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Vers la première synthèse totale d'ellagitannins *C*-arylglucosidiques. Une approche biomimétique.

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(Bando VINCI 2008 cap. III)

The structure, known but not yet accessible by synthesis,
is to the chemist what the unclimbed mountain,
the unchartered sea, the untilled field,
the unreached planet, are to other men.
R.B. Woodward

Wonder is the beginning of all science.
Aristotele, *Metaphysics*, I,2,982b

Nothing great in the world has been accomplished without passion.
F. Hegel

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List of Abbreviations and Acronyms

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Δ	Reflux
Ac	Acetate
anal.	Elemental Analysis
aq.	Aqueous
Ar	Aromatic
Bn	Benzyl
Bu	Butyl
CC_{50}	cytotoxic concentration 50%
TLC	Thin Layer Chromatography
CIMS	Chemical ionization mass spectrometry
COSY	Correlation spectroscopy
cat.	Catalytic
Cq	Quaternary carbon
DCC	*N,N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinon
DEAD	Diethylazodicarboxylate
DHHDP	Dehydrohexahydroxydiphenoyl
DIAD	Diisopropylazodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
DTBS	Di-*tert*-butylsilylene
EC_{50}	Effective concentation 50%
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EIMS	Electronic impact mass spectrometry
eq	Equivalent
ESIMS	Electrospray ionization mass spectrometry
Et	Ethyl
G	Galloyl unit
Hex	Hexyl
HHDP	Hexahydroxydiphenoyl
HMBC	Heteronuclear multiple bond correlation

HMQC	Heteronuclear quantum correlation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared
lit.	Literature
Me	Methyl
Mol. Wt.	Molar weight
MOM	Methoxymethyl
m.p.	Melting point
NHTP	Nonahydroxyterphenoyl
Nu	Nucleophile
MOM	Methoxymethyl
Ph	Phenyl
PIFA	Bis(trifluoroacetoxyiodo)benzene
ppm	Parts per million
Pr	Propyl
quant.	Quantitative
R_f	Retention factor
NMR	Nuclear Magnetic Resonance
ROESY	Rotating frame Overhause effect spectroscopy
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-butyl-dimethylsilyl
TBDPS	*tert*-butyl-diphenylsilyl
Tf	Triflate
THF	Tetrahydrofuran
UV	Ultraviolet

General Introduction

"*No matter how many three-dimensional models of a compound are built, the number of time its connectivities are drawn on paper, or the length of time spent mentally contemplating its structural intricacies, these actions alone can never reveal all the secrets of a molecule. It is the physical act of creation, the process of synthesis, that holds the key unlocking some of these closely guarded and often highly valuable pieces of information. After all, every molecule, just like a person, is unique sum of its individual parts. Its physical characteristics, its personality, if you will, emerge from the specific combination of its atom bonds, and stereocenters; to remove or alter just one of these items would be essentially the same as close friend transforming in a complete stranger*"[1]

K.C. Nicolau

Organic chemistry is a discipline that involves study of structure, properties, composition, reaction and preparation of hydrocarbons and their derivatives.

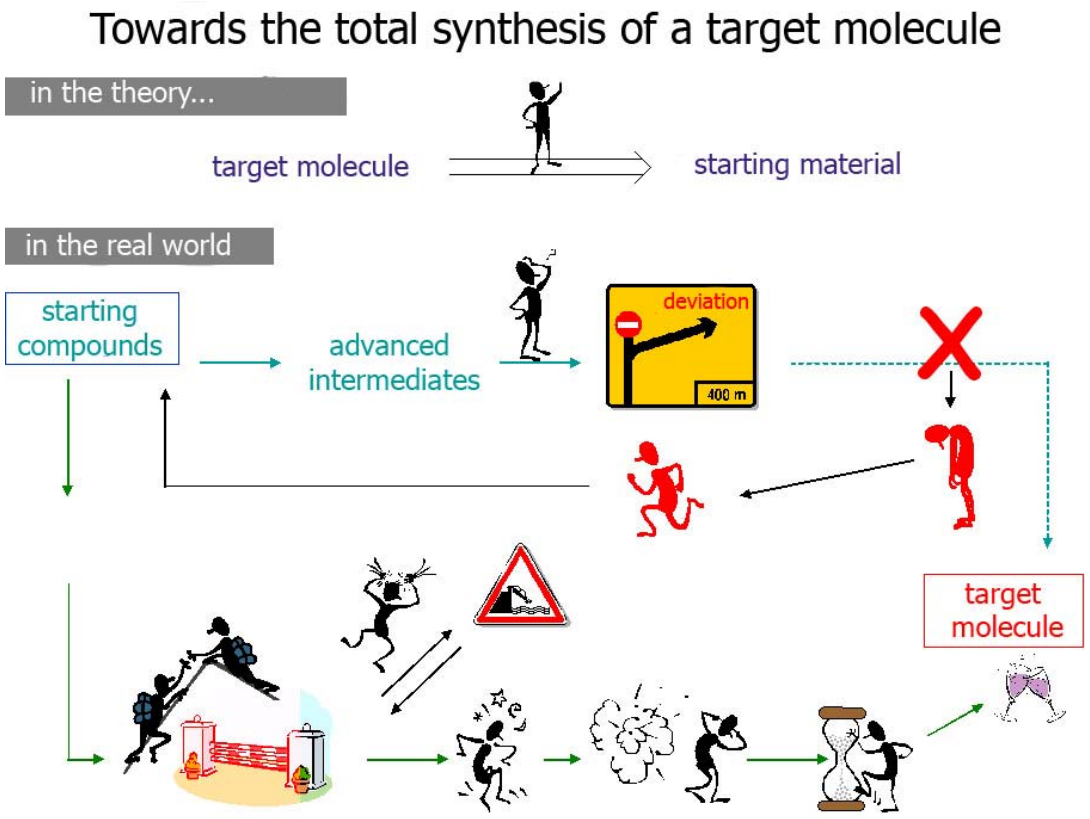
Organic compounds are structurally diverse and their applications are numerous. They are constituents of many products (i.e. paints, plastics, food, explosive, drugs, petrochemicals, to name but a few) and, with very few exceptions, they form the basis of all earthly life processes.

Organic synthesis of a novel compound is a problem solving task, where a synthesis is designed for a target molecule by selecting optimal reactions from optimal starting materials. A chemist that I had the opportunity to met during my Ph.D. compared once the organic chemist to an architect, a molecular architect, who builds molecular complex architectures, starting from simple molecular entities (the bricks) and exploiting their intrinsecal reactivity (the cement).

Complex compounds can have tens of reaction steps that sequentially build the desired molecule.The scientific practice of creating novel synthetic routes for complex molecules is called *total synthesis*.

There are several strategies to design a synthesis. The modern method of retrosynthesis, developed by E. J. Corey,[2] starts with the target molecule and splices it into pieces according to known reactions. The pieces, or proposed precursors, receive the same treatment, until available and ideally inexpensive starting materials are reached. Then, the retrosynthesis is written in the opposite direction to give the synthesis. A "synthetic tree" can be constructed, because each compound and also each precursor has multiple syntheses.

Accomplishing a total synthesis is far to be an easy task. The *défaillances* of the retrosynthetic plain due to an unexpected reactivity are generally – unfortunatly! - not discussed.



But the defeats and difficulties are the main driving forces of this branch of chemistry. The defeats train and stimulate the discovery of new reactions, allow to evaluate the real potential of the available synthetic methodologies, contribute to the evaluation of theoretical hypothesis.

Moreover, since a total synthesis project will often span a variety of reactions, it serves to prepare chemists for pursuit in process chemistry, where knowledge of chemical reactions and a strong and accurate sense of chemical intuition are necessary.

The birth of this multifacet science that is organic synthesis is marked by Wöhler's synthesis of urea in 1828.[3] This milestone even as trivial as it may seem by today contributed to a demystification of Nature. Organic synthesis is considered, to a large extent, to be responsible for some of the most exciting and important discoveries of the twentieth century in chemistry, biology, and medicine, and it continues to fuel the drug discovery and

development process with myriad processes and compounds for new biomedical breakthroughs and applications.

It is in this context that the present thesis work is inserted with the aim to develop an efficient methodology to the synthesis of *C*-arylglucosidic ellagitannins, natural products characterized by interesting chemical and biological properties.

The work herein exposed was carried out from february 2008 to december 2009 at the European Institute of Chemistry and Biology of Bordeaux, under the supervision of Dr. Denis Deffieux and Prof. Stéphane Quideau in the context of a collaboration between the Quideau's research group at the University of Bordeaux I (France) and the research group directed by Prof. Stefano Manfredini at the University of Ferrara (Italy).

In this thesis manuscript, a short historical perspective of ellagitannins isolation from natural sources and total synthesis is briefly discussed in the first chapter. The two following chapters have been focused on the synthetic strategy developed to the preparation of the advanced precursors of *C*-arylglucosidic ellagitannins. The conclusion and perspectives for future studies are discussed in the fourth chapter. Finally the fifth chapter contains the experimental section.

The research project object of this study was winner of a fellowship (Bando Vinci 2008) from the French-Italian University, an institution that favors the scientific exchange between the two countries. Every year, hundreds of projects take part to the selection, and the research poject herein exposed was classified as 3rd.

This PhD work has been object of several scientific communications to international congress:

Oral Communications

- VIII Giornata della Chimica dell'Emilia Romagna, 16 December 2008, Ferrara (Italy)
  Natangelo A., Malik G., Charris J., Deffieux D., Pouysegu L., Manfredini S., Quideau S. "*Towards the total synthesis of C-aryl glycosidic ellagitannins for antitumoral evaluation*" **Prize for the best oral communication.**
- Journée scientifique de l'Institut des Sciences Moléculaires 12 December 2008, Bordeaux (France)
  Natangelo A., Malik G., Charris J., Deffieux D., Pouysegu L., Manfredini S., Quideau S., *"Towards the total synthesis of* C*-arylglycosidic ellagitannins".*

Posters

- IX Giornata della Chimica dell'Emilia Romagna, 4 December 2009, Bologna (Italy)
  Towards the total synthesis of C-glycosidic ellagitannins Vescalagin and Castalagin, A. Natangelo, G. Malik; J. Charris, D. Deffieux, L. Pouysegu, S. Manfredini and S.Quideau.
- XXIVth International Conference on Polyphenols (ICP), 8-11 Juillet 2008, Salamanca (Espagne)
  Studies towards the total synthesis of nonahydroxyterphenoyl-containing C-glycosidic ellagitannin vestali, G. Malik, A. Natangelo, J. Charris, D. Deffieux, S. Quideau.

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Chapter 1

Ellagitannins Structural Description and Total Synthesis

In all things of nature there is something of the marvelous.
Aristotele, *Parts of Animals*, I.645a16

1.1 Ellagitannins : a class of bioactive plant polyphenols

Ellagitannins constitute one of the major classes of polyhydroxyphenyl-bearing polyphenols derived from the secondary metabolism of gallic acid in plant species of the *Angiospermea.*[4] This class of natural compounds has long been regarded as the active principles of many plant extracts used in traditional medicines.[5,6]

Today, the regular intake of fruits and vegetables is highly recommended in the human diet, mainly because the polyphenols they contain are thought to play important roles in long-term health maintenance and reduction in the risk of chronic and degenerative diseases, such as atherosclerosis and cancer.[7-13]

This increasing recognition of the benefits brought about by plant polyphenolics for human health has sparked a new appraisal of various plant-derived food and beverages, such as fruit juices, olive oil, chocolate, coffee, tea and even alcoholic beverages such as wine and cider.

It has been suggested that France's high red wine consumption is a primary factor in the general trend of a low incidence of coronary heart disease in French people, despite having a diet relatively rich in saturated fats. This observation was defined “French Paradox” by Dr. Serge Rènaud, a scientist of Bordeaux University in France.[12,14]

1.1.1 Ellagitannins structural properties

Ellagitannins belong to the hydrolyzable tannins family, a subclass of the group of tannin molecules. To date, after more than 50 years of investigations,[6,15-27] more than 1000 members of this subclass of hydrolyzable tannins have been isolated from various plant sources and fully characterized, thus constituting by far the largest group of known tannin molecules.

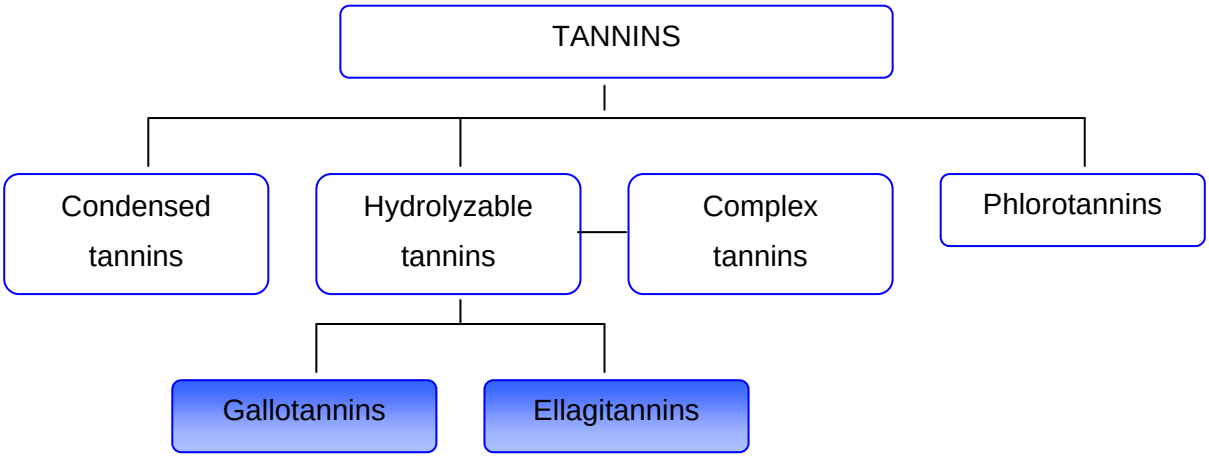


Figure 1. Tanninsclassification [4,28]

The ellagitannin chemical structures are basically composed of a central sugar core, typically D-glucopyranose, to which are esterified gallic acid units that are further connected together through C–C biaryl and C–O diaryl ether bonds as a result of intra- and intermolecular phenolic oxidative coupling processes.[28-30]

The oxidative coupling of two galloyl units yields an axially chiral 6,6'-dicarbonyl-2,2',3,3',4,4'-hexahydroxybiphenyl bisester group, commonly referred to as the hexahydroxydiphenoyl (HHDP) unit, which is the characteristic structural element of the monomeric ellagitannins (Figure 2).

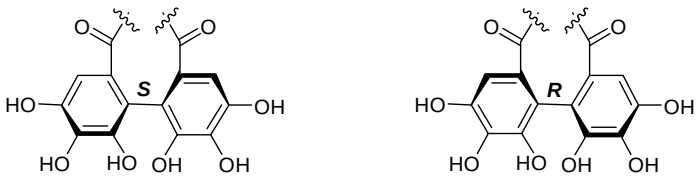


Figure 2. Axially chiral hexahydroxydiphenoyl biester (HHDP)

The chirality is due to the atropisomerism caused by the inhibition of free rotation around the axis.

In the majority of ellagitannins with an axially chiral glucose-bond HHDP unit, both the configuration of the biaryl unit and the conformation of the glucosyl unit are determined by their linkage positions. An HHDP unit bound to the 2,3- or 4,6- or 1,6-positions of D-glucopyranose in the natural products always has the *(S)*-configuration, while most 2,4- or 3,6-coupled HHDP units favor the *(R)*-configuration.

Two chair conformations can be distinguished, designated $^4C_1$ and $^1C_4$, respectively. The first numeral indicates the number of the ring carbon atom above the "seat of the chair (C)," and the second numeral (subscript) indicates the number of the ring carbon atom below the plane of the seat (spanned by C-2, C-3, C-5, and the ring O). Chair conformations are designated from structures with the ring oxygen atom in the top right corner of the ring "seat," resulting in the clockwise appearance of the ring numbering.

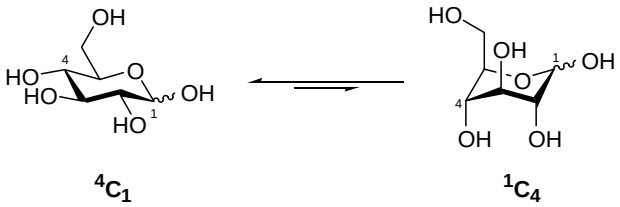


Figure 3. Chair conformations of D-glucose

The resulting D-glucose conformation in ellagitannins is determined by the coupling positions of the HHDP unit to the glucopyranose ring. While the glucopyranosyl assumes a $^4C_1$ conformation in the case of 2,3- or 4,6-HHDP coupling, a 1,6- or 3,6- or 2,4-HHDP coupling always favors the thermodynamically less stable $^1C_4$ conformation.

