Plant Polyphenols

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Gallotannins and Tannic Acid: First Chemical Syntheses and In Vitro Inhibitory Activity on Alzheimer's Amyloid β-Peptide Aggregation**

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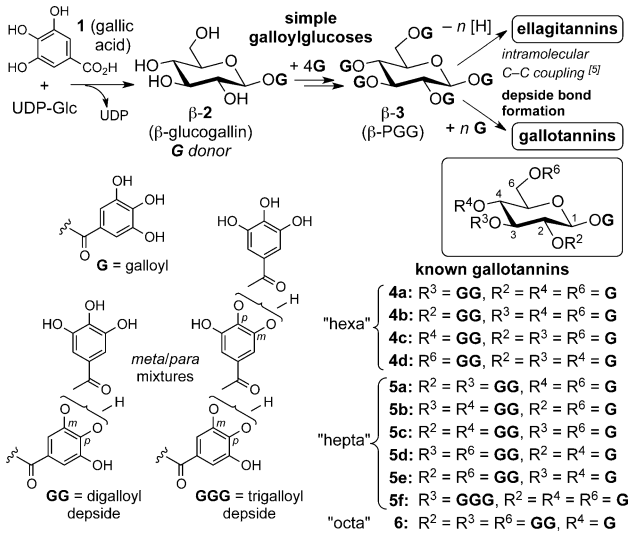
Abstract: *The screening of natural products in the search for new lead compounds against Alzheimer's disease has unveiled several plant polyphenols that are capable of inhibiting the formation of toxic β-amyloid fibrils. Gallic acid based gallotannins are among these polyphenols, but their antifibrillogenic activity has thus far been examined using "tannic acid", a commercial mixture of gallotannins and other galloylated glucopyranoses. The first total syntheses of two true gallotannins, a hexagalloylglucopyranose and a decagalloylated compound whose structure is commonly used to depict "tannic acid", are now described. These depsidic gallotannins and simpler galloylated glucose derivatives all inhibit amyloid β-peptide (Aβ) aggregation in vitro, and monogalloylated α-glucogallin and a natural β-hexagalloylglucose are shown to be the strongest inhibitors.*

Abnormal amyloid β-peptide (Aβ) accumulation and aggregation into toxic fibrils is one of the major processes occurring during the progression of Alzheimer's disease (AD), which today affects approximately 36 million people worldwide.[1a,2] Although the etiology of this severe neurodegenerative disorder, which causes dementia in the elderly, remains unknown,[1b,2] a global effort was initiated in the early 1990s to search for neuroprotective therapeutic agents with antifibrillogenic activity.[1c,d] In this context, natural-product screening programs were implemented with the aim of identifying molecules that are capable of preventing the aggregation and/or promoting the clearance of Aβ.[1c,e] A few recent investigations have focused on plant polyphenols, which are known for their antioxidant activity and their metal-chelation and protein-binding abilities, a set of properties that makes them potentially good candidates as multifunctional drugs for the treatment of AD and other fibrillogenic neurodegenerative disorders, such as Parkinson's and Huntington's diseases.[1c,e,3] Curcuminoids, such as curcumin itself, stilbenoids, such as resveratrol, and flavonoids, such as myricetin and epigallocatechin gallate (EGCg), all belong to a select group of plant polyphenols that have been identified as inhibitors of Aβ aggregation, mainly in vitro.[1c,4] Gallic acid based polyphenols, such as the gallotannins and ellagitannins (Scheme 1),[3a,5,6a,b] have surprisingly been mostly left aside in these investigations, likely because of the difficulties associated with accessing them in pure form.



Scheme 1. Biosynthesis of gallotannins and ellagitannins and representative examples of fully characterized isolated or enzymatically prepared gallotannins. UDP = uridine-5′-diphosphate.

