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Bio-inspired Total Synthesis of (–)-Vescalin, A Nonahydroxy-triphenoylated *C*-Glucosidic Ellagitannin

Antoine Richieu, Philippe A. Peixoto, Laurent Pouységu, Denis Deffieux,* and Stéphane Quideau*

In memoriam Professor Takuo Okuda

Abstract: The first total synthesis of the 2,3,5-*O*-(*S*,*R*)-**N**ona**H**ydroxy**T**ri**P**henoylated (**NHTP**) *C*-glucosidic ellagitannin (–)-vescalin was accomplished through a series of transformations mimicking the sequence of events leading to its biogenesis. The key steps of this synthesis encompass a Wittig-mediated ring opening of a glucopyranosic hemiacetal, a *C*-glucosidation event via a phenolic aldol-type reaction, and a Wynberg–Feringa–Yamada-type oxidative phenolic coupling, which forged the **NHTP** unit of (–)-vescalin.

(–)-Vescalin (**1**) is a member of the *C*-glucosidic ellagitannin subclass of gallic acid-derived polyphenolic secondary metabolites[1] that are produced by dicotyledonous plant species of the Angiospermea, and in particular by some of the more highly evolved species belonging to the Rosidae, Hamamelidae and Dilleniidae subclasses.[2] (–)-Vescalin (**1**) was first isolated from *Quercus* (oak) and *Castanea* (chestnut) species of the Fagaceae family (Hamamelidae), together with its α-epimer (+)-castalin (**2**) and their congeners (–)-vescalagin (**3**) and (–)-castalagin (**4**) (Figure 1).[3] The double axially chiral 2,3,5-*O*-nonahydroxytriphenoyl (NHTP) unit, also referred to as the flavogallonyl unit,[1b] is the special structural feature of these ellagitannins, which are otherwise typified by their glucose core in an open-chain form and their *C*-arylglucosidic bond.[1c] Since their first structural characterization fifty years ago by Mayer and his colleagues,[3] the assignment of the configuration of their C-1 center was revised in 1990 by Nishioka and his colleagues,[4a] and the atropisomerism of their terarylic NHTP unit was very recently revised by Tanaka's group (Figure 1).[4b]

Despite the uniqueness of these natural products, albeit occurring in many common plant species, very little is known about their biogenesis, and only hypothetical proposals have been discussed in the literature on the basis of phytochemical observations and isolation of key precursors made by Okuda's group,[5] as well as thoughts and exploration on/of the chemical reactivity of putative intermediates.[6] Accordingly, all of the *C*-glucosidic ellagitannins could derive from the ellagitannin pedunculagin (**5**),[7] whose glucopyranosic ring is subjected to opening in aqueous media (Scheme 1). The resulting free hydroxy group at C-5 would be enzymatically galloylated to generate the open-chain aldehyde liquidambin (**6**), which was isolated by Okuda's group in 1987 from *Liquidambar formosana* of the Hamamelidaceae family (Hamamelidae).[5b] The aldehyde function and the 2,3-*O*-hexahydroxydiphenoyl (HHDP) unit of **6** could then react together in a phenolic aldol-type reaction manner to forge the characteristic *C*-arylglucosidic bond.

