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First and biomimetic total synthesis of a member of the *C*-glucosidic subclass of ellagitannins, 5-*O*-desgalloylepipunicacortein A†

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The first total synthesis of a member of the *C*-glucosidic subclass of ellagitannins, 5-*O*-desgalloylepipunicacortein A, was accomplished by relying on a biomimetic aldol-type formation of its characteristic *C*-aryl glucosidic bond through the exploitation of the inherent chemical reactivity of a glucopyranosic hemiacetal precursor.

Ellagitannins constitute one of the major classes of polyphenolic natural products derived from the secondary metabolism of dicotyledonous plant species of the *Angiospermea*.[1] Nearly 1000 members of this class of so-called hydrolyzable tannins have today been isolated from various plant sources, fully characterized, and shown to exhibit remarkable biological activities related to *inter alia* their antioxidant, antiviral and host-mediated antitumor properties.[1–3] Such a natural molecular diversity is really impressive when one considers that the core structure of all of these metabolites initially relies on the assembly of two simple building blocks, D-glucopyranose and gallic acid (*i.e.*, 3,4,5-trihydroxybenzoic acid). Typical examples of monomeric ellagitannins are the tellimagrandins and pedunculagin, which feature biarylic hexahydroxydiphenoyl (HHDP) ester units at the 2,3- and/or 4,6-positions of their glucopyranose core (Fig. 1). *C*-Aryl glucosidic variants constitute an intriguing subclass of ellagitannins featuring the structural characteristic C–C linkage between the carbon-1 atom of an *open-chain* glucose core and an aromatic carbon of a galloyl-derived unit esterified to the 2-position of the glucose core. This C-1-linked galloyl-derived moiety can be part of a terarylic nonahydroxyterphenoyl (NHTP) unit triply esterified to the 2-, 3- and 5-positions of the glucose core, such as in vescalagin and its C-1 epimer castalagin (Fig. 1). These two ellagitannins are notably found in fagaceous woody plants such as *Quercus* (oak) species[4] and are known to exhibit antiviral and antitumor activities.[5] The C-1-linked galloyl-derived moiety can also be part of a 2,3-HHDP unit such as in simpler structures of the punicacortein A series (**1a–d**, Fig. 1).[6]

Punicacortein A (**1a**) and/or its C-1 epimer **1b** have notably been isolated from the bark of the pomegranate tree (*Punica granatum* L., Lythraceae),[6a] from the leaves of the oak tree species

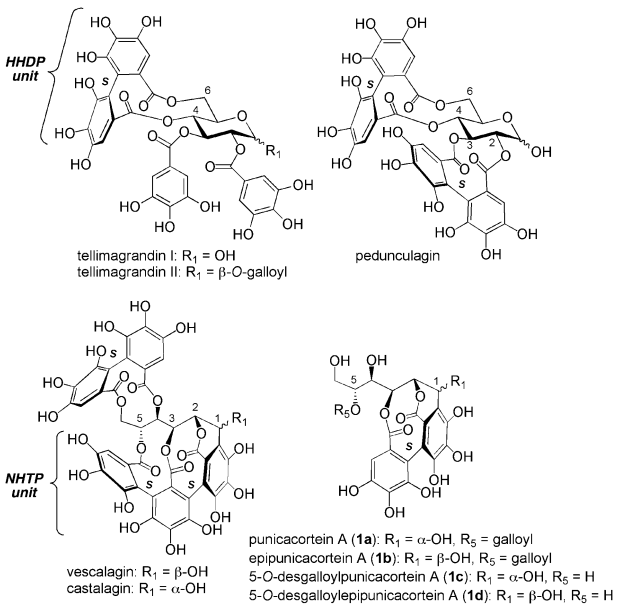

Fig. 1 Structures of tellimagrandins, pedunculagin, vescalagin, castalagin and punicacorteins A (**1a–d**).