Concerning the gallotannins, to the best of our knowledge, investigations have been limited to the evaluation of 1) their ultimate precursor, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (β-PGG, β-**3**; Scheme 1), which was shown to inhibit Aβ fibril formation and to destabilize pre-formed Aβ fibrils in vitro and in vivo,[7a] and 2) commercial tannic acid (TA), which was reported to destabilize Aβ fibrils in vitro.[7b] TA is the sole available standard that is commonly but inappropriately used to assess the (biological) properties of gallotannins.[8,9a] It is usually depicted as the *meta*-depsidic 1,2,3,4,6-

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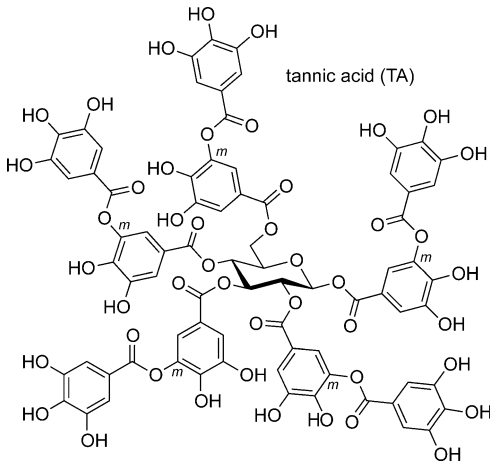
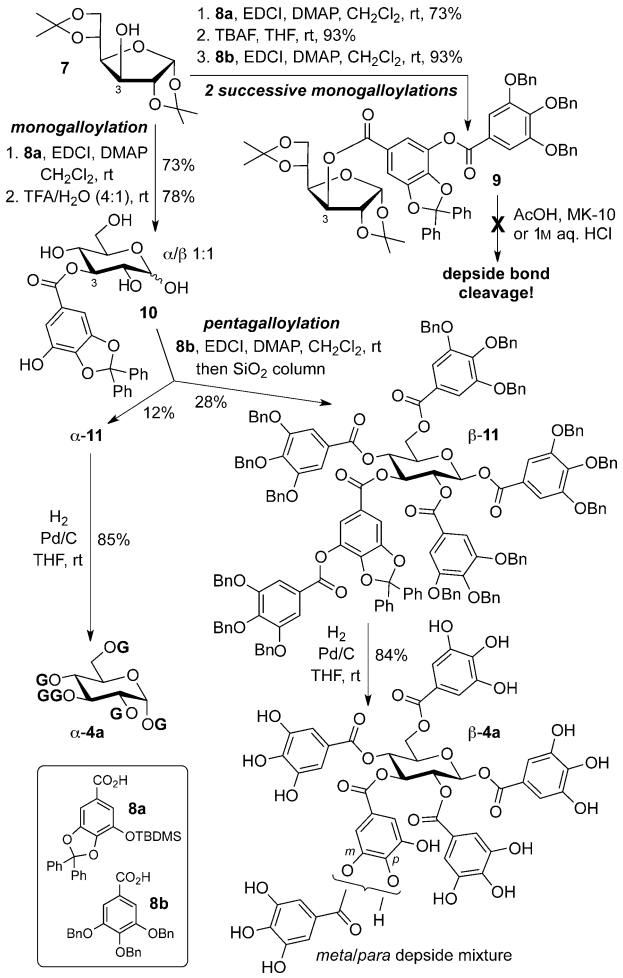


Figure 1. Structural representation commonly used to depict tannic acid (TA).

pentakis-*O*-digalloyl-β-D-glucopyranose shown in Figure 1, although commercial TA is in fact a complex and varying mixture of different gallotannins and simpler galloylglucoses.[9a,b]

These literature precedents, along with our interest in the chemistry and the biological activities of plant polyphenols,[3a,5a–c] led us to consider the chemical synthesis of gallotannins and to evaluate them as inhibitors of Aβ aggregation in vitro. True gallotannins are derived from β-**3** by additional galloylation(s), and are hence characterized by the presence of one or more depsidically linked (short) polygalloyl chains (Scheme 1). Natural hexa- to octagalloylglucoses (i.e., **4a**–**4d**, **5a**–**5f**, and **6**) were isolated from the galls of *Rhus semialata* (Chinese gall) or *Quercus infectoria* (Turkish gall) in the 1980s.[6c–e] Their characterization led to the determination of the on-glucose positions of the di- and trigalloyl chains, which equilibrate into *meta/para*-depsidic mixtures in solution.[6a,b,e] Enzymatic syntheses of some hexa- and heptagalloylglucoses from β-**3** have been described,[6a,b] but a chemical synthesis of naturally occurring gallotannins has not been reported thus far. We herein report the first total chemical syntheses of two gallotannins, namely hexagalloylglucose **4a** and decagalloylglucose **14** (TA), in both anomeric forms.