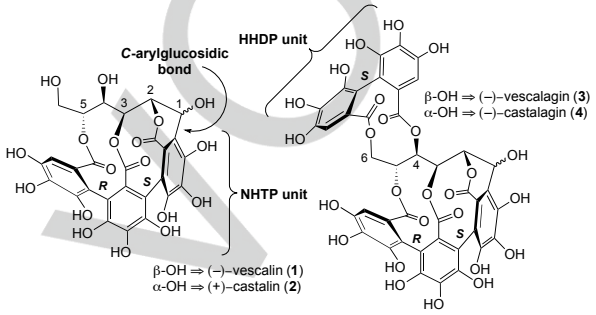
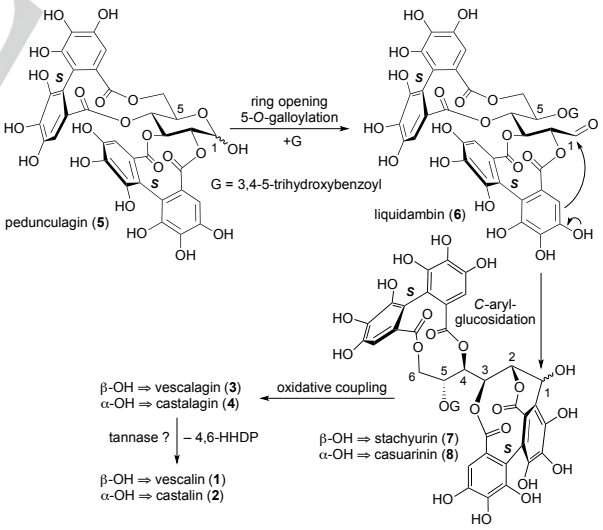


Figure 1. Chemical structures of vescalin (**1**) and its fagaceous congeners.

This chemical event would lead to the formation of the epimeric stachyurin (**7**) and casuarinin (**8**).[4a,7d,8] An enzymatically-induced oxidative coupling between their 5-*O*-galloyl and 2,3-*O*-HHDP groups would furnish vescalagin (**3**) and castalagin (**4**). The 4,6-*O*-HHDP unit of these epimers would be hydrolytically cleaved off, perhaps via the catabolic action of a tannin acyl hydrolase (*i.e.*, tannase),[3a,9] to generate vescalin (**1**) and castalin (**2**) (Scheme 1).



Scheme 1. Putative biosynthetic pathway to vescalin (**1**) and related *C*-glucosidic ellagitannins.

These metabolism considerations had fuelled our earlier work that led to a biomimetic synthesis of a first member of the *C*-glucosidic ellagitannin group, the 2,3-*O*-(*S*)-HHDP-bearing 5-*O*-desgalloylepipunicacortein A (**9**, Scheme 2).[10] This initial success laid some of the groundwork for the next and primary challenge of accomplishing the chemical synthesis of a terarylic NHTP-bearing *C*-glucosidic ellagitannin. Herein, we thus