1.1.2 Hydrolyzable tannins classification basisd on their structural properties

A. Haslam's classification

Hydrolyzable tannins natural products are more than 1000 different molecular entities emanating from a single precursor [β-penta-O-galloyl-D-glucopyranose (β-PGG, **28**)], characterized by the presence of five gallic acid units esterified on a central D-glucose core.[31]

The resulting structural variety is so large that subdividing it into distinct categories in a logically ordered manner was far from being a trivial task.

Haslam *et coll.* first proposed to subdivide the two known subclasses of hydrolyzable tannins (i.e., gallotannins and ellagitannins) into three groups A, B and C (Figure 4).

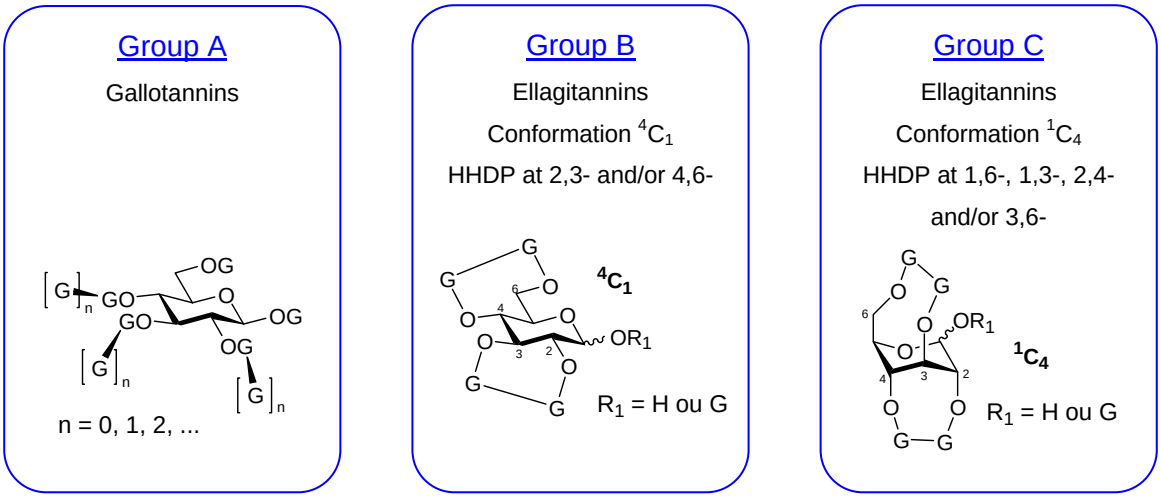
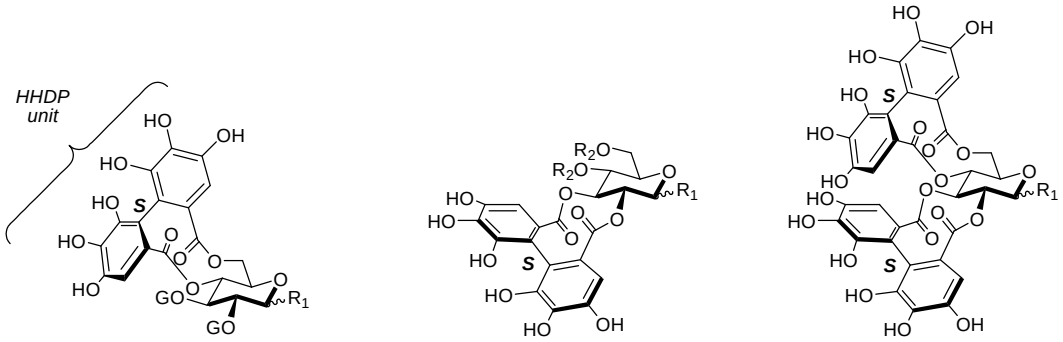


Figure 4. Hslam's hydrolyzable tannins classification

B. Okuda's classification

A second more exhaustive classification was proposed by Okuda [19,20,32] on the basis of the oxidation level of the galloyl ester groups.

Gallotannins are so classified as **type-I** hydrolyzable tannins. **Type II** gathers the HHDP-bearing ellagitannins at 2,3 and 4,6 positions with a D-glucopyranose in $^4C_1$ stable conformation (atropoisomery of HHDP unit is exclusively *S*). The monomeric tellimagrandins I and II (**1** and **2**, *Tellima grandiflora*), casuarictin (**6**, *Casuarina stricta*),[33] pedunculagin (**8**) and potentillin (**7**, *Potentilla kleiniana*)[34,35] belong to this class.



1: R_1 = OH, tellimagrandin I
2: R_1 = β-OG, tellimagrandin II

3: R_1 = β-OG, R_2 = G, pterocarinin C
4: R_1 = α-OG, R_2 = H, sanguiin H-4
5: R_1 = β-OG, R_2 = H, sanguiin H-5

6: R_1 = β-OG, casuarictin
7: R_1 = α-OG, potentillin
8: R_1 = OH, pedunculagin

Figure 5. Okuda's classification of hydrolyzable tannins : monomeric ellagitannins of type II

Type III ellagitannins are those featuring the DHHDP unit. In this case the most common conformation of D-glucopyranose is the $^{1}C_{4}$ as exemplified in the structure of geraniin (**9**, *Geranium thunbergii*).[36] The only exception is rapresented by the isoterchebin (**22**, *Citynus hypocystis*), characterized by the presence of a DHHDP unit at the 4,6- position of a D-glucopyranose core in $^{4}C_{1}$ conformation (Figure 6).

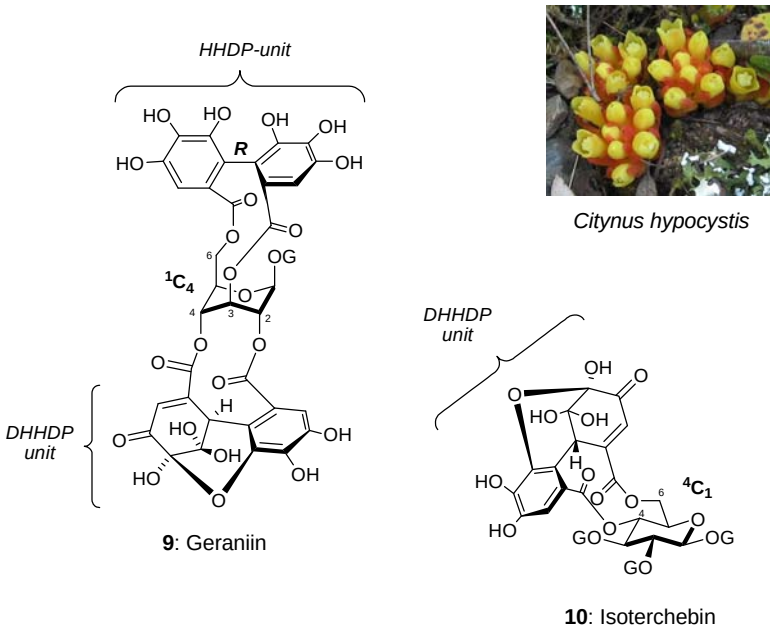
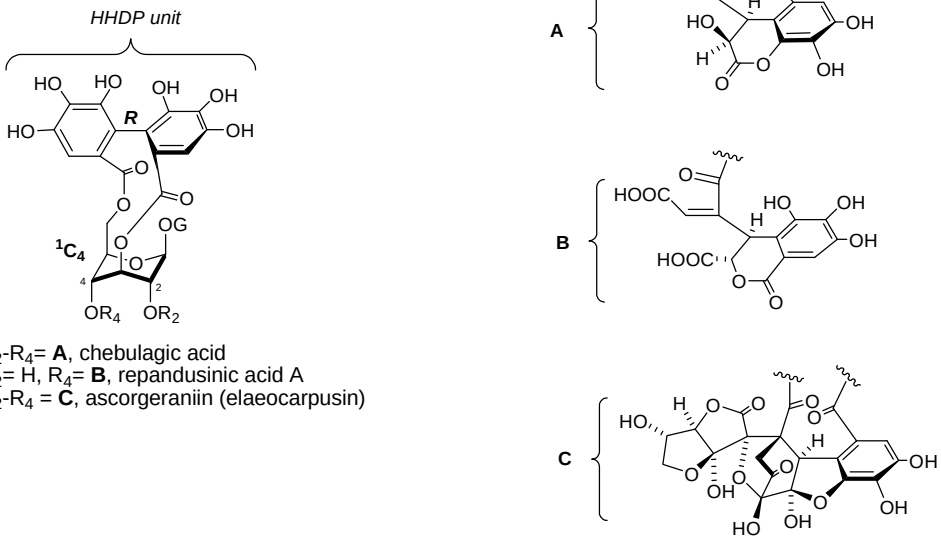


Figure 6. Okuda's classification of hydrolyzable tannins : monomeric ellagitannins of type III

Ellagitannins in which the DHHDP unit has suffered additional transformations, such as the chebulagic acid (**11**) and ascorgeraniin (**13**), constitute the **type-IV** group. The chebuloyl and elaeocarpusoyl ester groups are only two examples of a large series of ester units derived from the parent DHHDP unit.

Several other DHHDP-derived units have been identified as resulting from the condensation reaction of ascorbic acid and geraniin (**9**) DHHDP unit to give ascorgeranin (or elaeocarpusin, **12**)[37,38] (Figure 7).

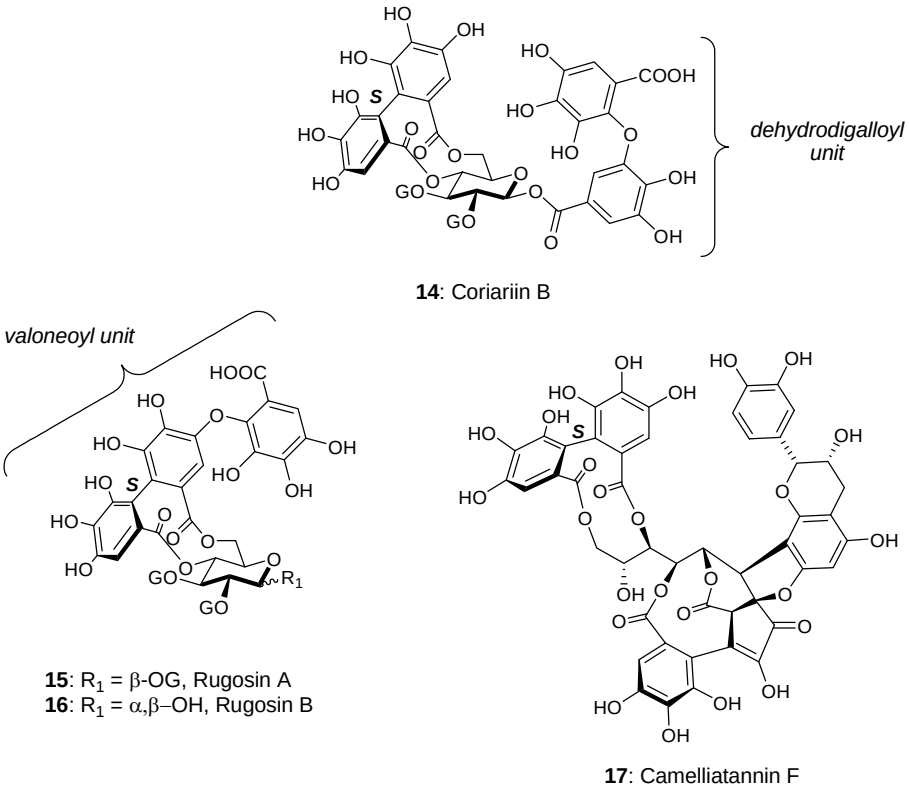


11: R_2-R_4= **A**, chebulagic acid
12: R_2= H, R_4= **B**, repandusinic acid A
13: R_2-R_4 = **C**, ascorgeraniin (elaeocarpusin)

Figure 7. Okuda's classification of hydrolyzable tannins : monomeric ellagitannins of type IV

This classification still left out many monomeric ellagitannins deriving from structural modifications as the opening of the D-glucopyranose core, the formation of *C*-arylglucosidic bonds and condensation reactions taking place at the glucose C-1. Since these ellagitannins mostly display the characteristic structural features of compounds belonging to primary types II-IV, Okuda *et coll.* classified these structures into **types II+**-**IV+**.[19]

Type II+ principally gathers HHDP-bearing *C*-arylglucosidic ellagitannins, such as stachyurin (**18**, Figure 9). The dehydroellagitannins with moieties resulting from a diaryl ether linkage with another polyphenolic unit belong to the **type-III+** group. For examples, we can notice rugosins A and B (**15** and **16**, *Rosa rugosa*)[39] and coriariin B (**14**, *Coriaria japonica*),[40] with a valoneoyl group linked to the 3,6-positions of a 2,4-DHHDP-bearing glucopyranose. Transformed dehydroellagitannins that feature moieties resulting from a C–C linkage with another polyphenolic unit belong to the **type-IV+** group. The camelliatannin F (**17**, *Camellia japonica*)[27] is an example (Figure 8).



14: Coriariin B

15: R_1 = β-OG, Rugosin A
16: R_1 = α,β–OH, Rugosin B

17: Camelliatannin F

Figure 8. Okuda's classification of hydrolyzable tannins : monomeric ellagitannins of type III+ and IV+

This classification work becomes further complicated by the fact that ellagitannins of **types II** and **II+** oligomerize *via* various modes basisd on oxidative coupling reactions between free and C–C-coupled galloyl groups, as well as on condensation reactions at the C-1 center of *C*-glucosidic ellagitannins.

The description of these further classes goes over the purpose of these manuscript of thesis.

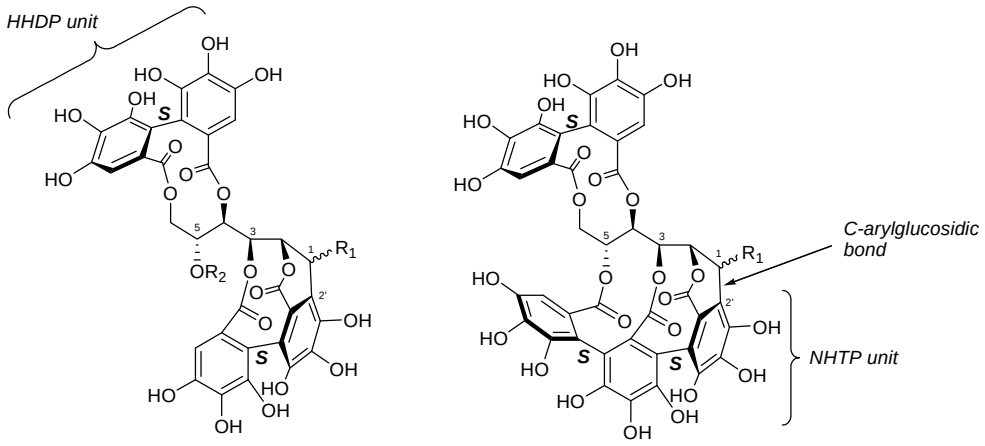
The aim of this introduction was in fact to collocate the *C*-arylglucosidic ellagitannins in the context of the family of hydroyzable tannins.

For more details, see the book recently edited by S. Quideau completely dedicated to ellagitannins chemistry.[31]

1.2 *C*-Glucosidic ellagitannins : A special subclass of ellagitannins

C-arylglucosidic ellagitannins constitute a tannin subclass in which a C–C bond links the C-1 atom of an "open-chain" glucose core to the C-2' atom of a galloyl-derived unit esterified to the 2-position of the glucose core. Their C-1-linked galloyl-derived unit is either part of a HHDP ester group bridging the 2- and 3-positions of the glucose core, as exemplified in the

punicacorteins **23** and **24** or part of a terarylic nonahydroxyterphenoyl (NHTP) variant (also known as the flavogalloyl group) that is attached *via* three ester bonds to the 2-, 3- and 5-positions of the glucose core, as exemplified in the structures of vescalagin (**21**) and castalagin (**22**). In addition to these examples, one can also cite their 5-degalloylated analogues, as the casuariin (**20**), first isolated from *Stachyurus* (*Stachyuraceae*) and *Casuarina* (*Casuarinaceae*) species,[33,41] together with stachyurin (**18**) and casuarinin (**19**).[16,33,41]

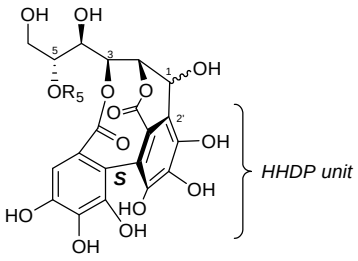


18: R_1 = β-OH, R_2 = G, stachyurin
19: R_1 = α-OH, R_2 = G, casuarinin
20: R_1 = α-OH, R_2 = H, casuariin

21: R_1 = β-OH, vescalagin
22: R_1 = α-OH, castalagin

Figure 9. *C*-arylglucosidic ellagitannins

Punicacortein A (**23a**) was isolated for the first time in 1986 by Nishioka *et coll*. from *Punica granatum*[42] and was also found in *Rosa taiwanensis*[43] and *Osbeckia chinesis*.[44] Punicacortein A (**23**) presumably results from hydrolytic cleavage of the 4,6-HHDP unit of casuarinin (**19**). Its degalloylated form **24** was isolated for the first time in 1988 by Osawa from *Osbeckia Chinensis*.[44]



23a: α-OH, R_5 = G, punicacortein A
23b: β-OH, R_5 = G, epipunicacortein A
24: α-OH, R_5 = H, degalloylpunicacortein A



Punica granatum

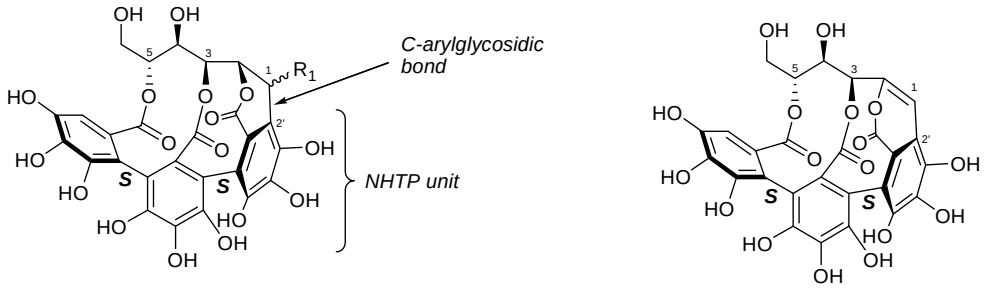
Figure 10. Punicacortein A and its C-1 epimer

Epipunicacortein A (**23b**) was isolated for the first time in 1991 by Nishioka *et coll*. from *Quercus aliena.*[45]

Vescalagin (**21**) and its C-1 epimer castalagin (**22**) were isolated from *Castanea* (chestnut) and *Quercus* (oak) woody species of the *Fagaceae* family for the first time by Mayer *et coll.*[46-48] Their structures were fully determined much later after revision of their respective configuration at C-1 by the Nishioka's group.[25] In addition to this *C*-arylglucosidic ellagitannins, oak heartwood contains two compounds, named vescalin (**25**) and castalin (**26**), that, as vescalagin and castalagin, are also extracted from oak by the wine during aging.[49] Their occurrence in oak presumably results from hydrolytic cleavage of the 4,6-HHDP unit of **21** and **22**, and their presence in wine can additionally be due to the same hydrolysis taking place in the wine itself.