We first focused our efforts on the synthesis of the two anomers of hexagalloylglucose **4a**, namely the 3-*O*-digalloyl-1,2,4,6-tetra-*O*-galloyl-D-glucopyranoses α-**4a** and β-**4a**. Our initial approach was based on the preliminary construction of a fully protected *meta*-depsidic digallic acid, followed by its installation on the free O3 alcohol of a glucose unit. A methyl digallate derivative could be easily prepared, but its clean saponification into the desired digallic acid could not be achieved without affecting its depside bond (see the Supporting Information). We thus envisaged the elaboration of the digalloyl depside directly on the glucose core, using the known and differently protected gallic acids **8a** and **8b**[9a,c,d] in two successive galloylations (Scheme 2). Commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) was selected as the starting material to introduce the first galloyl moiety at the O3 position of the glucose unit. The reaction of **7** with



Scheme 2. Synthesis of the hexagalloylglucoses α-**4a** and β-**4a**. Bn = benzyl, DMAP = *N*,*N*-dimethyl-4-aminopyridine, EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, MK-10 = montmorillonite K-10, TBAF = tetrabutylammonium fluoride, TBDMS = *tert*-butyldimethylsilyl.

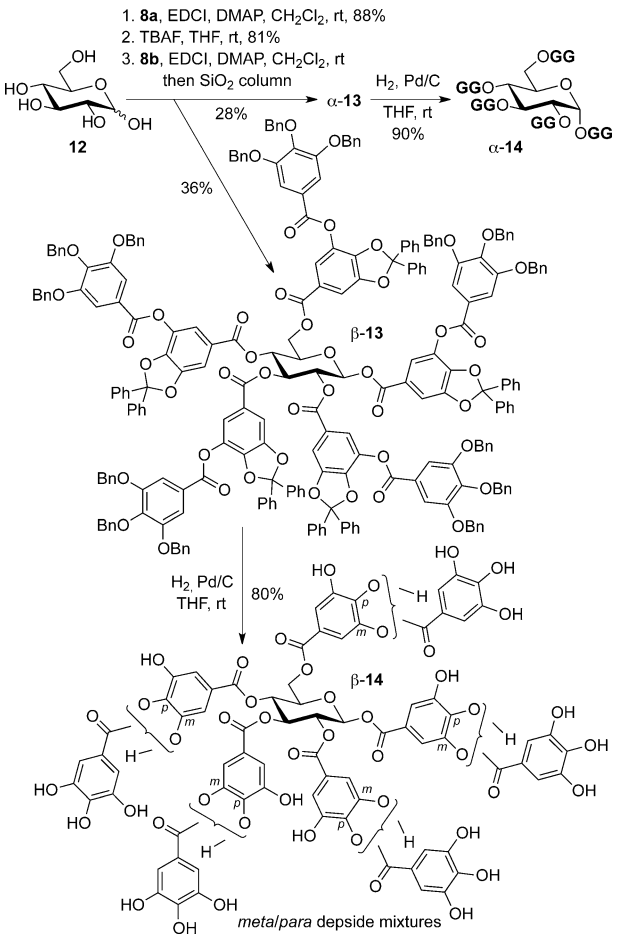
O-silyl gallic acid **8a**[9c] under mild non-acidic Steglich-type conditions gave the corresponding 3-*O*-galloylated D-glucofuranose in 73% yield (Scheme 2). A TBAF-mediated desilylation, followed by a second galloylation reaction, this time using tribenzylated gallic acid **8b**,[9d] afforded the protected *meta*-depsidic digalloylglucofuranose **9**. Unfortunately, this entity did not survive the acidic conditions required to remove the isopropylidene acetals (see the Supporting Information). Gratifyingly, a simultaneous desilylation/deacetalization reaction of the former 3-*O*-galloylated D-glucofuranose made from **7** using aqueous trifluoroacetic acid (TFA) directly afforded the desired 3-*O*-galloylated reducing D-glucose, which then mutarotates to give its most thermodynamically favored glucopyranosic form **10**. This compound was then engaged in a pentagalloylation reaction with **8b** (Scheme 2). Careful separation by column chromatography enabled us to isolate the fully protected hexagalloyl-D-glucopyranoses α-**11** and β-**11** in 12 and 28% yield, respectively. Attempts to improve the yield of this pentagalloylation step, either by heating the reaction mixture