Quercus aliena BLUME (Fagaceae),[6c] and from the roots of *Rosa taiwanensis* Nakai (Rosaceae).[6d] The 5-*O*-desgalloylated variant **1c** has been isolated from *Osbeckia chinensis* L. (Melastomataceae)[6b] and **1d** has been biochemically generated from **1b** by the hydrolytic action of a tannase.[6c] It is reasonable to suppose that these *open-chain* *C*-glucosidic ellagitannins have 1-*O*-desgalloylated glucopyranosic precursors, the hemiacetal function of which acts as the trigger for the glucose ring opening. The electrophilic aldehyde function hence unveiled would thus be exposed to an intramolecular aldol-type attack by the phenolic 2,3-HHDP unit that would then result in the formation of the characteristic *C*-glucosidic bond of these ellagitannins (*vide infra*).[2,7]

Several ellagitannins have been successfully synthesized since the pioneering and first total synthesis of tellimagrandin I (Fig. 1) in 1994 by Feldman and co-workers,[8] but a large majority of these ellagitannins belong to the glucopyranosic type.[8,9] No ellagitannin of the *C*-glucosidic type has yet succumbed to total synthesis efforts. We thus decided to embark on such an enterprise with the aim of testing the biosynthetic plausibility of the aforementioned pathway from glucopyranosic to *C*-glucosidic ellagitannins. The 5-*O*-desgalloyl(*epi*)punicacorteins A (**1c** and **1d**, Fig. 1) were selected as targets for this work. Our retrosynthetic analysis of these two epimeric compounds implied the synthesis of the glucopyranosic derivative (*S*)-**3** (Scheme 1). This perbenzylated compound constitutes the immediate precursor of a phenolic

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds along with copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c0cc04007j

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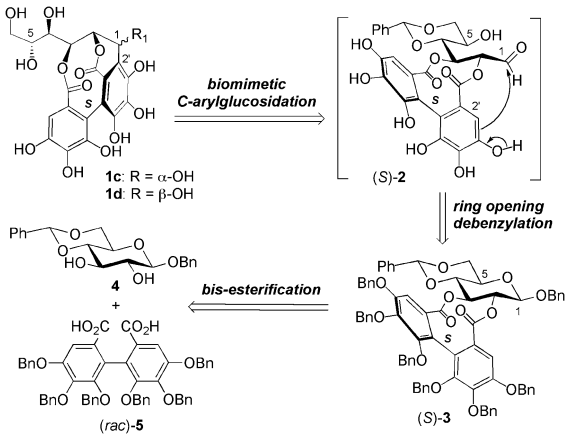
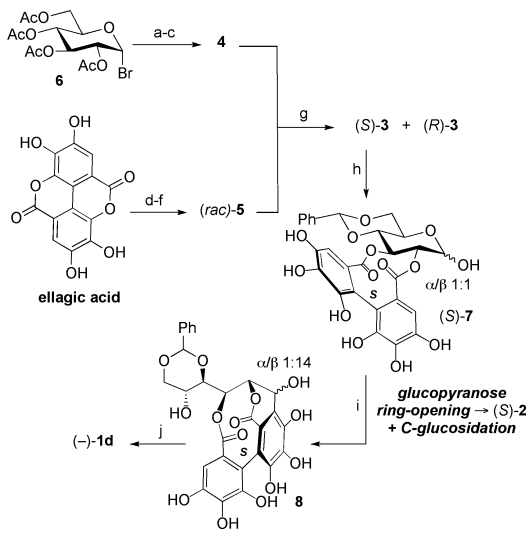


Scheme 1 Retrosynthetic route to 5-*O*-desgalloyl(*epi*)punicacorteins A (**1c** and **1d**).

reducing glucopyranosic entity that should be selectively amenable to the desired intramolecular *C*-aryl glucosidation reaction, simply by taking advantage of its inherent chemical reactivity under conditions allowing its conversion into the transient *open-chain* aldehyde (*S*)-**2** (Scheme 1). We here opted for a rapid access to the benzylated 2,3-(*S*)-HHDP-bearing glucopyranose **3** *via* a bis-esterification reaction between the known β-D-glucose derivative **4**[10] and hexabenzyloxydiphenic acid (**5**, Scheme 1), an approach first introduced by Nelson and Meyers[11] and successfully developed thereafter by the Khanbabaee group in a series of ellagitannin total syntheses.[9b]