They were hemisynthesized by Quideau *et coll*.[50] by adaptation of the method previously described by Scalbert *et coll.*[51,52] After 39h at 60°C in a 10% aqueous HCl solution, vescalagin (**21**) was converted into **25** (81% yield) with concomitant formation of ellagic acid (**78**), the bis-lactone formed from the release of the 4,6-HHDP unit.

Hydrolysis of castalagin (**22**) took longer (65h) to go to completion under the same conditions, and surprisingly led to a 65:35 mixture of **26** and **25**. Other minor product formed is the vescalene (**27**). It was hypotised that the formation of **25** was due, in this case, to an epimerization of **26**.



25: R_1 = β-OH, Vescalin
26: R_1 = α-OH, Castalin

27: Vescalen

Figure 11. NHTP-bearing *C*-arylglucosidic ellagitannins

1.2.1 *C*- arylglucosidic ellagitannins biosynthesis

The biosynthetic steps leading to glucopyranosic ellagitannins from their gallotannin precursor, β-pentagalloylglucopyranose (β-PGG, **28**), are just today starting to get elucidated, thanks to the work initiated by Gross.[53]

Pentagalloylglucose (**28**) has been individuated as immediate precursor of two subsequent routes, one leading to gallotannins which are characterized by additional galloyl residues bound to the pentagalloylglucose core; the other leading to ellagitannins *via* oxidative processes that yield C–C linkages between adjacent galloyl groups of pentagalloylglucose.

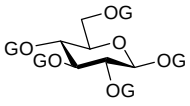
In 1950, Schmidt and Mayer[15,54] were the first to postulate that the HHDP residues of ellagitannins should originate from the dehydrogenation of neighboring galloyl groups of pentagalloylglucose (**28**).

This hypothesis was confirmed by Haslam in 1994.[30] They suggested that the two galloyl groups at C-4 and C-6 can be interconnected to form one HHDP group, thus yielding tellimagrandin II (**2**) as a primary ellagitannin metabolite that can be subjected to further oxidation reactions to give casuarictin (**6**).

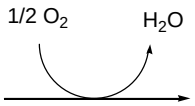
Niemetz and Gross confirmed this hypotesis.[55] They found that the oxidation of β-PGG (**28**) catalyzed by an oxidase extracted from the leaves of *Tellima grandiflora* led to the formation of tellimagrandin II (**2**) in a regiospecific and stereospecific way.

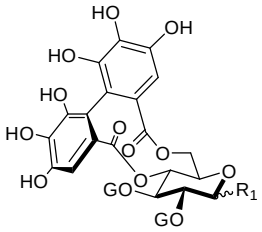


Tellima grandiflora



28: β-PGG

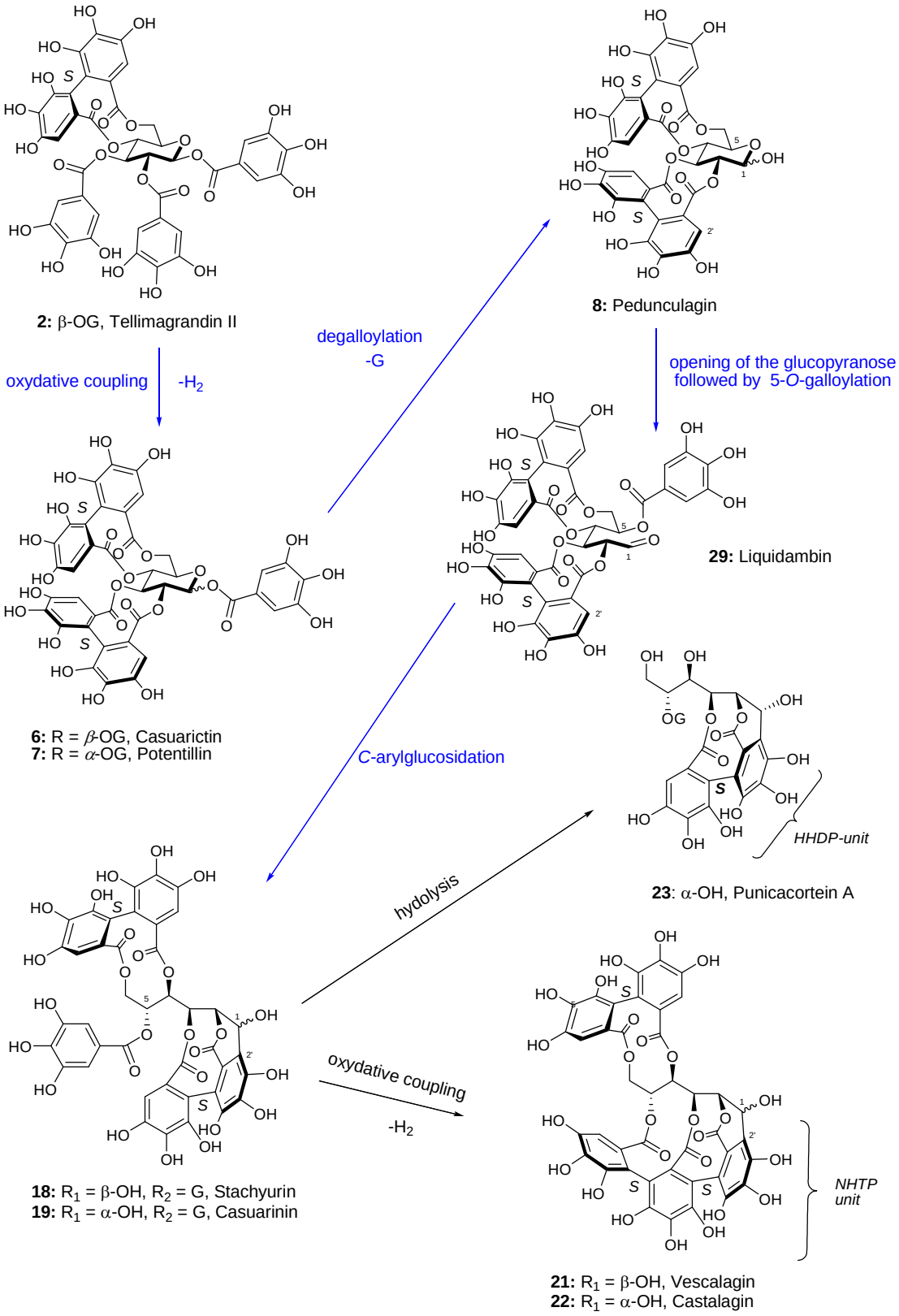




2: R_1 = *β*-OG, Tellimagrandin II

Scheme 1. β-PGG oxidation to tellimagrandin II

The biochemical event that mediates the passage from the glucopyranosic ellagitannin to the open-chain *C*-glucosidic ellagitannin class remains a matter of speculation. Interesting observations have been made from the study of a plant species in which members of the two classes co-exist.[16,56,57] It was proposed the following biogenetic filiation (Scheme 2): from tellimagrandin II (**2**) to casuarictin (**6**) via oxidative C–C coupling between the 2- and 3-galloyl groups followed by 1-*O*-degalloylation to pedunculagin (**8**).[56]



Scheme 2. Proposed biosynthetic pathway from tellimagrandin II to *C*-arylglucosidic ellagitannins

Further investigations on *Liquidambar formosana* enabled the Okuda group to find one important piece of the puzzle missing. They isolated the open-chain aldehyde liquidambin (**29**)[58] (Scheme 2). One can thus assume that an opening of the pedunculagin (**8**) glucopyranose ring is the first key event that opens up the door to the *C*-glucosidic ellagitannins. Then follows the intramolecular aldol-type nucleophilic addition of the phenolic 2,3-HHDP unit to the aldehyde function of the resulting liquidambin (**29**), thus giving rise to a *C*-glucosidic bond such as in stachyurin (**18**) and its C-1 epimer casuarinin (**19**). Their HHDP hydrolysis leads to punicacortein A (**23**), while the oxidative coupling between the 5-galloyl and 2,3-HHDP groups would furnish vescalagin (**21**).[13]

The proposed biosinthetic pathway (Scheme 2) is just an hypotesis. The order of the transformation and their mechanism is incertain.

1.3 Biological activity of *C*-glucosidic ellagitannins

Many plant species containing ellagitannins have been used for the treatment of diseases, especially in Asia:[59] it is notable that the comparison of the amounts and pharmacological properties of ellagitannins and other components in plants shows that some of these ellagitannins could be playing the main role in the medicinal application of these plants (Table 1).

Ellagitannins share with other polyphenols two fundamental physico-chemical properties that are often cosidered responsible of their therapeutic action in traditional herbal remedies. The first one is their capability to scavenge reactive oxygen species in cellular prooxidant states and/or oxidatively generated free radicals such as those derived from lipid oxidation. This antioxidant activity is commonly thought to enable the prevention of age-related health deteriorations such as carcinogenesis, neurodegenerative and cardiovascular diseases, including atherosclerosis.

The second property common to other polyphenols is the complexation of proteins through weak interactions between peptide side chains and polyphenol aromatic rings.[12]

Besides these general activities basisd on chemical reactivity and structural features common to any polyphenolic substance (i.e., antioxidation and complexation), ellagitannins are capable of expressing remarkable biological activities such as antibacterial activity, antitumor and antiviral effects.

The molecular mechanism at the basis of these effects is not yet fully elucidated.

Recent studies have showed that the HHDP unit of ellagitannins confers them a globular structure very organized that renders them capable of interacting in a specific manner with biological target defined as some proteins involved in DNA replication.[29,50]



Geranium thunbergii
(geraniin)



Mallotus japonicus
(*mallotusinic acid)*



Agrimonia pilosa
(*agrimoniin*)



Cornus officinalis
(*cornusiin A*)



Punica granatum
(*granatin B*)



Geum japonicum
(*gemin A*)



Rosa rugosa
(*rugosin A*)



Trapa japonica
(*trapanin B*)



Liquidambar formosana
(*casuarictin*)



Camellia japonica
(*carmelliatannin A*)



Oenothera erythrosepala
(*oenithenin B*)



Terminalia chebula
(*chebulinic acid*)

Table 1. Selection of ellagitannin-rich medicinal plants[31]

A. Antiviral activity

Several monomeric and dimeric ellagitannins, as tellimagrandin I (**1**) and geraniin (**9**)[60,61] inhibit replication of *Herpes simplex* virus *in vitro* by blocking viral adsorption to cultured cells with EC_{50} ranging from 20 to 100 nM and CC_{50} > 16 μM.[62]

Many dimeric ellagitannins have been found able to inhibit the reverse transcriptase from RNA tumor virus.[63] Other ellagitannins as gemin D[64] (monomeric) and camelliin B[65] (dimeric) have shown potent inhibitory effect on HIV reverse transcriptase activity.[66]

B. Antitumoral activity

Several reports have been reported in the last decades on the inibitory effect of polyphenols on the incidences and propagation of cancers.

Several ellagitannins extracted from plants are inhibitors of human topoisomerase II (top2).[67]

DNA top2 are ubiquitous nuclear enzyme that are essential for the removal of torsional constraints associated with DNA processes such as replication, transcription, chromosome condensation and segregation.[68-70] They cleave the DNA backbone, leading to the formation of top2-DNA covalent cleavage complexes and to transient DNA double-strand breaks that allow the passage of intact DNA duplexes through the breaks. DNA continuity is then restored by the reverse reaction referred to as religation.

Thus top 2 enzym represent attractive targets for the inhibition of cell proliferation.

Various natural products were tested for their potential antiproliferative activity and their inhibitory status towards DNA top2. In particular some *C*-arylglucosidic ellagitannins tested resulted to be fully inhibitors of the top2 mediated decatenation of kinetoplastic DNA *in vitro*.[50,71] Among the most active molecules there are the epimeric pair vescalin (**25**) and castalin (**26**), together with vescalen (**27**).

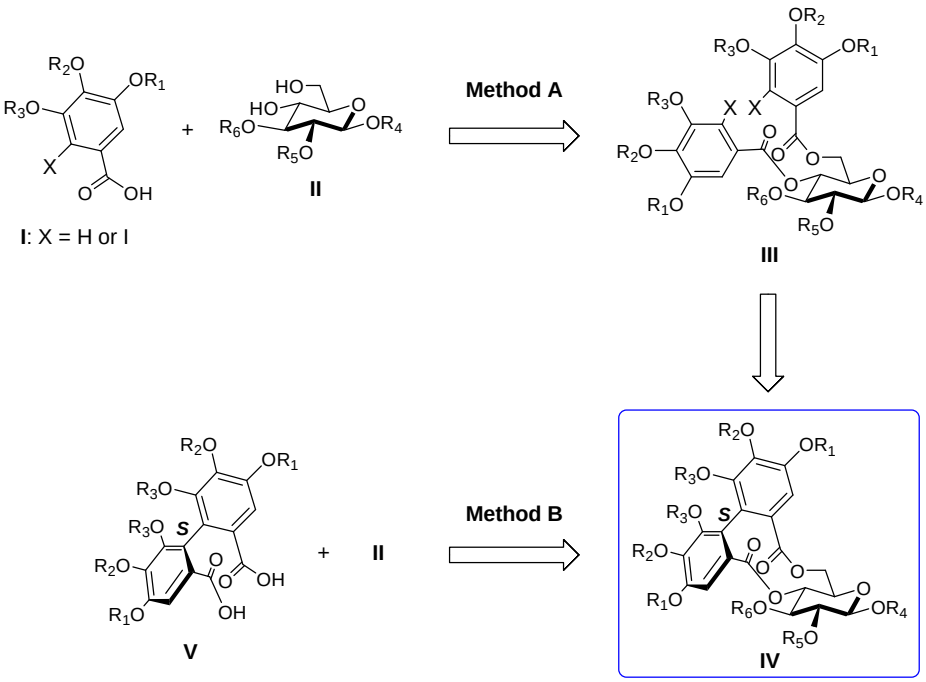
1.4 Ellagitannins Total Synthesis

The above mentioned biological properties, and the fact that ellagitannins are usually non toxic for humans, make them important and interesting compounds for pharmaceutical purposes. However, the full exploitation of their chemistry and mode of action is hindered by their limited accessibility in adeguate purity and amount from natural sources. Therefore the development of efficient synthetic routes towards the ellagitannins has received considerable

attention in the last years to improve the availability of lead compounds and to develop methodologies for the generation of analogues with enhanced pharmacological properties.