in CH_2Cl_2 at reflux or by employing microwave-assisted acylation conditions, led to the degradation of **10** and/or **11**. Nevertheless, the two anomers of hexagalloylglucose **11** could be individually subjected to a final hydrogenolysis of their diphenylmethylene ketal and fifteen benzyl ethers under classical palladium-mediated conditions in THF at room temperature for 24 hours. The hexagalloyl-D-glucopyranoses α-**4a** and β-**4a** were thus obtained in good yields (ca. 85% each, 100 mg scale).

The NMR spectral data of these hexagalloylglucoses were successfully compared with those previously reported for isolated and enzymatically prepared β-**4a**.[6b,c,e] Most notably, ^{13}C NMR analysis of our synthetic β-**4a** in [D_6]acetone/D_2O (9:1) showed that the C3 carbon of the glucose resonates at lower field ($\delta = +1.6$ ppm) than that of β-**3**, which is indicative of the presence of the digalloyl motif on the C3 position of the sugar.[6c,e] Seven carbonyl carbon signals were detected, five of which were assigned by HMBC NMR experiments to the five galloyl carbonyl groups esterified to the glucose core, and the other two signals were attributed to the galloyl carbonyl groups esterified to the O3 galloyl unit of the digalloyl depside, which is in *meta*/*para* equilibrium in [D_6]acetone/D_2O. To confirm the operational effectiveness of this equilibrium, which results from an intramolecular transesterification,[6e,10] we prepared the *meta*- and *para*-depsidic variants of 3-*O*-digalloyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **22** (see the Supporting Information). Both *meta*- and *para*-**22** quickly equilibrated in [D_6]acetone in the course of their ^{13}C NMR analysis, which afforded identical spectra of the *meta*/*para*-depside mixtures.

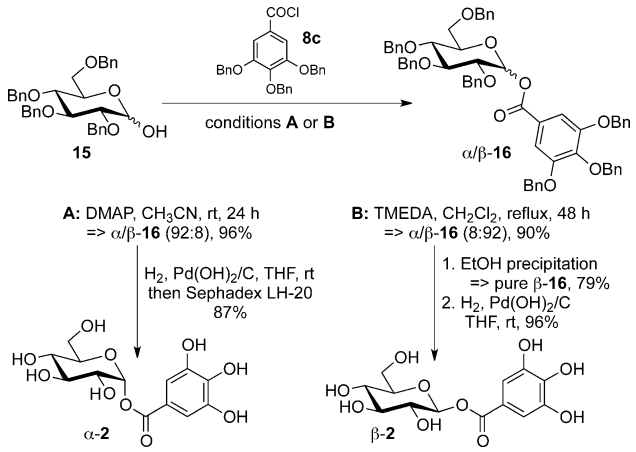
We next moved to the synthesis of the decagalloylglucoses **14**, whose elaboration requires the challenging simultaneous installation of five digalloyl depsides. The pergalloylation of commercial D-glucose (**12**) with **8a** was successfully performed in 88% yield (Scheme 3). A TBAF-mediated desilylation afforded a PGG analogue bearing one free phenolic *meta*-hydroxy group on each of the five galloyl moieties. This compound was next engaged in a second pentagalloylation step, this time using **8b**, to give a 1:1 α/β mixture of the fully protected decagalloylglucose **13** (Scheme 3). Careful separation by column chromatography led to α-**13** and β-**13** in relatively good yields (28 and 36%, respectively). The removal of their five diphenylmethylene ketal and fifteen benzyl ether groups again occurred smoothly by hydrogenolysis, thus affording the desired 1,2,3,4,6-pentakis-*O*-digalloyl-D-glucopyranoses α-**14** and β-**14** in high yields and conveniently on a scale of 50–100 mg. As expected, NMR characterization of these compounds, which are present as *meta*/*para*-depsidic mixtures in solution, was difficult. Attempts to visualize the separation of these mixtures by reverse-phase HPLC analysis were unsuccessful, but electrospray ionization (ESI) mass spectrometric analysis of each anomer gave the correct *m*/*z* value of 1724 for the [M+Na^+] species (see the Supporting Information).

