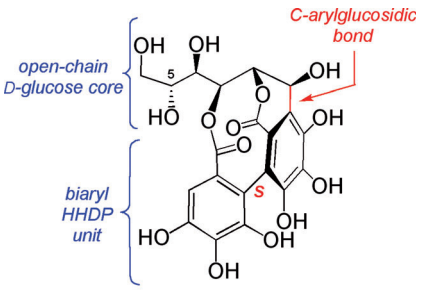
Received: February 16, 2012
Published online: ■■ ■■, 0000

A route to *C*-glucosidic ellagitannins was exemplified by the synthesis of 5-*O*-desgalloylepipunicacortein A (see structure). The hexahydroxydiphenoyl unit of the natural product was either derived from ellagic acid or built atroposelectively. The key step was a biomimetic ring-opening *C*-arylglucosidation.



5-*O*-desgalloylepipunicacortein A

Natural Products

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Synthetic Studies toward *C*-Glucosidic Ellagitannins: A Biomimetic Total Synthesis of 5-*O*-Desgalloylepipunicacortein A