The first total synthesis of an ellagitannin, the tellimagrandin I (**1**), was reported by Feldman in 1994.[72] Since there, several total synthesis of natural ellagitannins[72-92] and their permethylated derivatives[93-96] were successively reported.
The state of art on the ellagitannins total synthesis has been recently reviewed.[29,31,85]

The challenge for total synthesis untill today reported, was centered on achieving chemoselectivity, regioselectivity and stereoselectivity in the formation of the HHDP unit.
For these purposes, two general approaches have been developed (Scheme 3):
Method A : In the first approach, developed by Feldman in 1994,[72] the biaryl part of ellagitannins is constructed by the intramolecular diastereoselective oxidative coupling of two galloyl units (**I**), judiciously protected, attached to the D-glucose (**II**);
Method B : The second methodology involves a double esterification approach, in which an appropriately protected diphenic acid **V** is esterified with the sugar derivative **II**, to give **IV** directly. This concept was introduced by Meyers in 1994.[93]



Scheme 3. Two approaches towards ellagitannins total synthesis

In any case the evaluation and appropriate choice of protecting groups has a key role. The protecting groups must answer to two exigencies: (i) be orthogonal on the sugar and on the

galloyl unit; (ii) mainly in the case of the method A, allow the galloyl oxidative coupling with preservation of the ester linkages.

The early recognition that galloylated glucose substrates were likely to be biosynthetic precursors of the HHDP-containing ellagitannin products spurred much effort at developing oxidative coupling protocols which effected this transformation *in vitro*. Numerous studies from 1916 detailed the consequences of exposing various galloyl esters to a set of oxidizing conditions. In those cases where products could be identified, biaryl bond formation was detected in low yields.
This conspicuous failure to observe HHDP formation upon oxidative coupling of galloyl esters can be traced to the polyhydroxylic nature of the product (overoxidation, lactonization) it seemed plausible that prospecting among various partially etherified gallate derivatives as suitable candidates for controlling oxidation might prove rewarding.

In order to simplify the representation, the different protected galloyl units will be described as represented in Figure 12.

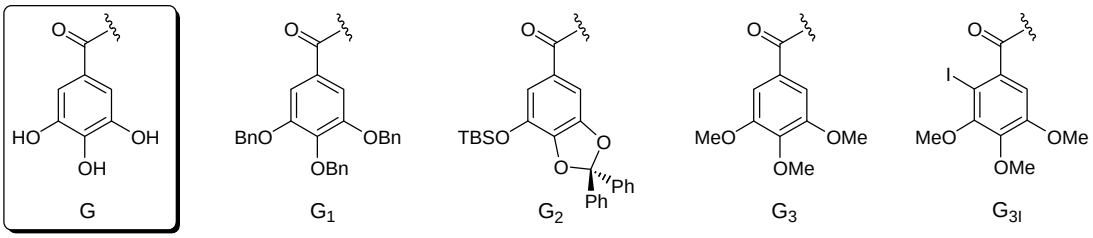


Figure 12. Abbreviation for the differently protected galloyl units

1.4.1 Stereochemistry of HHDP

One of the critical issue raised by the conversion of glucose-bound galloyl esters to an HHDP unit is the stereochemistry of bond formation. The oxidative coupling of two galloyl units yields an axially chiral 6,6'-dicarbonyl-2,2',3,3',4,4'-hexahydroxybiphenyl bisester group, commonly referred to as the hexahydroxydiphenoyl (HHDP) unit.
The chirality is due to the atropisomerism (from the Greek, a = not and tropos = turn)[97,98] resulting from hindered rotation around the single C-C bond where the steric strain barrier to rotation is high enough to allow for isolation of two conformers. Atropisomers differ from other chiral compounds in that they can be equilibrated thermally whereas in the other forms of chirality, isomerization is usually only possible chemically.

The most important class of atropisomers is constituted by biaryls with a complete set of *ortho* substituents. A minumum of three substituents is enough to have a barrier to rotation at room temperature.[99]

In general, there are two necessary preconditions for axial chirality in biaryl molecules (**I**, Figure 12): a rotationally stable axis and the presence of different substituents on both sides of the axis A ≠ B and A' ≠ B'.

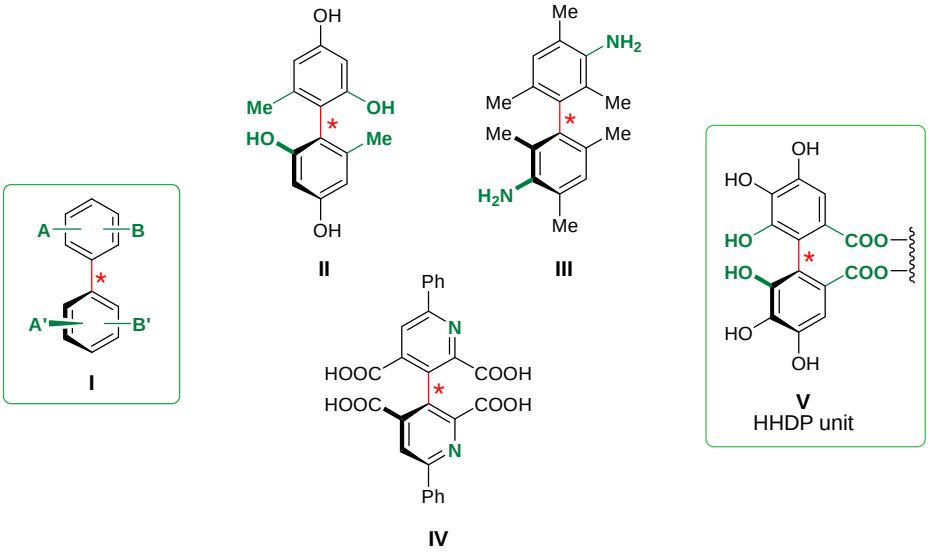
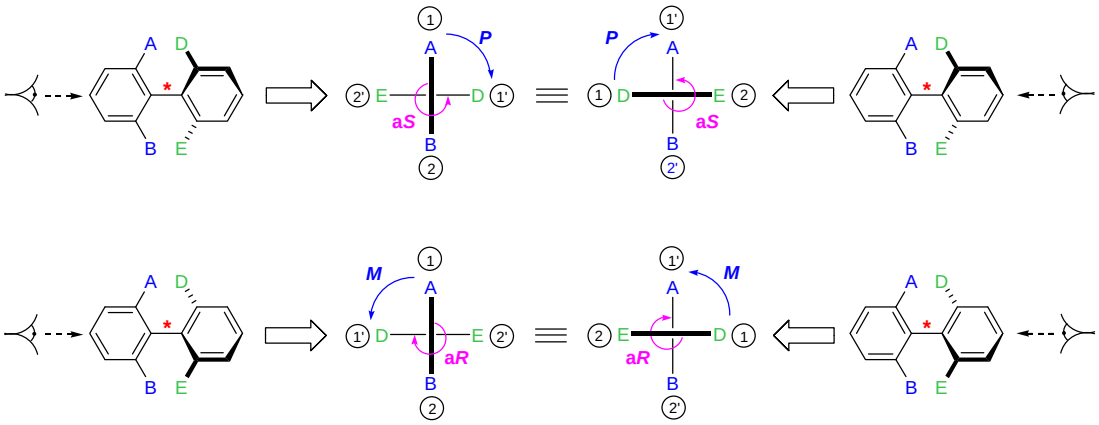


Figure 13. Selected substitution patterns that result in axial chirality[98]

If A = A' and B = B', the molecule has C_2 symmetry (but is still chiral) as in **III** and **IV** (Figure 13). Axially chiral biaryl compounds that bear different *ortho* substituents (**II**), are the most frequent. Surprisingly, even biaryl compounds with four constitutionally identical substituents may be chiral if these are connected pair wise through two bridges (**III**-**IV**). Although less common, axial chirality may also result from an inequivalence of *meta* substituents (**III**). Furthermore, heteroaromatic systems provide the possibility to introduce chirality merely from the position of the heteroatom (**IV**).

The absolute axial configuration[99,100] can be denoted by analysis of a Newman projection along the biaryl axis (Figure 14). After assignment of priority to the *ortho-ortho* (or *meta-meta* if A = B and A' = B') substituents according to the Cahn-Ingold-Prelog (CIP) rules. The priority order for the substituents is assigned on the first aromatic cycle: (1) for the group with major priority and (2) for the other. In the same way, for the distal ring the highest priority substituent is (1') and (2') for the other.



Priority A>B and D>E according to CIP rules

Figure 14. Assignment of absolute configuration in chiral biaryl species[98]

The analysis is done by following the shortest 90° path from the substituent of highest priority at the proximal ring to the highest-ranking one at the distal ring (i.e. here from A to A'). If this 90° turn is counterclockwise, the absolute configuration is M (for minus); if it is clockwise, then the descriptor is P.[98]

The second avalaible nomenclature employs the (a*R*) and (a*S*) descriptors where « a » stays for axial. In this case the highest priority is assigned to the proximal ring. The rotation path is from (1) to (2) then (1') to (2'). The configuration is (a*R*) if the path is clockwise, (a*S*) for the counterclockwise turn.

There is always a correspondence *P* ↔(a*S*) and *M* ↔(a*R*).

(In the following discussion the simplest notation *S* or *R* will be employed).

The HHDP (**V**, Figure 13), key structural elements of ellagitannins family, is characterized by an axial chirality.

In the majority of ellagitannins with an axially chiral glucose-bond HHDP unit, both the configuration of the biaryl unit and the conformation of the D-glucosyl unit are determined by their linkage positions.

An HHDP unit bound to the 2,3- or 4,6- or 1,6-positions of D-glucopyranose in the natural products always has the *(S)*-configuration, while most 2,4- or 3,6-coupled HHDP units favor the *(R)*-configuration.

These observations have led Schmidt[15,54] and Haslam[101-104] to postulate that the stereochemical outcome of biaryl formation in ellagitannin systems is dictated by the conformational preferences of the galloylated glucose core. The successful "biomimetic" diastereoselective bigalloyl coupling transformations briefly discussed in the following section are the first demonstrations of the validity of the Schmidt- Haslam hypothesis.

1.5 HHDP-formation via oxidative biaryl coupling (Method A)

Feldman was the first to develop an efficient methodology for the diastereoselective formation of HHDP[105,106] that was applied to the first total synthesis of tellimagrandin I (**1**) in 1994.

The diastereoselective formation of the crucial biphenyl C-C bond between monophenol galloyl moieties (G_2OH) at O-*2* and O-*3* positions on an appropriately protected glucose-derived precursor was realized by oxidation with $Pb(OAc)_4$ (Wessely oxidation).

This $Pb(OAc)_4$ mediated oxidation was then extended to several ellagitannnins total synthesis realized by Feldman *et coll.*[29,72-74,77,81,83,84,88]

1.5.1 Total synthesis of tellimagrandin I and II (4,6-HHDP)

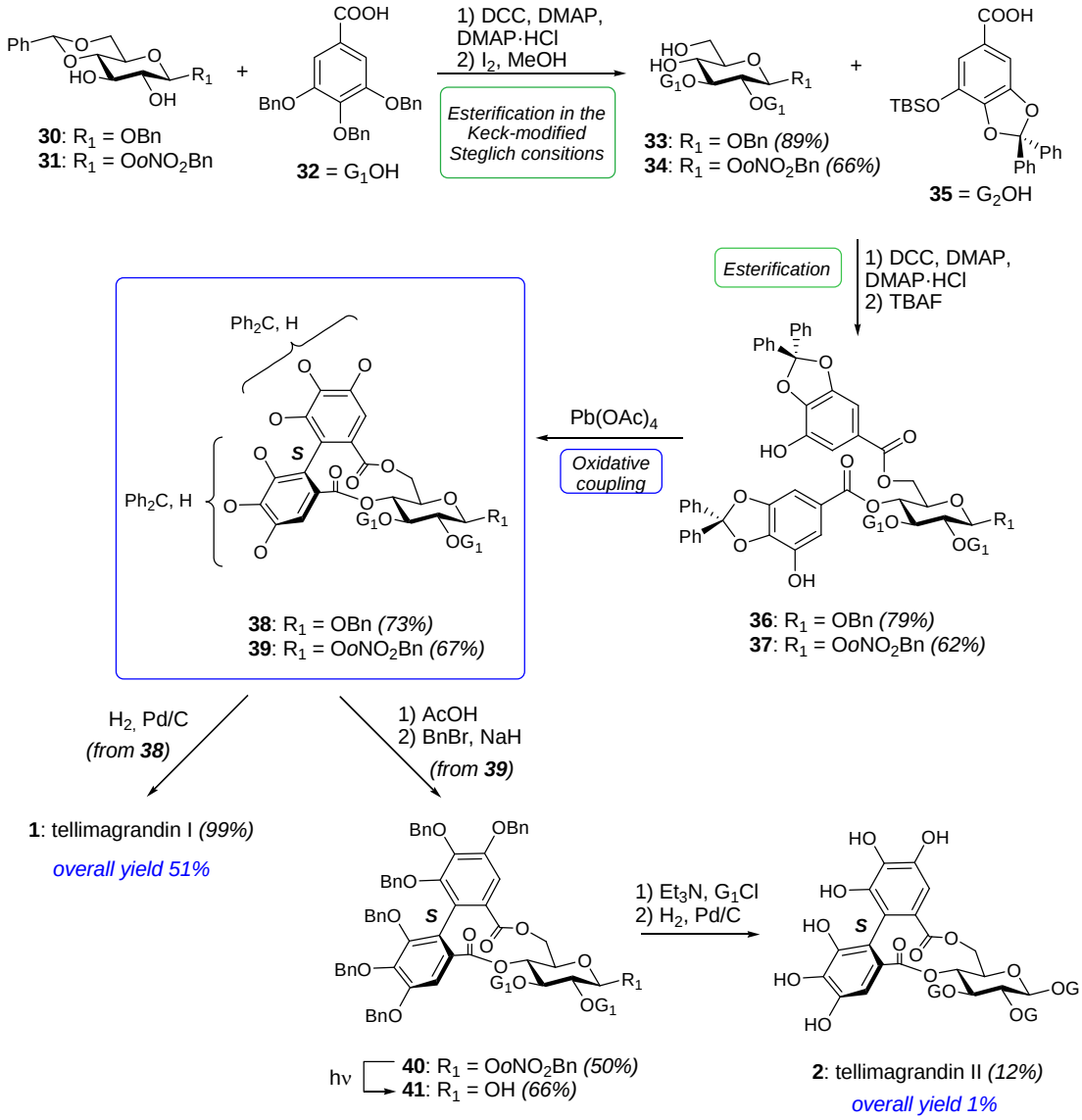
Tellimagrandins I (**1**) and II (**2**) are characterized by the presence of a (*S*)-HHDP unit at 4,6- of a D-glucopyranose and two other galloyl moieties at the positions 2 and 3. Tellimagrandin II (**2**) has an additional galloyl unit at the anomeric position of the sugar. The synthetic strategies (Scheme 4) are identical for the two molecules, the difference being the protecting group strategy at the anomeric position of the starting sugar (**30** or **31**).[29,72,81]

The starting sugar (**30**, for tellimagrandin I; with a photolabile *ortho*-nitrobenzyle and **31**, for tellimagrandin II) was protected with a benzylidene group at 4,6 position. The alcohol functions were esterified in the Keck[107] modified Steglich[108] conditions with perbenzylated gallic acid (**32** = G_1OH). The benzylidene was then removed by hydrolysis and the alcoholic functions generated were esterified with an opportunely protected gallic acid moiety **35** (= G_2OH) to give, after desilylation with tetrabutylammonium fluoride (TBAF) the compounds **36** and **37**. The key step of stereoselective coupling was then realized with $Pb(OAc)_4$ to give **38** and **39** (only *S* atropisomer was obtained!) as a mixture of regioisomeric diphenyl ketal isomers. Simple hydrogenation of this mixture liberated all the hydroxyl moieties and furnished natural tellimagrandin I (**1**) completely free of contaminants with an overall yield of 51% on 6 steps.

Tellimagrandin II (**2**) was obtained *via* a two steps deprotection/protection strategy on the mixture **39** leading to the perbenzylated compound **40**. The selective removal of the

photolabile *ortho*-nitrobenzyl followed by β-selective acylation at the anomeric position and hydrogenolysis lead tellimagrandin II (**2**) with an overall yield of 1% in 10 steps.

(Feldman supposed that the presence of the electron poor *ortho*-nitrobenzyl group at the anomeric position is the cause of the lower yield obtained in the case of tellimagrandin II).