With the gallotannins **4a** and **14** in both anomeric forms in hand, we decided to complete the series with simpler galloylglucoses in view of their evaluation as inhibitors of Aβ aggregation. The two anomers of pentagalloylglucose (PGG, α-**3** and β-**3**; see Scheme 1) were readily prepared in



Scheme 3. Synthesis of the decagalloylglucoses α-**14** and β-**14**.

very good yields according to previously reported procedures (see the Supporting information).[9d] The synthesis of the monogalloylglucoses α- and β-glucogallin (α-**2** and β-**2**) from their corresponding hepta-*O*-benzyl precursors **16** required some modifications, as the final $PdCl_2$-based hydrogenolytic debenzylation described in the early 1960s[11a] only led to degradation. We thus reconsidered this synthesis, and first studied the anomeric galloylation of commercial 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**15**; see the Supporting Information). High and reverse anomeric selectivities were obtained under two sets of conditions using 3,4,5-tribenzyloxybenzoyl chloride (**8c**)[9d] as the acylating agent (Scheme 4). After a reaction in the presence of DMAP in MeCN at room temperature for 24 hours (conditions A), **16** was isolated in 96% yield as a 92:8 α/β mixture. Interestingly, this ratio was reversed to 8:92 when **15** was treated with **8c** in the presence of TMEDA in CH_2Cl_2 at reflux for 48 hours (conditions B).[9e] Precipitation of this anomeric mixture (90% yield) using EtOH afforded pure β-**16** in 79% yield. Debenzylation of the 92:8 α/β mixture of **16** by hydrogenolysis using Pearlman's catalyst in THF, followed by gel filtration chromatography on Sephadex LH-20, afforded pure α-**2** in 87% yield. Pure β-**16** was also similarly debenzylated to give β-**2** in 96% yield (Scheme 4), typically on scales of 100 to 500 mg. This two-step synthesis of β-glucogallin constitutes a facile alternative to



Scheme 4. Synthesis of α- and β-glucogallin (α-**2** and β-**2**). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

both its extraction from plant materials and its synthesis according to previously reported, but cumbersome procedures.[11]

All of these synthetic (poly)galloylglucoses, together with commercially available gallic acid (**1**), the methyl and ethyl gallates, and tannic acid (TA, Sigma–Aldrich No. 16201), were then screened as inhibitors of the aggregation of the Aβ(25–35) fragment,[12] in an in vitro UV-based routine assay[4b,h] using curcumin as a reference (see Table 1 and the Supporting Information). EtOH was preferred over MeOH for the preparation of stock solutions to prevent the methanolysis of the depsidic gallotannins,[9b] whose structural integrity was confirmed by reverse-phase HPLC analysis and detection at 280 nm during the assay (see the Supporting Information). Almost all of the tested compounds exhibited inhibitory activities at least close to or equal to that of curcumin (51%). The previously tested[7] β-PGG (β-**3**) and commercial TA gave the lowest inhibition percentages, and the decagalloylglucoses **14** were hardly more effective than curcumin. Most remarkably, the strongest inhibitions were observed with non-natural α-glucogallin (α-**2**) and the natural hexagalloylglucose β-**4a** (73 and 86%, respectively). Interestingly, hexagalloylglucoses are the most abundant gallotannins (ca. 22%) in commercial tannic acid, which does not appear to contain any decagalloylated variants, at least in detectable amounts.[9a] Moreover, significant inhibition was also observed with **1** and the simple gallates, thus indicating that the pyrogallol motif itself is likely to be the key pharmacophore in this inhibitory action. The effects of α-**2** and β-**4a** were then confirmed with the full Aβ(1–42) peptide, with aggregation inhibition values of 59 and 52% (Table 1).