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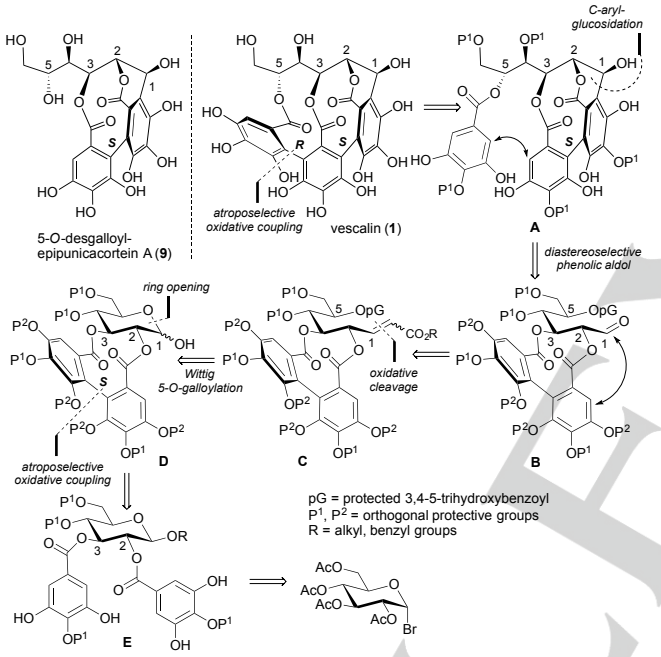
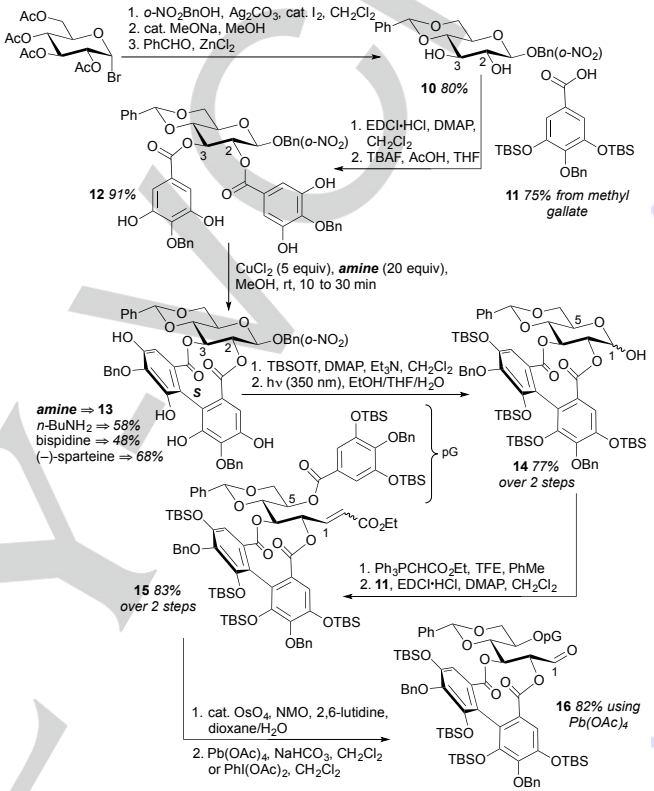
describe the first total synthesis of (–)-vescalin (**1**), which is moreover known for exhibiting valuable biological activities notably as a potent inhibitor of human DNA topoisomerase IIα *in vitro*,[11a,b] and as an anti-actin agent *in cellulo*.[11c] Its natural abundance in fagaceous species is highly variable and rather low (*ca* 0.1-1.5 mg/g of dry oak wood),[12a] although it can be obtained by acidic hydrolysis of vescalagin (**3**),[3a,11a] which is much more abundant (*ca* 10-15 mg/g of dry oak wood, up to > 40 mg/g of dry chestnut wood)[12] and readily extractable in gram-scale quantities.[3a,11a,13] Our main incentive for selecting (–)-vescalin (**1**) as a target of choice for total synthesis work was to elaborate a tactic for the atroposelective construction of its NHTP unit, which constitutes the last remaining major milestone for the chemical synthesis of the series of natural products to which **1** belongs.[10b,14] The added difficulty that we imposed on ourselves was to follow the current biosynthesis hypotheses (Scheme 1) as blueprints to develop a synthesis strategy relying on the same sequence of key chemical events.



Scheme 2. Retrosynthetic analysis of vescalin (**1**).

Our retrosynthetic analysis depicts this strategy (Scheme 2), for which the focal oxidative coupling step leading to the intramolecular formation of the nonahydroxyteraryl unit is planned at a very late stage of the synthesis and with a control of the desired atroposelectivity solely relying on the chirality of the substrate. This substrate (**A**), which will have to be appropriately protected for the success of the intended oxidative phenolic coupling, features the characteristic *C*-arylglucosidic bond. This bond will be forged from an aldehydic liquidambin analogue **B** through a biomimetic phenolic aldol-type reaction. This key aldehyde will be obtained by oxidative cleavage of an olefinic ester **C**, which will be generated by a classical Wittig reaction on a glucopyranosic hemiacetal **D**, followed by a 5-*O*-galloylation. The 2,3-*O*-(*S*)-HHDP-bearing glucopyranose **D** could be generated from a 2,3-*O*-digalloylated precursor **E**, itself prepared from tetra-*O*-acetyl-α-D-glucopyranosyl bromide (Scheme 2). Thus, our synthesis began with the 3-step conversion of this commercial glucopyranosyl bromide into the *ortho*-nitrobenzyl 4,6-*O*-benzylidene-β-D-glucopyranoside **10** (Scheme 3), which was bisacylated with the orthogonally protected gallic acid **11**, as previously described (see the Supporting Information).[10b] The Steglich-type bisacylation was followed by a TBAF-mediated desilylation to afford the **E**-type 2,3-*O*-digalloylated glucopyranoside **12** in 91% yield from **10**.