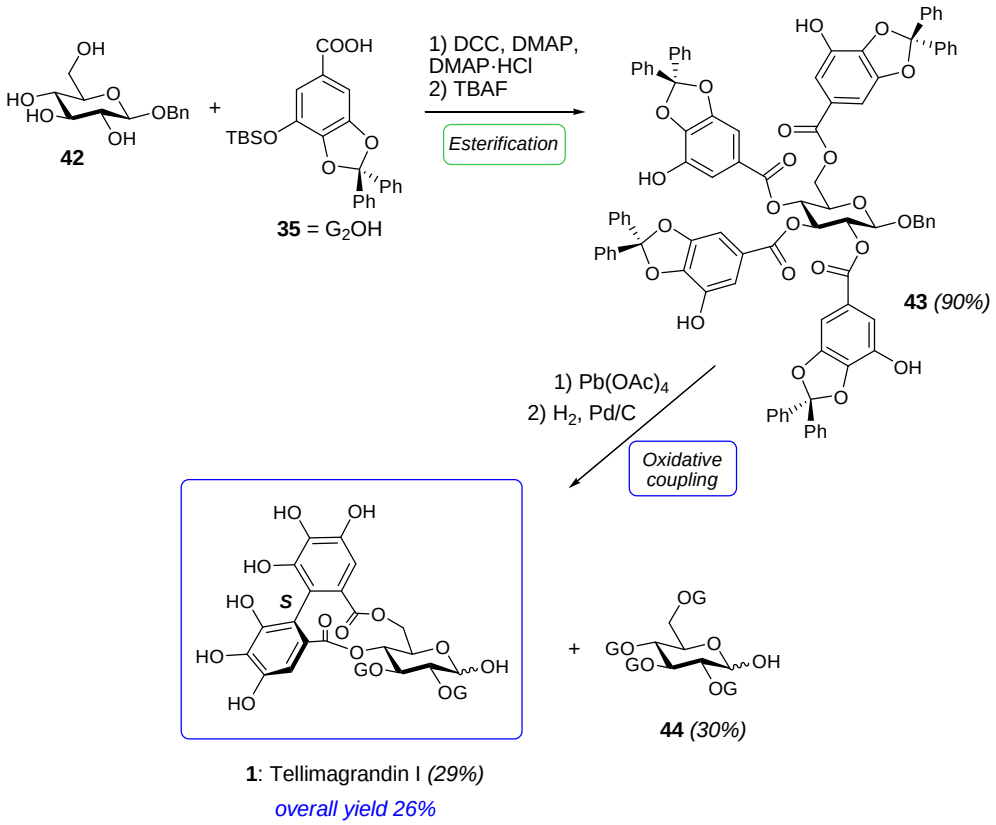


Scheme 4. Tellimagrandin I and II total synthesis

A more concise alternative synthetic strategy was proposed by Feldman for the tellimagrandin I synthesis (Scheme 5).[72,77]

In this case, the starting sugar derivative (**43**), bearing four galloyl moieties G_2, was employed to explore the possibility of having a regioselective O-4,O-6 galloyl coupling.

Upon treatment with 1.1 equiv of $Pb(OAc)_4$, they observed the formation of the expected compound as the only cyclised material! Hydrogenation of the crude reaction mixture afforded natural tellimagrandin (**1)** in *29%* yield.

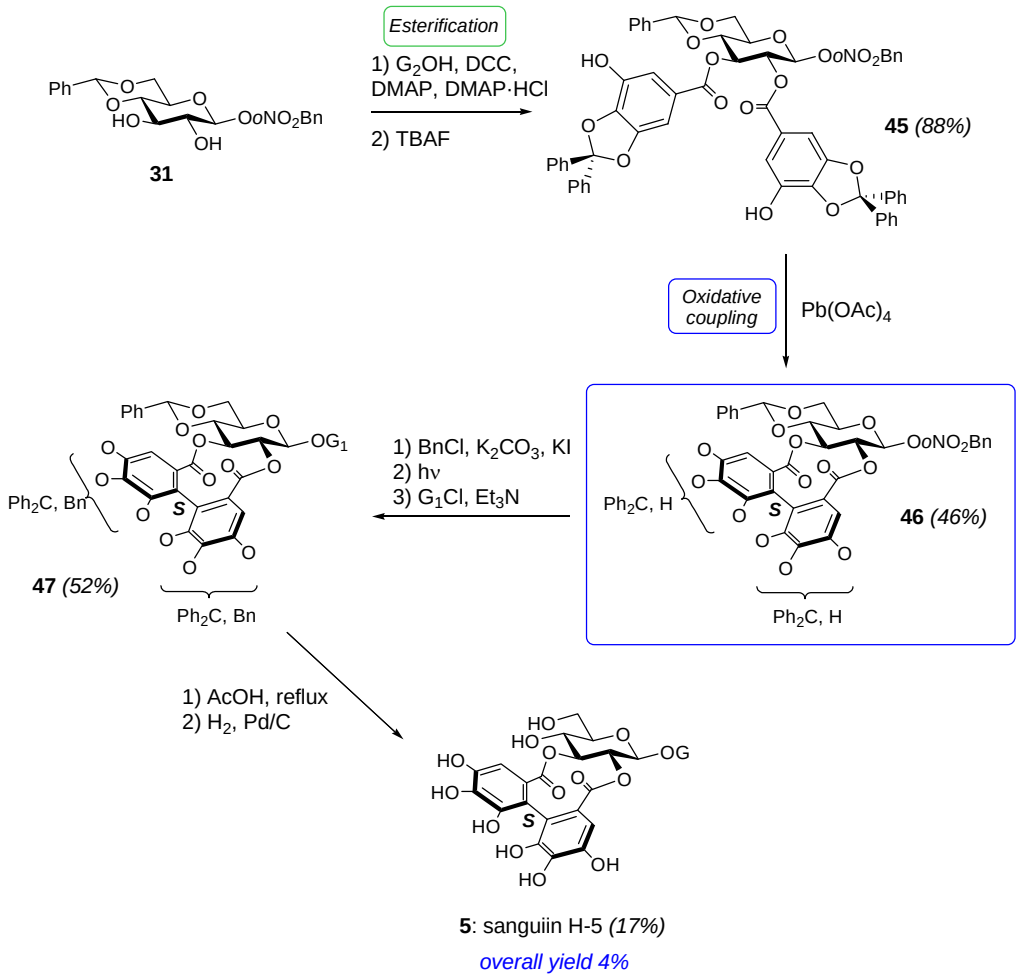


Scheme 5. Alternative approach to tellimagrandin I: regioselectivity of the coupling reaction

1.5.2 Total synthesis of sanguiine H-5 (2,3-HHDP)

The sanguiin H-5 (**5**), also known as isostrictinin,[16] is a structurally simple member of ellagitannins. The successful synthesis of this molecule addressed the two critical challenges: (i) formation of only the (*S*)-atropisomer of the HHDP group via selective oxidation of the protected O-2 and O-3 galloyl moieties, and (ii) stereochemically controlled establishment of the β-anomeric galloyl linkage. The strategy proposed by Feldman[73] (Scheme 6) started with the diol **31** with the photolabilee *o*-nitrobenzyl at the anomeric position. Galloylation at the 2- and 3-positions of the glucopyranose core, followed by desilylation of the diester so obtained, led to **45**. $Pb(OAc)_4$-mediated oxidation furnished the expected regioisomeric mixture **46**. Benzylation of the free phenols in this mixture, followed by photolytic cleavage of the anomeric protecting group in the derived benzyl ether products, and β-selective galloylation with G_1Cl afforded the regioisomeric mixture **47** as a single

stereoisomer at C-1. Hydrolytic removal of the benzylidene acetal and the diphenyl ketals of the mixture **47** followed by hydrogenolysis to remove the benzyl protecting groups led to crude sanguiin H-5 (**5**) with an overall yield of 4% on 8 steps.

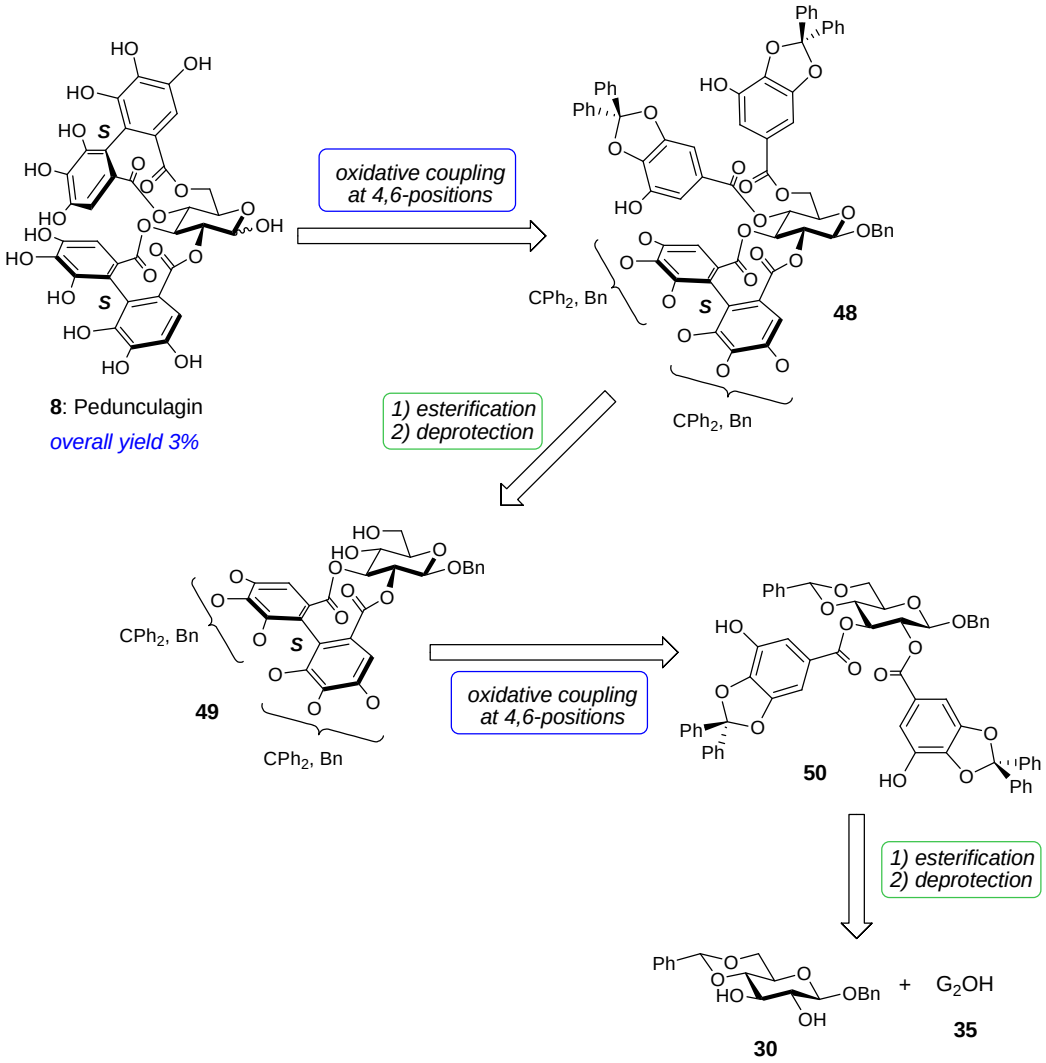


Scheme 6. Sanguiin H-5 total synthesis

1.5.3 Total synthesis of pedunculagin (2,3,4,6-HHDP)

Taking inspiration from the strategies developed for the synthesis of tellimagrandin I (**1**, 4,6-HHDP) and sanguiin H-5 (**5**, 2,3-HHDP), Feldman *et coll.* carried out in 1996 the total synthesis of pedunculagin **8**[74] wich bears two HHDP units at 2,3- and 4,6- positions of D-glucopyranose (Scheme 7). The results obtained on the synthesis of tellimagrandin I showed that the 2,3- coupling is impossible in the presence of another HHDP in 4,6- positions in the classical conditions of oxidation with $Pb(OAc)_4$.[72,77] The alternative depicted in Scheme 7 consists in: (i) construction of the HHDP unit at 2,3- positions of the intermediate **50** with a benzylidene group in 4,6-, then (ii) benzylidene cleavage and acylation with the two G_2 units

(iii) followed by further $Pb(OAc)_4$ coupling. A last hydrogenolysis step led to pedunculagin **8** with an overall yield of 3% on 9 steps.



Scheme 7. Retrosynthetic analysis of pedunculagin

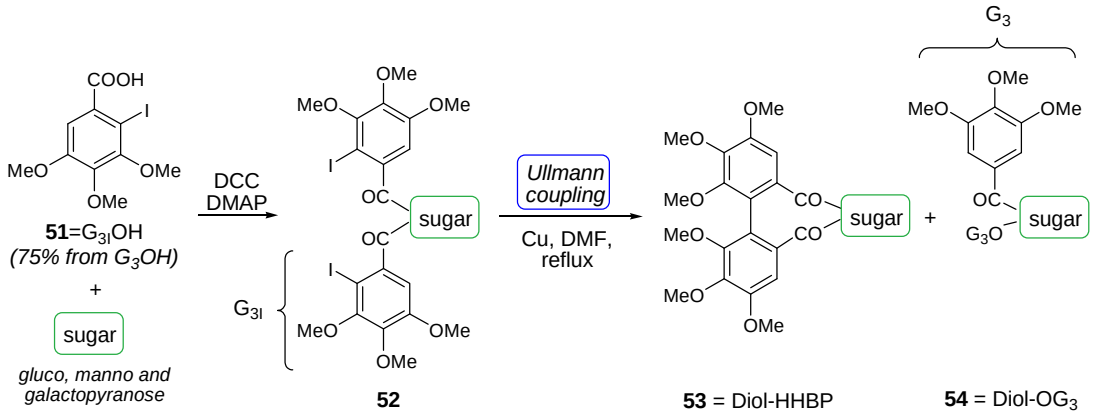
1.5.4 Ullmann Coupling

Reductive coupling of suitably activated galloyl synthons *via* Ullmann procedures has been successfully employed by Martin *et coll.* to deliver derivatives of the HHDP unit in protected form on several sugar derivatives (Scheme 8 and Scheme 9 report the results obtained from the application on the glucose).[96]

Internal biaryl coupling reactions of carbohydrate derivatives carrying two 2-iodo-3,4,5-trimethoxybenzoyl groups **52** under Ullmann conditions (Cu^0 in dimethylformamide at reflux)

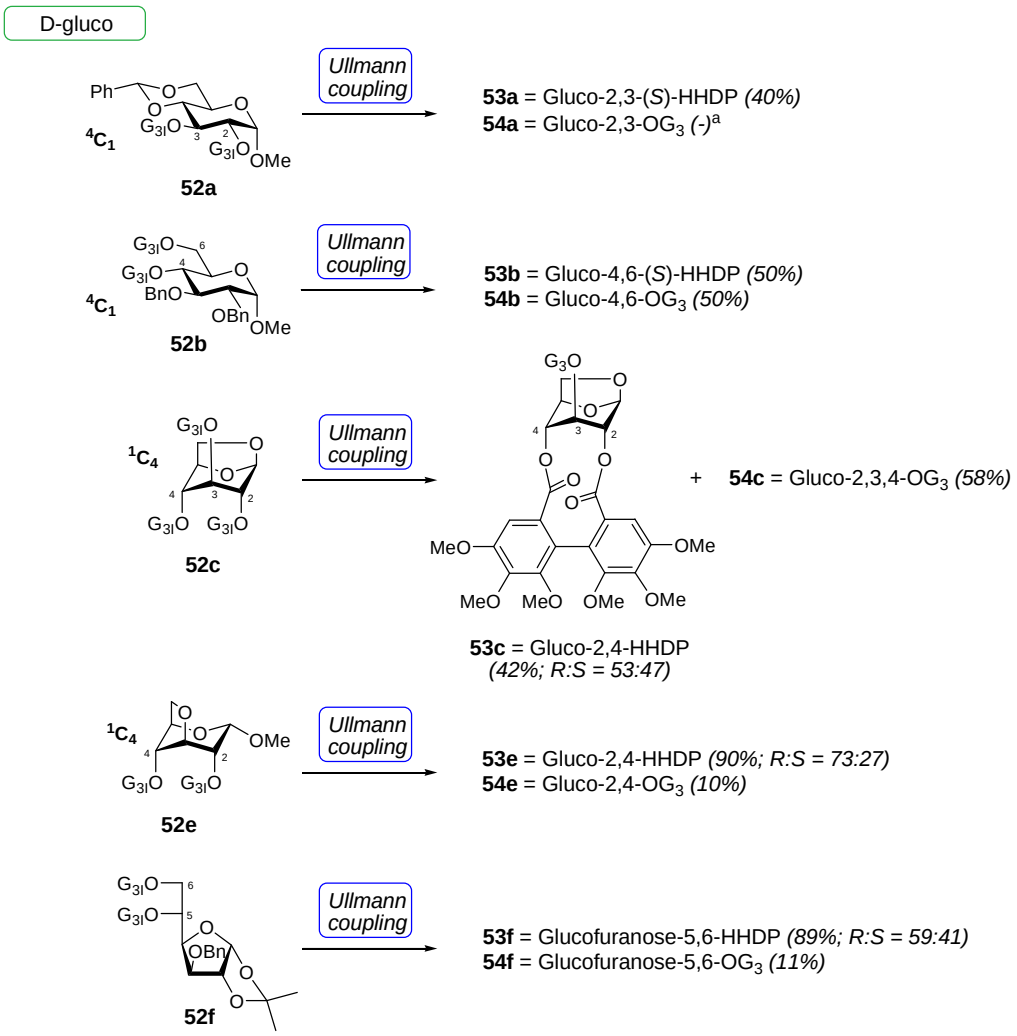
were investigated. With substituents at positions 2,3 or 4,6 of a D-glucopyranoside, 2,3 of a D-mannopyranoside, and 3,4 of a D-galactopyranoside, the coupling was found to

proceed with a very high degree of stereoselectivity, leading exclusively to the (*S*)-epimer **53** of the resulting hexamethoxydiphenoyl residue from the D-*gluco* and D-*galacto* substrates, and to the (*R*)-epimer from the D-*manno* substrate. With substituents at positions 2,4 of D-glucopyranose derivatives in the 1*C*4 conformation and at positions 5,6 of a D-glucofuranose derivative, the coupling proceeded efficiently but with modest stereoselectivity.