Our synthesis thus commenced with the preparation of the known β-D-glucose diol **4**,[10] which was accomplished in an overall yield of 83% from the commercially available bromo-α-D-glucose tetraacetate **6** submitted to a Koenigs-Knorr procedure[12] and manipulation of standard protecting groups (Scheme 2).[13] The racemic hexabenzyloxydiphenic acid (**5**) was prepared in 27% overall yield according to the Schmidt three-step alkaline benzylation of the commercially available and inexpensive ellagic acid bislactone (Scheme 2).[14] The bis-esterification of (*rac*)-**5** with the 1,4,6-*O*-protected glucopyranose **4** was accomplished under Steglich conditions using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). No significant diastereoinduction was observed from the enantiopure sugar **4**, the two diastereoisomers (*S*)-**3** and (*R*)-**3** being obtained in a ratio very close to 1 : 1.[15] Separation by column chromatography on silica gel afforded the desired atropisomer (*S*)-**3** in 35% yield. The pure atropisomer (*S*)-**3** was then submitted to standard palladium-mediated hydrogenolysis conditions in tetrahydrofuran (THF) for 24 h. The 4,6-*O*-benzylidene acetal protecting group resisted these conditions, but the seven benzyl groups were cleaved to furnish the bipyrogallolic sugar derivative **7** quantitatively as a nearly 1 : 1 (α/β) anomeric mixture (Scheme 2). With this reducing sugar in hand, we were ready to explore conditions leading to the opening of the glucopyranose ring with concomitant formation of the characteristic *C*-aryl glucosidic bond of the target epimers **1c/d**.



Scheme 2 Synthesis of 5-*O*-desgalloyl-*epi*-punicacortein A (**1d**): (a) BnOH, Ag_2CO_3, I_2 (cat.), CH_2Cl_2 (92%); (b) NaOMe, MeOH (quant.); (c) PhCHO, $ZnCl_2$ (90%); (d) BnCl, K_2CO_3, NaI, acetophenone, 140 °C (50%); (e) BnCl, KOH, NaI, 145 °C (87%); (f) KOH, acetone/MeOH/H_2O (5 : 5 : 0.3), reflux (63%); (g) DCC, DMAP, CH_2Cl_2 (35% for (*S*)-**3**); (h) H_2, Pd/C, THF (quant.); (i) phosphate buffer solution (0.2 M, pH 5.3), 65 °C (β-**8** isolated in 32%); (j) H_2, $Pd(OH)_2$/C, THF (93%).

To the best of our knowledge, only one relevant precedent of this transformation has been reported by Tanaka and associates, and it concerns the hemisynthetic conversion of pedunculagin (see Fig. 1) into the epimeric pair of *C*-glucosidic ellagitannins, casuariin and its β-epimer 5-*O*-desgalloylstachyurin.[16] Heating the starting glucopyranosic ellagitannin at 70 °C for 2.5 h in an aqueous pH 7.5 phosphate buffer solution afforded casuariin and 5-*O*-desgalloylstachyurin in 6% and 34% yield, respectively.[16] In our case, these conditions were not found suitable and induced the degradation of the starting hemiacetal **7**.

After numerous variations of the reaction parameters (pH, temperature, and duration), a partial yet effective conversion of **7** into the *C*-glucoside **8** as a 14 : 1 (β/α) epimeric mixture was accomplished in a pH 5.3 phosphate buffer solution at 65 °C for 48 h. At a slightly higher pH (*i.e.*, pH 6.4), this conversion was much less efficient, the HPLC profile of the reaction mixture already showing obvious signs of degradation, while slightly more acidic conditions (*i.e.*, pH 4.0) favoured the cleavage of the 4,6-*O*-benzylidene acetal group over the desired *C*-arylglucosidation event (see ESI† for details).