Scheme 3. Synthesis of a liquidambin-like precursor of vescalin (**1**).

The reason why we opted for *para*-benzylated galloyl groups is because this partial protection enables to direct the reactivity of galloyl groups toward the desired oxidative coupling using copper(II)-amine complexes under anaerobic conditions, as per the recommendation of Feringa and Wynberg.[15] The intramolecular oxidative coupling of *para*-benzylated galloyl groups was first implemented under such conditions by Yamada and his co-workers, who successfully applied it in the total synthesis of several glucopyranosic HHDP-bearing ellagitannins.[16] We also relied on the same method to forge a **D**-type 2,3-*O*-(*S*)-HHDP-bearing intermediate in the synthesis of the *C*-glucosidic ellagitannin **9**.[10b] Here, **12** was initially treated with $CuCl_2$ and a large excess of *n*-$BuNH_2$ in freshly distilled MeOH at room temperature for 30 min to furnish the desired (*S*)-biaryl **13** as the sole atropisomer in 58% isolated yield (see Table S1 in the Supporting Information). Its silylation had to be performed using excesses of TBSOTf (10 equiv) and Et_3N (20 equiv) in the presence of DMAP (1 equiv) in refluxing CH_2Cl_2 for 6 h to afford the desired tetrasilylated product, which was then irradiated at 350 nm for 48 h to furnish the **D**-type glucopyranose **14** in 77% yield over these two steps. Unlike the synthesis of **9**,

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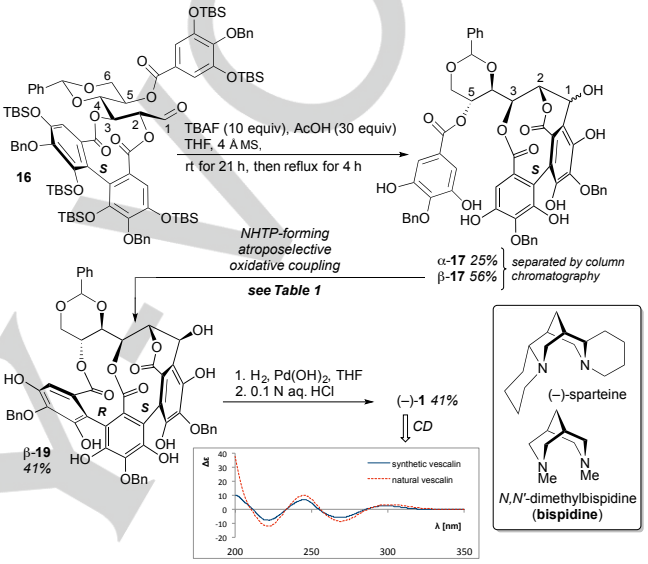
for which the opening of analogous **D**-type glucopyranoses was a transient transformation during the formation of the *C*-arylglucosidic bond,[10b] this synthesis of **1** required access to an open-chain glucose derivative that could be sequentially amenable to the 5-*O*-galloylation and *C*-arylglucosidation events (Scheme 2). We opted for a Wittig olefination to force the opening of the glucopyranose ring, which is a tactic that was successfully employed by Yamada's group for the passage from $^4C_1$ to $^1C_4$ conformations of glucopyranosic intermediates in their synthesis of the ellagitannin corilagin.[16a,17] Thus, after a few experimentations (see Table S2 in the Supporting Information), the use of the conjugated phosphorane PPh_3CHCO_2Et in the presence of trifluoroethanol (TFE, 2 equiv) in anhydrous toluene (Vilarrasa's conditions)[18a] was found to efficiently promote the conversion of the cyclic hemiacetal **14** into the expected open-chain olefinic ester (*E*/*Z* = 8:2*)*, which was 5-*O*-galloylated using **11** under Steglich-type conditions to furnish the **C**-type olefinic ester **15** in 83% yield from **14**. An osmium-catalyzed dihydroxylation[17,18b,c] of the olefin (*E*)-**15**, followed by an oxidative cleavage of the resulting diol using either $Pb(OAc)_4$ or $PhI(OAc)_2$,[18c] were then performed to afford the **B**-type liquidambin-like vescalin precursor **16** in 82% *vs* 62% yield from **15** (Scheme 3, see details in the Supporting Information).