Scheme 8. HHDP construction methodology developed by Martin

In all the conditions tested, a considerable amount of uncyclized starting compound without iodine was recovered in the end of reaction.

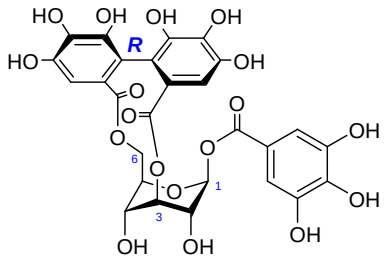


Scheme 9. Permethylated HHDP unit construction on D-glucose

These results were relevant to ellagitannin chemistry in that they provide further understanding of the structural requirements for highly diastereoselective biaryl coupling within carbohydrate units. They present the only inconvenient to have employed as methyl protecting groups, requiring hard deprotection conditions, leading to permethylated derivatives of natural ellagitannins.

1.5.5 Total synthesis of corilagin (3,6 - HHDP)

Yamada was the first to achieve the total synthesis of corilagin (**55**, *Caesalpinia coriaria*[109] Figure 15),[92] characterized by the presence of the HHDP group bridging the 3- and 6-oxygens of the glucose, with an axial chirality *R*.



55: Corilagin

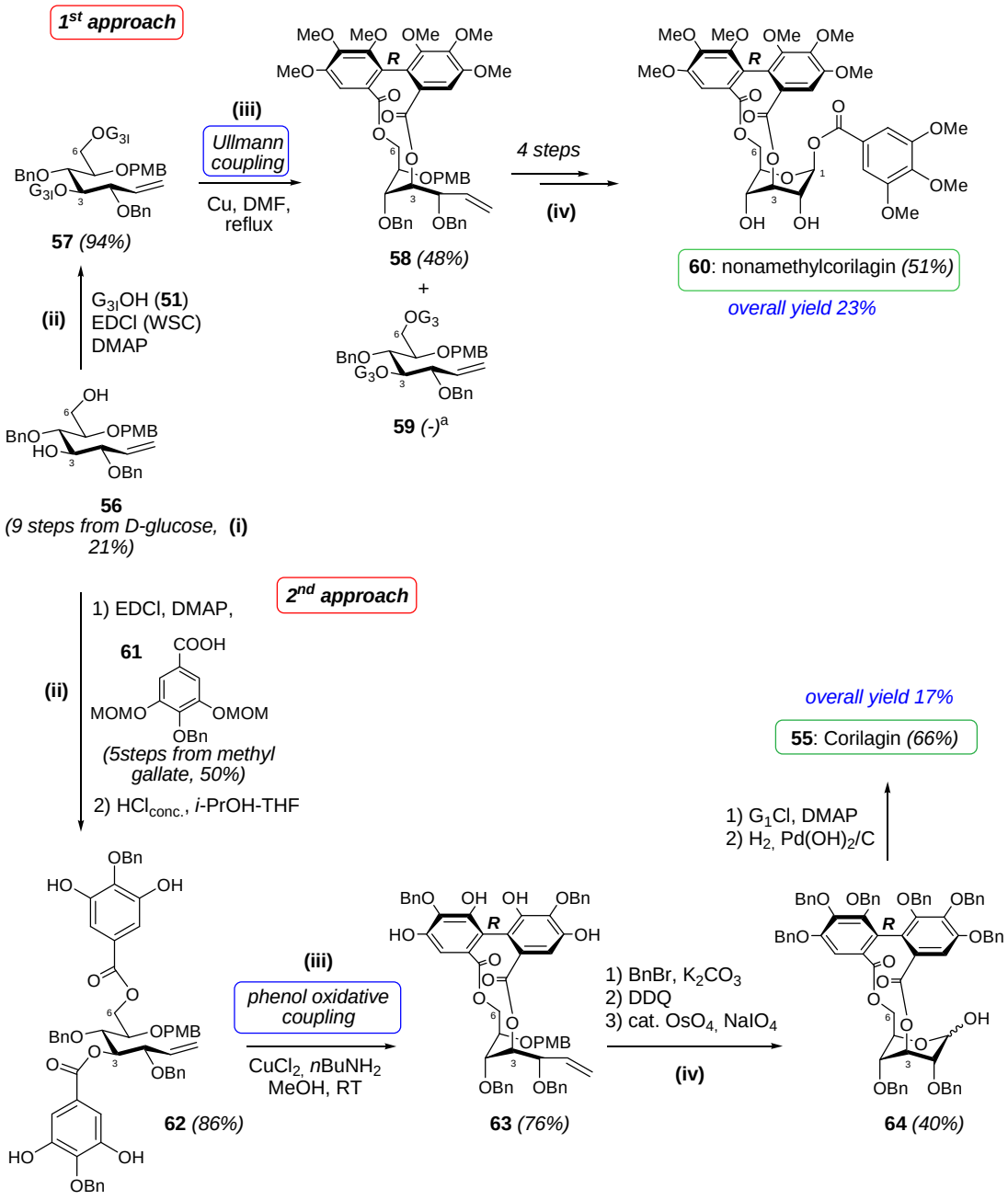
Figure 15. Corilagin structure

In 2004, he realized the synthesis of permethylated corilagin (**55**, Scheme 10), *via* the Martin's conditions (Ullmann coupling). The main effort was the building of the 3,6-bridged bis-macrolactone structure, which is holding the glucose ring in the contra-thermodynamic conformation, and makes inapplicable the classical conditions (methods A or B) until now exposed.

To overcome this difficulty the following strategy was employed:

- ring-opening of the pyranose to give the compound **56** (obtained in 9 steps from D-glucose);
- esterification of two galloyl moieties mono-iodinated G_{3I};
- preparation of the HHDP group by coupling of the two gallates on the 3- and 6-oxygens;
- stereoselective intramolecular coupling in the Ullmann condition leading to **58**;
- reconstruction of the pyranose and esterification of a further G_3 unit at the anomeric position.

By this approach, the permethylated corilagine (**60**) was obtained with an overall yield of 23% on 6 steps.



[a] *yield for the single step not given in the article*

Scheme 10. Total synthesis of corilagin and its permethylated derivative

The unattainable complete demethylation of nonamethylcorilagin (**60**) prevented the total synthesis. Other protecting group were tried but difficulty of the iodination of corresponding tri-*O*-benzyl- or MOM-protected gallates forced to abandon the use of Ullmann coupling for the HHDP preparation.

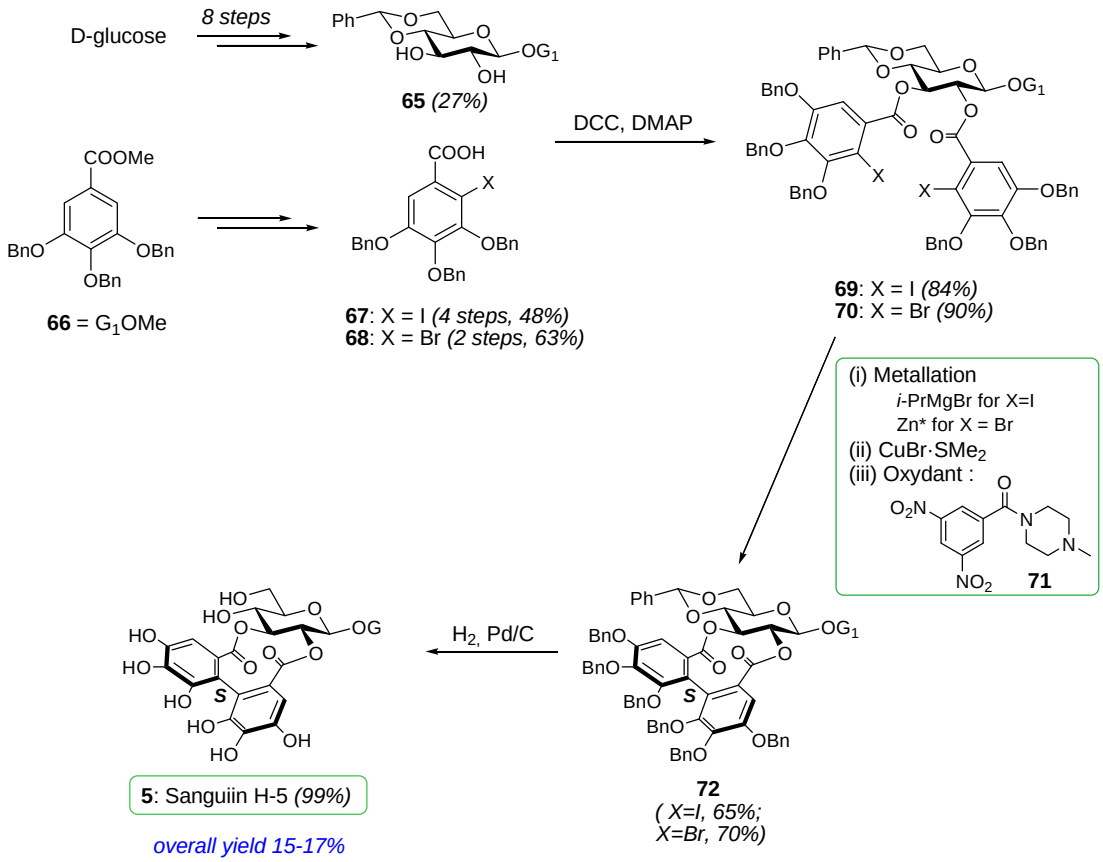
Taking inspiration from the Brussee's[110] work, Yamada realized in 2008 the first total synthesis of corilagin (**55**) through the key step of oxidative coupling realized between galloyl

moieties mono-benzylated (this symmetric protection allowed to avoid the regioisomers formation observed in the Feldman's synthesis).[92]

A $CuCl_2$·-amine complex was employed as oxidant and allowed the obtention of the corilagin **55** with an overall yield of 17% on 8 steps.

1.5.6 The strategy of Spring for the synthesis of sanguiin-H5

In 2008, Spring[91] proposed a total synthesis of sanguiin-H5 (**5**) alternative to the one proposed by Feldman basisd on a different coupling methodology.



Scheme 11. Total synthesis of sanguiine H-5 by Spring

The developed methodology consists of three steps :

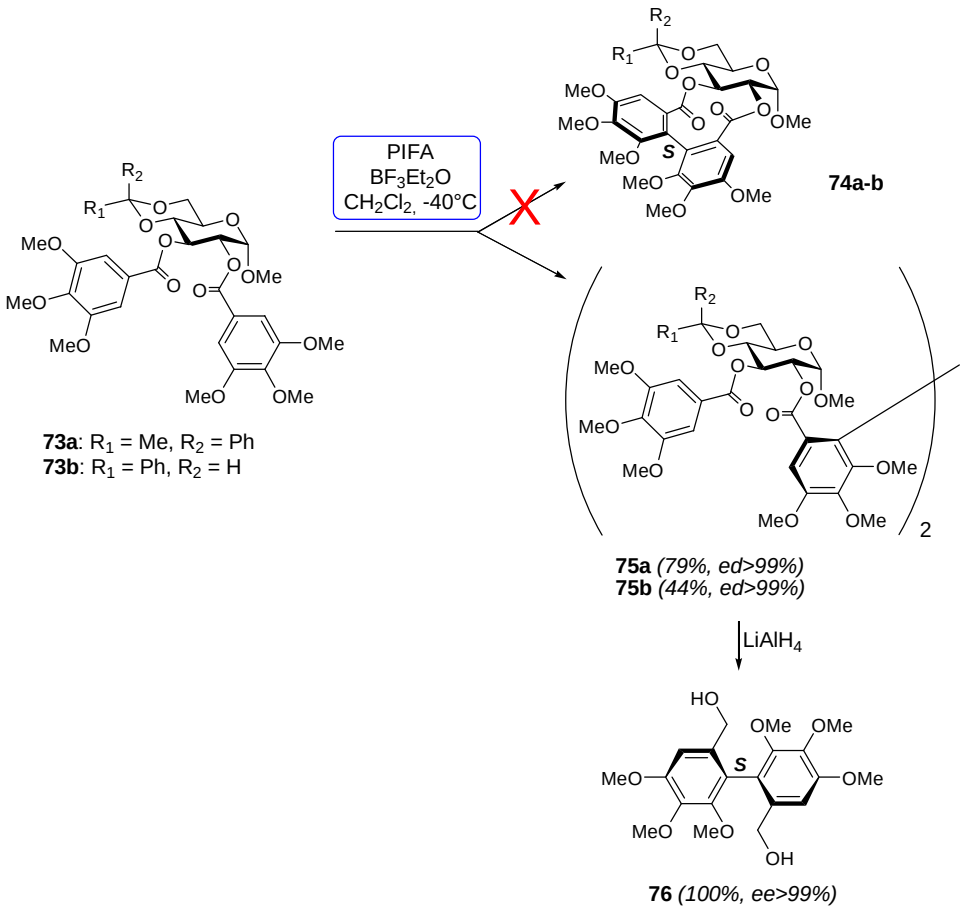
- metal-halogen exchange (iodine-magnesium[111] or bromide-zinc[112]);
- transmetallation with copper salts;
- oxidation of the obtained organocuprate.

By this way. Spring managed to obtain – in despite of Yamada – the iodination (and bromination) of benzylated methyl gallate units.

1.5.7 PIFA mediated oxidative coupling attempts

The last methodology for the HHDP construction in a biomimetic way (method A) that it will be discussed concerns the strategy employed by Kita for the obtention of compounds bearing a permethylated HHDB group type **74a-b**[113] exploiting the chemistry of hypervalent iodine-type reagent.

The reaction was carried out at –40°C with bis(trifluoroacetoxyiodo)benzene ($PhI(OCOCF_3)_2$, PIFA) and the Lewis acid $BF_3{\cdot}Et_2O$. 1,2-diaroyl derivatives (**73a**-**b**) of protected α-D-glucose underwent a smooth coupling reaction in the presence of PIFA–$BF_3{\bullet}Et_2O$, unexpectedly in an intermolecular way, to afford the dimers (**75a**-**b**) in good yields and with high diastereoselectivity.



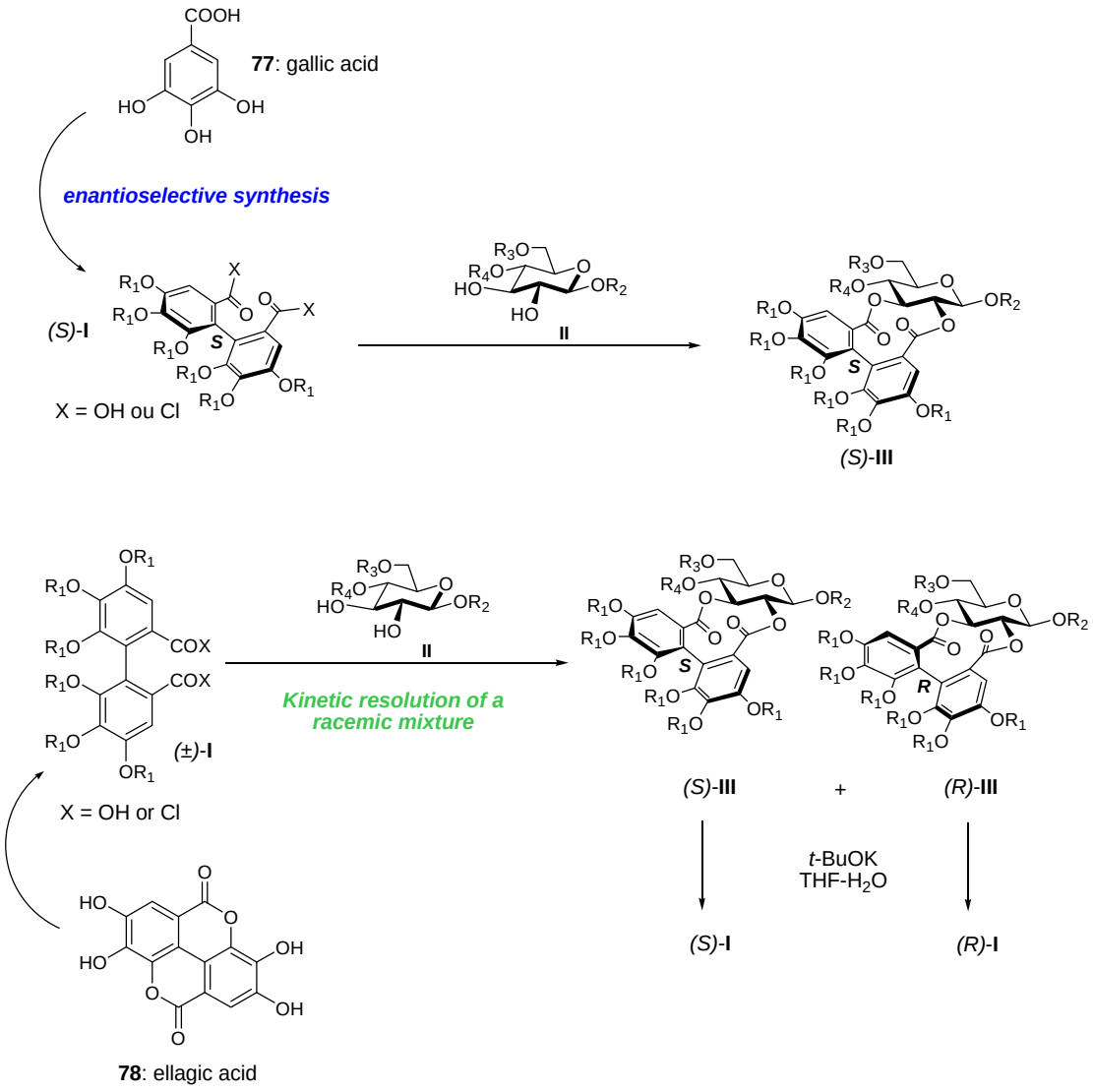
Scheme 12. PIFA mediated biaryl coupling attempts by Kita

1.6 Enantiomerically pure Ellagitannins via double esterification of hexahydroxydiphenic acid (Method B)

An alternative to the biomimetic oxidative cyclization strategy for ellagitannin synthesis consists in the convergent union of glucose diols with a fully formed, chiral HHDP unit. The method B is not biomimetic because it does not follow the biosynthetic pathway described by Gross[55] (Scheme 2). However it presents the advantage to reduce the steps number in respect to the above described method A (it does not need orthogonal and not-symmetrical phenols protection).