Table 1: Inhibition of amyloid β-peptide fibrillization.

Entry	Compound[a]	Inhibition[b] [%]	
		Aβ(25–35)	Aβ(1–42)
1	curcumin	**51 ± 12**	**49 ± 9**
2	gallic acid (**1**)	67 ± 8	–
3	methyl gallate	61 ± 11	–
4	ethyl gallate	61 ± 6	–
5	α-glucogallin (α-**2**)	**73 ± 13**	**59 ± 6**
6	β-glucogallin (β-**2**)	53 ± 15	–
7	α-pentagalloylglucose (α-**3**)	55 ± 15	–
8	β-pentagalloylglucose (β-**3**)	46 ± 1	–
9	α-hexagalloylglucose (α-**4a**)	69 ± 10	–
10	β-hexagalloylglucose (β-**4a**)	**86 ± 4**	**52 ± 10**
11	α-decagalloylglucose (α-**14**)	54 ± 13	–
12	β-decagalloylglucose (β-**14**)	57 ± 9	–

[a] A solution of each compound in EtOH was added to a buffer solution (pH 7.2) of the amyloid β-peptide, and fibrillization inhibition was monitored by UV spectroscopy at 200 nm (see the Supporting Information for details).[4b,h] [b] Each value is the result of three independent measurements.

The interaction between α-**2** and the Aβ(25–35) fragment was examined by NMR titration in a 30% [D_3]TFE solution to prevent peptide fibrillization.[13a] A qualitative mapping of the residues involved in the interaction indicated that the hydrophobic region of Aβ(25–35) (i.e., from Ala30 to Leu34) was the most disturbed area. An estimation of the dissociation constants from the chemical-shift changes in that region[13b] suggests the establishment of a 2:1 α-**2**/Aβ(25–35) cooperative site complex with K_{d1} and K_{d2} values of 1.2 and 2.1 mM for the first and second equilibria of this complex formation (see the Supporting Information). Moreover, the antifibrillogenic effect of the true natural gallotannin β-**4a** on the full-length Aβ(1–42) peptide was confirmed by visualization using transmission electron microscopy (see the Supporting Information).

In conclusion, we have achieved the first chemical syntheses of both anomers of two true (depsidic) gallotannins, hexagalloylglucose **4a** and decagalloylglucose **14**, whose β-form corresponds to the structure that is commonly but wrongly attributed to commercial tannic acid. Moreover, we have developed a convenient and selective access to both anomers of the monogalloylglucose glucogallin **2**, the β-form of which being the ubiquitous galloyl donor co-substrate in the biosynthetic galloylation of plant metabolites. The in vitro evaluation of these galloylglucoses as inhibitors of Alzheimer's amyloid β-peptide aggregation showed a strong general inhibitory activity, with α-glucogallin (α-**2**) and β-hexagalloylglucose β-**4a** exhibiting the strongest effects. Further studies on the inhibition of Aβ aggregation by other gallic acid based (poly)phenols, including the ellagitannins, are currently in progress.

Keywords: Alzheimer's disease · amyloid β-peptides · glucogallin · polyphenols · tannic acid

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[12] The numbers in brackets refer to the positioning of the amino acid residues in the amyloid β-peptide sequence; (1–42) means the full-length peptide, and (25–35) corresponds to the fragment from the residue at position 25 to that at position 35.

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