This precursor **16** resembles liquidambin (**6**, Scheme 1) in several structural criteria, including the C-1 aldehyde function, the 5-*O*-galloyl group and the 2,3-*O*-(*S*)-HHDP unit, which are both adequately protected in anticipation of the *C*-glucosidation step (*i.e.*, with fluoride-labile silyl groups in *meta*-positions) and the NHTP-forming terarylation step (*i.e.*, with benzyl groups in *para*-positions as per Yamada's method). Moreover, the cyclic benzylidene protecting group is a useful surrogate of the 4,6-*O*-HHDP unit of liquidambin, which should contribute to maintain the open-chain glucose core and the 2,3-*O*-HHDP unit of **16** in an appropriate conformational status for facilitating the intramolecular *C*-arylglucosidation reaction. This crucial role played by this cyclic protecting group was previously evidenced in the context of the synthesis of **9**.[10b] Hence, we had surmised that the desired *C*-arylglucosidation could here be achieved during the desilylation of **16**, as long as anhydrous yet acidic conditions could be imposed to the reaction medium. Such conditions should prevent any adventitious hydrolytic release of the 4,6-*O*-benzylidene group, while possibly offering a proton-mediated electrophilic assistance for the nucleophilic addition to the C-1 aldehyde function. This was successfully accomplished by treating **16** with TBAF (10 equiv) in the presence of acetic acid (30 equiv) and molecular sieves in anhydrous THF (Scheme 4, see Table S3 in the Supporting Information). The resulting **A**-type benzylic alcohol **17** was thus generated as a 1:2 α/β epimeric mixture, which was separated by column chromatography to furnish α-**17** and β-**17** in 25% and 56% yields, respectively. With the major epimer β-**17** in hands, we were thus ready to take on the focal and last C–C bond-forming step toward (–)-**1**, as per the Wynberg–Feringa–Yamada oxidative coupling approach (Table 1).[15,16] Initial attempts under standard Yamada's conditions in MeOH[16e] led to an undesired *n*-butylamino-containing oxidized derivative **18** (not shown, see the Supporting Information), the yield of which increased from *ca* 15% to 49% upon changing the solvent to MeCN (Entries 1 & 2). The use of the bidentate tetramethylethylenediamine (TMEDA) in MeOH provoked full degradation of the material (Entry 3). After trying several other amines without any success, we ended up using the natural tetracyclic diamine (–)-sparteine, well-known for its copper(II)-chelating properties[19a,b] and previously used for coupling naphthols into binaphthyls,[19c,d] and we were gratified by the observation of the atroposelective formation of the desired product β-**19** (Scheme 4) in 17% yield (Entry 4). Increasing the amount of $CuCl_2$ to 5 equivalents and of (–)-sparteine to 20 equivalents accelerated the reaction and increased the yield of β-**19** to 27% (Entry 5). This compound was the only isolatable NHTP-bearing product.



Scheme 4. Conversion of the liquidambin-like precursor **16** into vescalin (**1**).

Table 1. NHTP-forming atroposelective oxidative coupling.