Up to now, there are two approaches to produce enantiomerically pure ellagitannins according to the methodology B (Scheme 13) :

- Incorporation of a presynthesized enantiomerically pure diacid (*S*)-**I** [or (*R*)-**I**] HHDP into an appropriately substituted glucose core **II** to give only one atropoisomer (*S*)-**III** [or (*R*)-**III** respectively]
- Kinetic resolution of a racemic diacid mixture (±)-**I** obtained from ellagic acid (**78**) with a conveniently protected D-glucose **II**. The basic hydrolysis of the products (*S*)-**III** or (*R*)-**III** (in the Gassman conditions)[114] allows to obtain the enantiomerically pure diacids HHDP (*S*)-**I** and (*R*)-**I**.



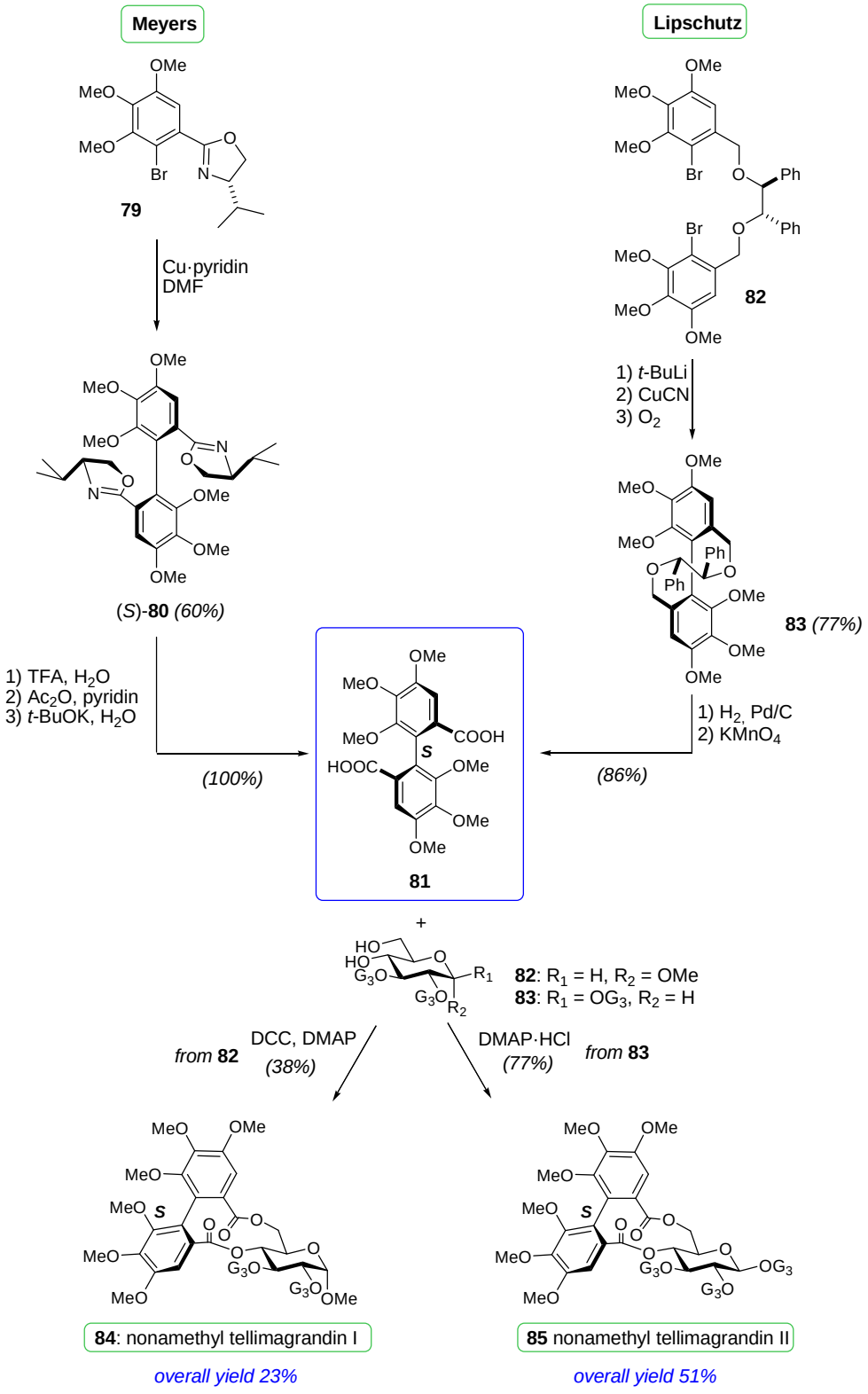
Scheme 13 Two ways towards the obtention of enantiomerically pure HHDP unit

1.6.A Enantioselective synthesis of a group (*S*)-HHDP

In 1994, Meyers[93] described the oxazoline mediated asymmetric Ullmann coupling to produce (*S*)-hexamethoxydiphenic acid *(S)*-**81**, wich was used to synthesize the *O*-permethyl derivative of naturally occurring tellimagrandin I (**84**) (Scheme 14).
The incompatibility of the removal condition of methyl protecting groups with the compounds did not allow to obtain the natural product.

Lipshut[94] also described an asymmetric synthesis of a biaryl system by an intramolecular oxidative coupling reaction of cyanocuprate intermediates. The bi-esterification of the diacid

in the Keck modified Steglich conditions[107] on the glucose derivative **83** led to nonamethyled telimagrandin II (**85**) with a chemical yield of 77%.

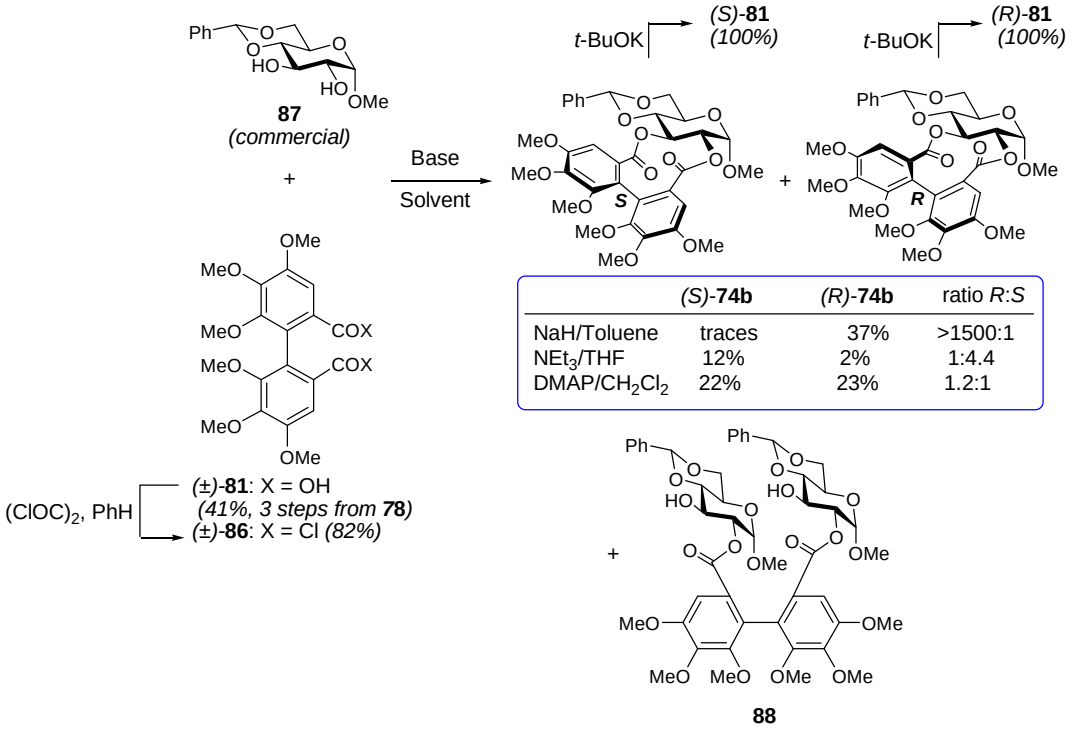


Scheme 14. Enantioselective synthesis of permethylated tellimagrandin I and II

1.6.B Kinetic resolution

The alternative strategy to the obtention of enantiopure HHDP diacid, proposed by Itoh in 1995,[95,115] consists in the realization of a kinetic resolution.

The optical resolution of axially chiral biaryls (±)-**81** acid (obtained in three steps from ellagic acid **78**)[95,116] or its chloride, can be realized through the esterification of a commercial sugar 4,6-*O*-benzylidene-α-D-glucopyranoside **87** (Scheme 15). The compounds (*S*)-**81** and (*R*)-**81** enantiomerically pure were so obtained after hydrolysis[114] of compounds (*S*)-**74b** and (*R*)-**74b** respectively.

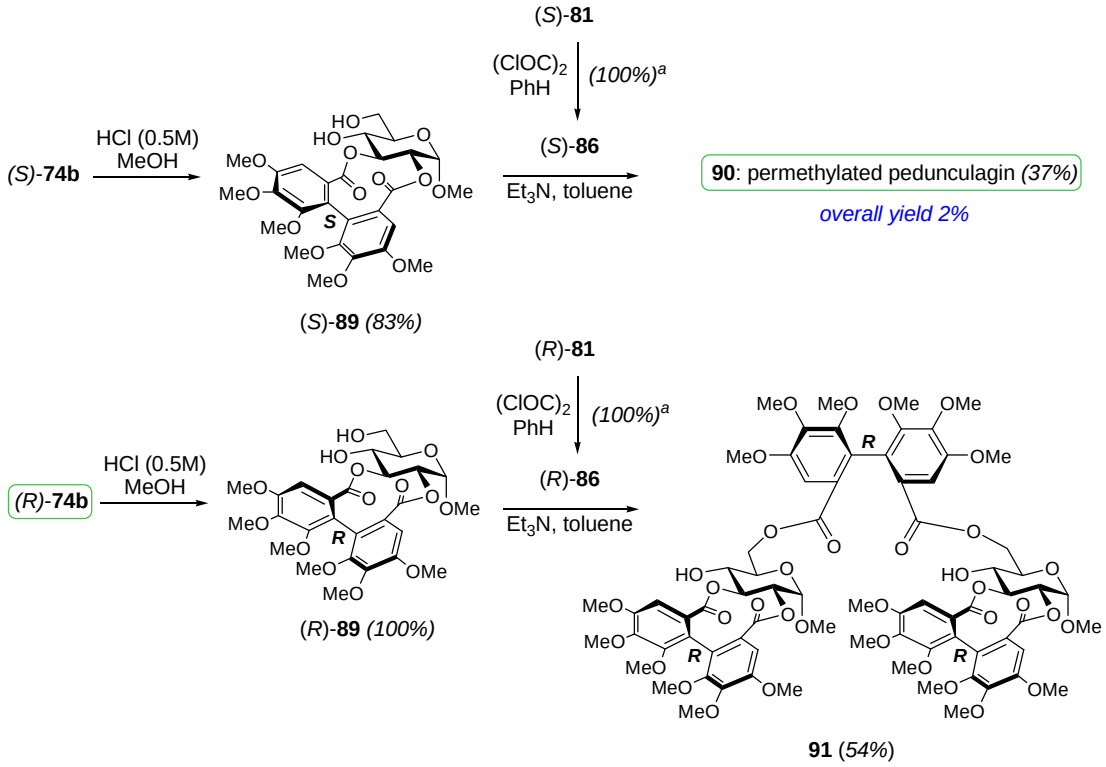


	(*S*)-**74b**	(*R*)-**74b**	ratio *R*:*S*
NaH/Toluene	traces	37%	>1500:1
NEt_3/THF	12%	2%	1:4.4
DMAP/CH_2Cl_2	22%	23%	1.2:1

Scheme 15. Kinetic resolution of HHDP racemic unit

It was assumed that the diastereoselectivity did not depend on thermodynamic differences between the two atropisomers but on kinetic differences in the intramolecular cyclization. It can then be controlled by varying the basis and the solvent employed. The best diastereoselectivity was observed when sodium hydride was employed in toluene. In this condition, the formation of the (*R*)-HHDP was favored. While triethylamine in tetrahydrofurane favored the atropoisomer *S*. The major by-product obtained in this reaction conditions was the dimer **88**.

Itoh *et coll.* employed this strategy in the total synthesis of permethylated pedunculagin (**90**). After benzylidene cleavage in acidic conditions on (*S*)-**89** the esterification with the acyl chloride (*S*)-**81** led to **90** with an overall yield of 31% on two steps.



[a] *crude basisd yields.*

Scheme 16. Total synthesis of per-methylated pedunculagine

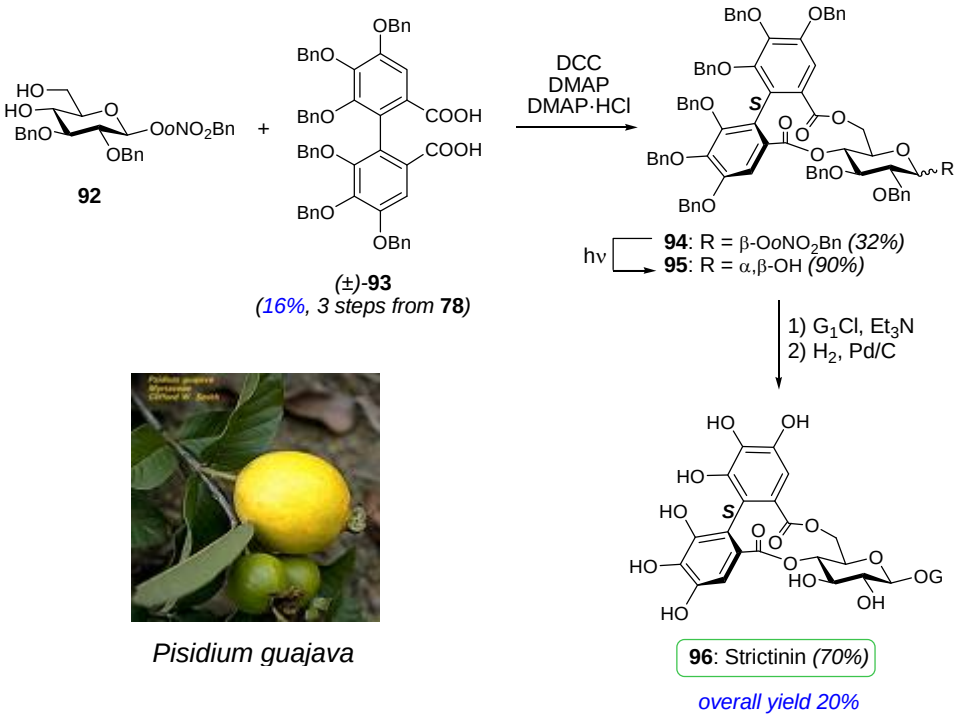
The same reaction sequence was applied to the compound (*R*)-**74b** in order to accomplish the total synthesis of permethylated platycaryanin D[117] (same structure than **90** with an *R* configuration of the HHDP). The introduction of the second (*R*)-HHDP unit in 4,6- led to an intermolecular reaction giving the dimeric compound **91**.

1.6.1 Total synthesis of strictinin (4,6-HHDP)

The strictinin (**96**, Scheme 17), isolated for the first time in 1982 by Okuda *et coll.* from *Casuarina stricta*[33,41] and *Pisidium guajava* leaves,[16] is constitued by an HHDP bonded to the oxygens 4 and 6 of a D-glucopyranose and a further galloyl group attached to the anomeric position of the sugar.