Purification of the pH 5.3 reaction mixture by preparative reverse-phase HPLC led to the isolation of the major *C*-glucoside product, the β-**8** epimer, in 32% yield (Scheme 2, the minor α-**8** epimer was not isolated), together with a nearly 1 : 1 anomeric mixture of the glucopyranose derivative **9** (23% yield, Fig. 2) resulting from the cleavage of the benzylidene acetal group of **7**, and this starting material recovered in 27% yield. Interestingly, the HHDP-bearing glucopyranose **9** could not be converted into **8** upon re-submission to similar reaction conditions, thus unveiling the important role played by the 4,6-*O*-benzylidene acetal unit in helping the formation of the glucosidic C–C bond. The presence of such a cyclic unit

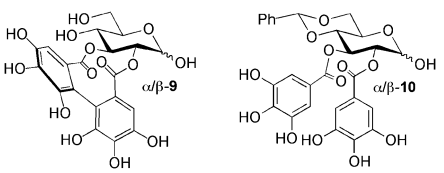


Fig. 2 Structures of the glucopyranosic hemiacetals **9** and **10**.

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probably contributes to maintaining the sugar core in a conformational status propitious for this intramolecular *C*-glucosidation reaction. With the same line of thought, we also submitted the 4,6-*O*-benzylidene-2,3-*O*-digalloylglucopyranose **10** (Fig. 2) to similar reaction conditions, but again, no formation of *C*-glucosidic bond was observed. In this case, we speculate that it is the absence of the conformational constraint otherwise brought by the biarylic 2,3-HHDP unit that seemingly prevented the reaction from occurring.

Thus, the reaction conditions we used to convert **7** into **8** expectedly engaged both anomers of **7** in a chemical equilibrium with their transient *open-chain* aldehydic form **2** (see Schemes 1 and 2). Unfortunately, this equilibrium was deprived of its participants over time because of the hydrolysis of **7** into **9**, hence causing a decrease in the yield of the desired *C*-glucosidic product **8**. Nevertheless, the major *C*-glucoside β-**8** was obtained in a modest but satisfying isolated yield (*i.e.*, 32%) under these conditions, mimicking those that are plausibly operational *in planta* during the genesis of *C*-glucosidic ellagitannins. Our experimental results are indeed in agreement with the current hypothesis on the biosynthesis of *C*-glucosidic ellagitannins that could all be most efficiently derived from a single glucopyranosic ellagitannin precursor bearing conformationally-constraining HHDP units at both its 2,3- and 4,6-positions, *i.e.*, pedunculagin (see Fig. 1).[2,7] Plant species in which these metabolites are often encountered, such as those of the *Hamamelidae*, *Rosidae* and *Dilleniidae* subclasses,[17] might have solved the inconvenience of the fleeting nature of an *open-chain* aldehydic form of pedunculagin by the action of a 5-*O*-galloyltransferase, as can be inferred from the occurrence of *C*-glucosidic ellagitannins bearing a galloyl unit at their 5-position (*e.g.*, see **1a/b** and vescalagin/castalagin in Fig. 1). Hence, the absence of 4,6-HHDP and 5-galloyl units in *C*-glucosidic ellagitannins such as the epimeric pair **1c/1d** could be due to post-*C*-glucosidation hydrolytic events.

Finally, the major *C*-glucoside β-**8** was cleared of its benzylidene moiety upon exposure to hydrogenolysis in the presence of Pearlman's catalyst to furnish 5-*O*-desgalloylepipunicacortein A (**1d**) in 93% yield (Scheme 2). All spectral data and the specific rotation of this synthetic **1d** ($[\alpha]_D^{25} = -38.9$, *c* 0.18, MeOH) coincide with those reported for the isolated compound ($[\alpha]_D^{22} = -37.5$, *c* 1.0, MeOH).[6c]

In summary, 5-*O*-desgalloylepipunicacortein A (**1d**) is the first *C*-glucosidic ellagitannin to be obtained *via* total synthesis, in 10 steps with overall yields of 9% from **6** or 3% from ellagic acid. The key step in this synthesis is the biomimetic formation of the *C*-aryl glucosidic bond that simply relies on an exploitation of the inherent chemical reactivity of a glucopyranosic hemiacetal precursor without resorting to the use of any activating or protecting groups. Moreover, this total synthesis sheds light on the biogenetic filiation of *C*-glucosidic ellagitannins, whose elaboration appears to necessitate the presence of conformationally constraining units at both the 2,3- and 4,6-positions of their sugar core, hence confirming pedunculagin as their most probable and unique glucopyranosic parent. Furthermore, this work represents an important step toward the chemical synthesis of more complex *C*-glucosidic ellagitannins such as the epimeric vescalagin and castalagin.

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