Entry	$CuCl_2$ equiv	Amine (equiv)	Conditions:[a] rt, solvent, time	**18** %[b]	β-**19** %[b]
1	2	*n*-$BuNH_2$ (30)	MeOH, 30 min	15	0
2	2	*n*-$BuNH_2$ (30)	MeCN, 30 min	49	0
3	2.5	TMEDA (10)	MeOH, 60 min	0	0
4	2.5	(–)-sparteine (10)	MeOH, 60 min	0	17
5	5	(–)-sparteine (20)	MeOH, 10 min	0	27
6	5	**bispidine** (20)	MeOH, 15 min	0	41

[a] 10 mg scale, [β-**17**] = 5-10 mM. [b] isolated yields.

Although these results were encouraging, we were nevertheless convinced that the use of such a chiral alkaloid has no influence on the atroposelectivity of the reaction, which is essentially induced by the asymmetry of the glucosidic substrate. However, we surmised that the 3,7-diazabicyclo[3.3.1]nonane scaffold of sparteine must play an advantageous role as a copper(II)-

chelating inductor[19] of the intramolecular C–C bond formation. Thus, we performed this oxidative phenolic coupling reaction using the simpler and achiral sparteine analogue *N*,*N'*-dimethylbispidine,[20] which also rapidly led to the formation of β-**19**, isolated in 41% yield (Entry 6), together with *ca* 17% of recovered starting β-**17**. Longer reaction times caused degradation of these materials, likely through methanolysis and overoxidation. The capacity of both this bispidine and (–)-sparteine to induce the intramolecular coupling of the digalloylated glucopyranoside **12** into **13** (Scheme 3) was then also verified. In this case, (–)-sparteine turned out to be more efficient than both the bispidine and *n*-butylamine, affording the biaryl **13** in a significantly increased yield of 68% (Scheme 3).

Finally, a hydrogenolytic debenzylation of β-**19**, followed by a hydrolytic release of the 4,6-*O*-benzylidene group (Scheme 4), gave rise to (–)-vescalin (**1**) in 41% yield, after purification by preparative reverse-phase HPLC, which inevitably occasions some loss of such a polyphenolic material. All characterization criteria, including circular dichroism data, are in agreement with those of natural vescalin,[3,4] hence attesting that the penultimate copper(II)/bispidine-mediated coupling step of this synthesis forged its NHTP unit with the correct atropisomerism.

In summary, we have accomplished the first total synthesis of a NHTP-bearing *C*-glucosidic ellagitannin in 16 steps with an overall yield of *ca* 2% through a route that is closely tailored to the proposed biosynthetic pathway leading to these unique plant polyphenols. Facile adaptations of this work should provide convenient access to both simpler and more complex *C*-glucosidic ellagitannins, such as punicacorteins A, stachyurin/casuarinin, and vescalagin/castalagin.[10]

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Keywords: ellagitannins • natural products • oxidative coupling • plant polyphenols • total synthesis

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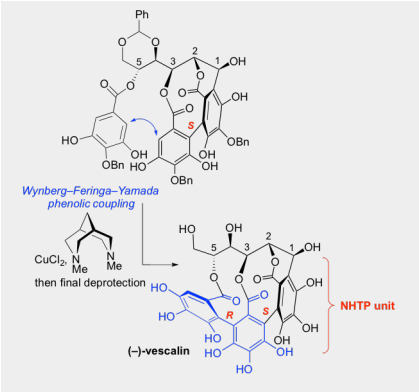
The total synthesis of a first member of the **n**ona**h**ydroxy**t**ri**p**henoylated (**NHTP**) *C*-glucosidic ellagitannins, (–)-vescalin, is described via a route closely tailored to the commonly proposed sequence of events leading to its biogenesis. Its characteristic 2,3,5-(*S*,*R*)-**NHTP** unit was elaborated thanks to a copper(II)-mediated Wynberg–Feringa–Yamada-type phenolic coupling using the achiral bicyclic diamine *N*,*N*'-dimethylbispidine.



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Bio-inspired Total Synthesis of (–)-Vescalin, A Nonahydroxy-triphenoylated *C*-Glucosidic Ellagitannin