Khanbabaee *et coll.* accomplished its total synthesis in 1997[76] through the diastereoselective esterification of a racemic perbenzylated diacid HHDP (±)-**92** (obtained in three steps from

ellagic acid **78**)[118,119] on the conveniently protected sugar **92** in the Keck-modified Steglich conditions[107] (Scheme 17).



Scheme 17. Total synthesis of strictinin

The atropoisomeric *S* compound **96**, was the only product obtained in these conditions with a yield of 32%.[79] The photolysis of the *ortho*-nitrobenzyle protecting group followed by esterification of the perbenzylated galloyl unit G_1 and hydrogenolysis (in the same conditions carried out by Feldman for the synthesis of tellimagrandin II, **2**)[81] of benzyl groups led to strictinin **96** with an overall yield on four steps of 20%.

This total synthesis of Khanbabaee constitutes a first exmple of ellagitannin synthesis in a little steps number. It avoids in fact several protection-deprotection steps needed by the Feldman's approach.

1.6.2 Total synthesis of gemine D, hippomanin A and 1,3-di-O-galloyl-4,6-O-(S)-hydroxydiphenoyl-β-D-glucopyranoside (4,6-HHDP)

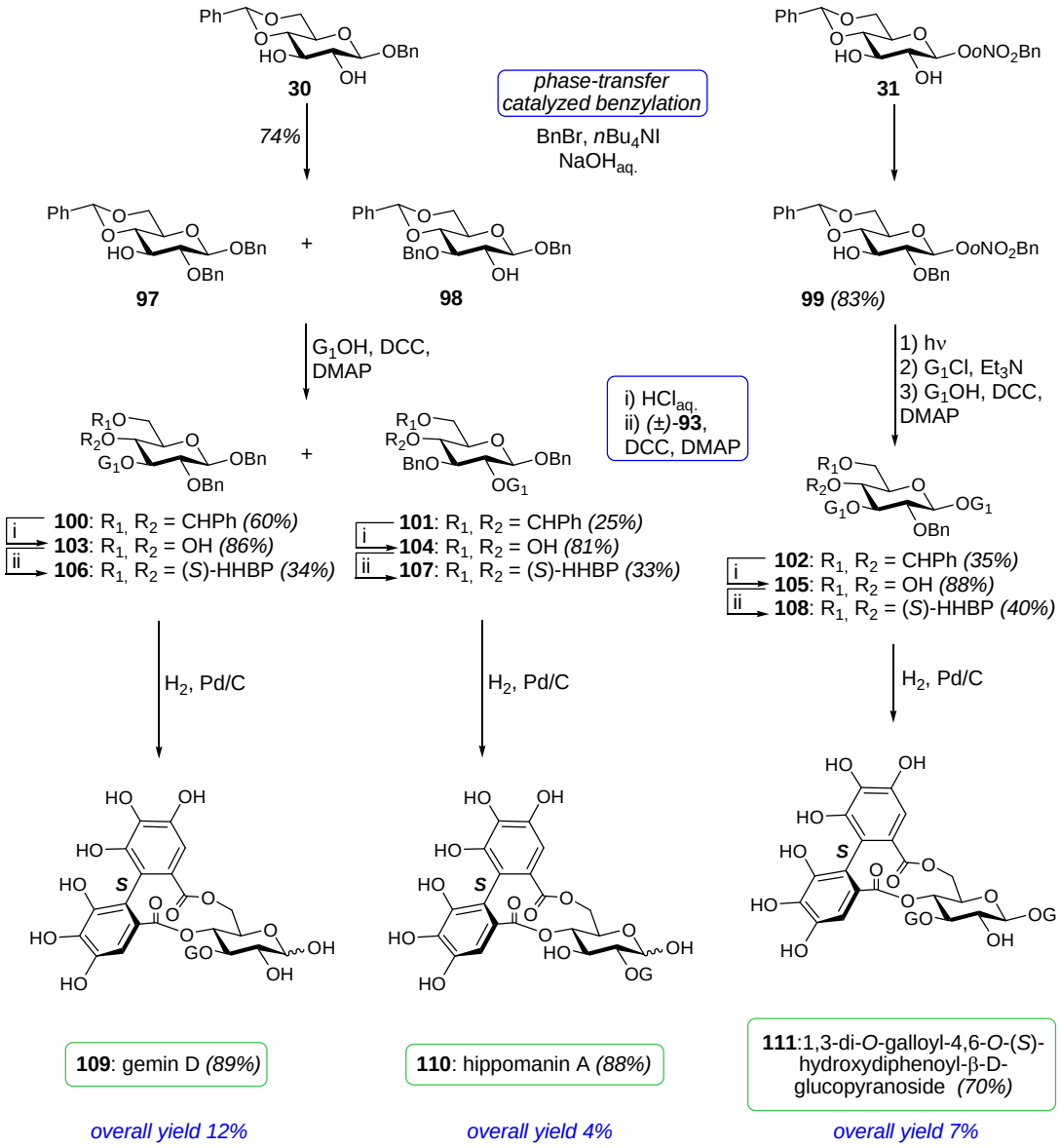
The same approach employed for the strictinin synthesis was applied to the total synthesis of gemin D (**109**, *Geum japonicum* and *Camellia japonica*),[64,120] hippomanin A (**110**, *Hippomane mancinella*)[121,122] and the natural compound **111** (1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hydroxydiphenoyl-β-D-glucopyranoside, isolated from *Reaumuria hirtella* and *Tamarix pakistanica*).[26,123] All these compounds are isomers because they are characterized by the presence of an HHDP-unit at 4,6- positions of a glucopyranose core and one or two galloyl groups linked to the remaining free oxygen of the D-glucopyranose (3-*O*-G for the gemin D **109**, 2-*O*-G for the hippomanin A **110** and 1,3-di-*O*-G for the compound **111**) (Scheme 18).

These compounds were synthesized[80,86] through the same biesterification step of the racemic diacid HHDP (±)-**93** as in the total synthesis of strictinin **96**, possessing an (*S*)-HHDP moiety located at 4,6 positions of the glucopyranose. For the synthesis of these ellagitannins it was necessary to develop a methodology for the selective esterification at 1, 2 and/or 3 positions to give the intermediates **97**, **98** and **99**. Khanbabee *et coll.* demonstrated that this regioselectivity can be obtained through benzylation of the 2,3-glucopyranoside diols **30**-**31** using tetrabutylammonium iodide (Bu_4NI) as phase-transfer catalyst exploiting the intrinsecal distinct reactivity of the different hydroxyl on differently protected glucopyranosides.

Both the regioisomers **97** and **98** were obtained from the reaction on **30** as not purifiable mixture. The mixture was then acylated with the benzyl-protected gallic acid $\mathbf{G_1OH}$ to assemble the frameworks of **109** and **110**.

The biesterification on the compound **105** led to the formation of the diasteroisomer *S* with a chemical yield of 40%. A more polar fraction was also obtained but not characterized. It was supposed containing the (*R*)-HHDP diastereoisomer.[86]

The syntheses of these naturally occuring ellagitannins was then completed by hydrogenolysis of the benzyl groups.



Scheme 18. Total synthesis of gemin D, hippomanin A and 111

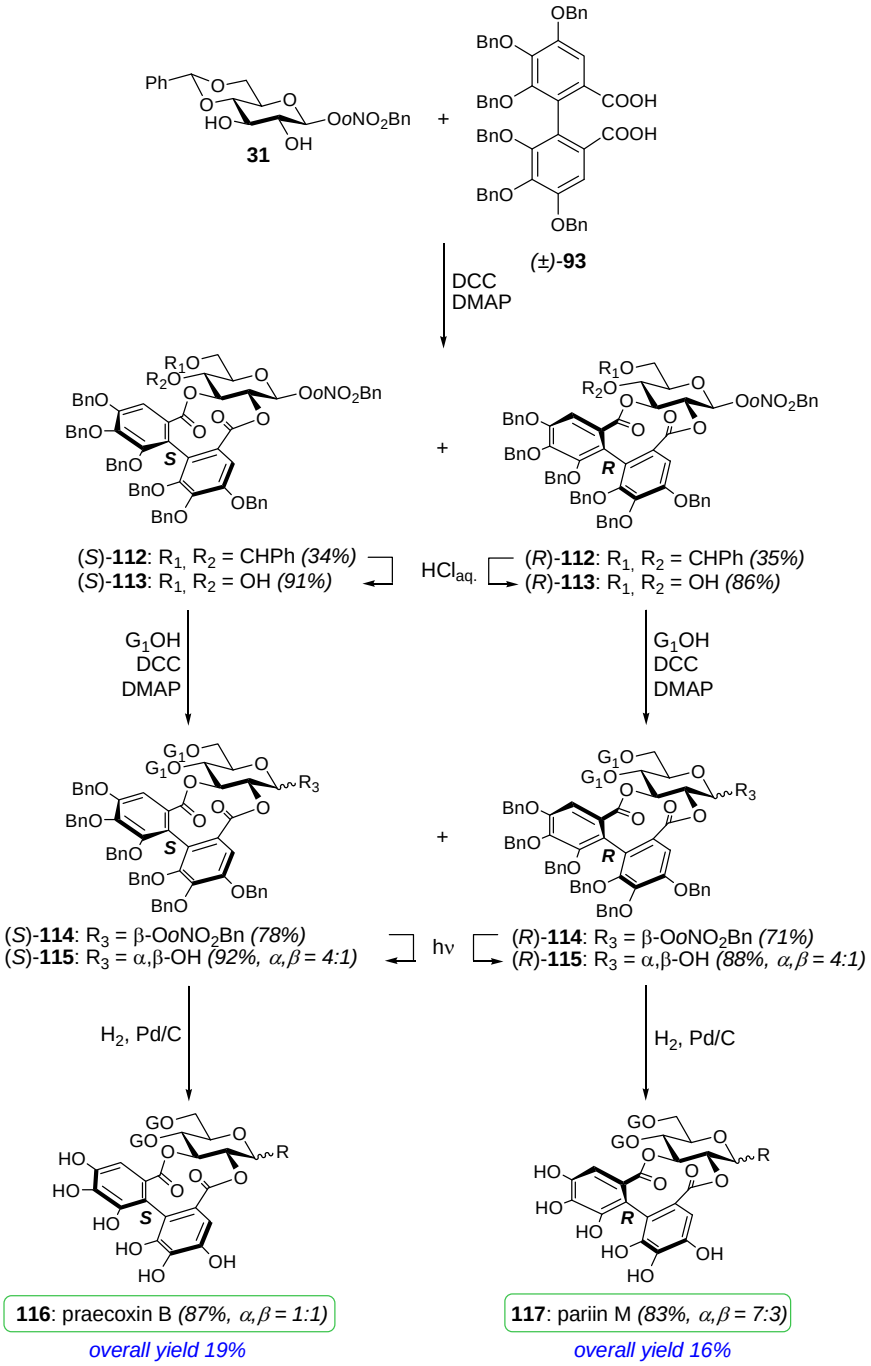
1.6.3 Total synthesis of praecoxin B, pterocarinin C, pariin M and mahtabin A (2,3-HHDP)

As mentioned above, the chirality of the hexahydroxydiphenoyl (HHDP) moieties located at the 2,3- or 4,6-positions of the glucopyranoside core of the natural ellagitannins are invariably in the (*S*)-series as in praecoxin B (**116**) and pterocarinin C (or pterocaryanin C, **3**), extracted from *Stachyurus praecox*[124,125] and *Tibouchina semidecandra.*[126] In contrast, 2,4- or 3,6-HHDP-substituted ellagitannins exhibit the (*R*)-configuration as in the pariin M (**117**).

The total synthesis (Scheme 19) of both atropisomers **3** and **116** was accomplished by Khanbabee.

The biesterification in the classical Steglich conditions[108] of **31** with the racemic unit HHDP (±)-**93** gave access to both the atropoisomers *S* and *R* (**112**), that were purified by column chromatography. The absolute configuration of the units HHDP was confirmed by comparison of the optical properties of the products obtained from hydrolysis in the Gassman conditions[114] and the data reported in the literature.[119]

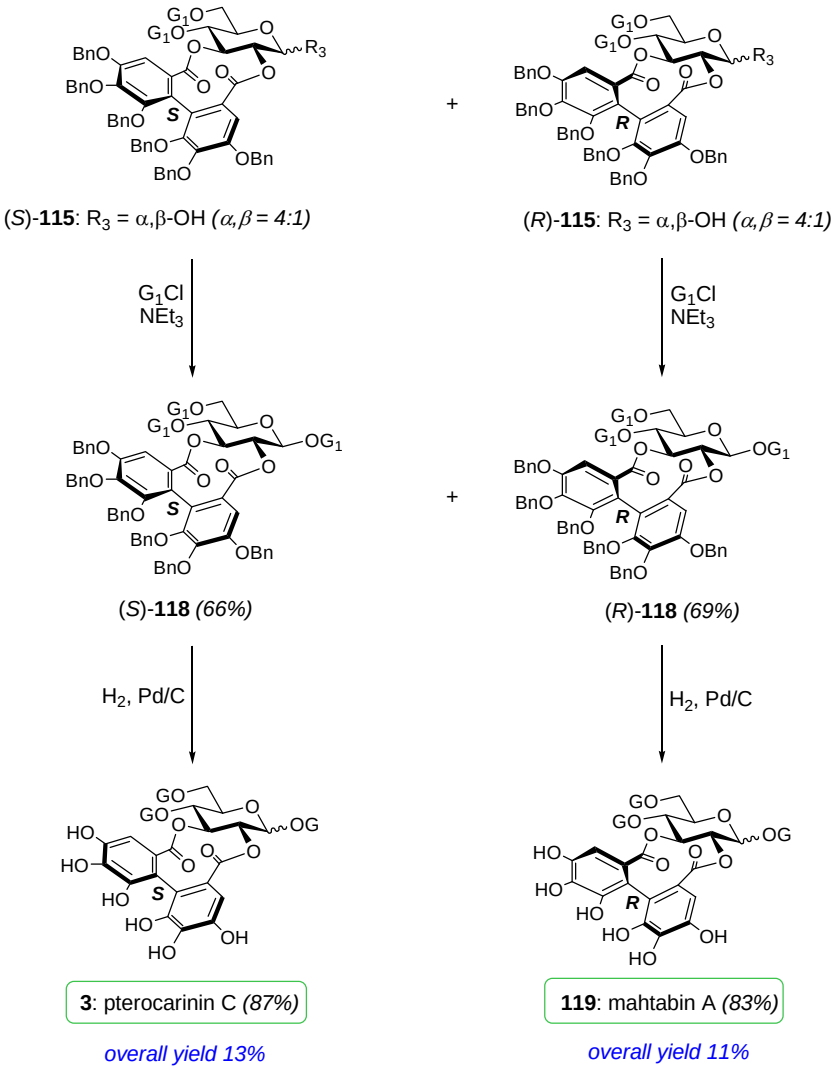
It is interesting to observe that in these esterification conditions the two atropisomers are obtained in a ratio 1 :1, without any diastereoselectivity.



Scheme 19. Total synthesis of praecoxin B and pariin M

Benzylidene cleavage in the conditions of acid hydrolysis and the esterification of two further perbenzylated galloyl unit G_1 led to compounds (*S*)-**114** and (*R*)-**114** completely protected. Two further steps of deprotection were needed to give praecoxin B **116** and pariin M **117** as α/β anomers mixtures.

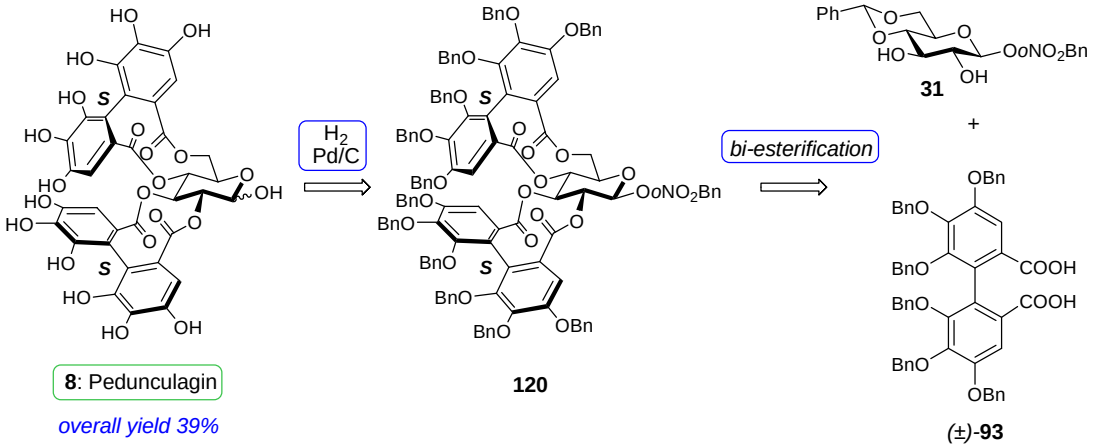
Galloylation of the intermediates (*S,R*)-**115** followed by hydrogenolysis led to pterocarinin **3** and mahtabin **147** (Scheme 20).



Scheme 20. Total synthesis of pterocarinin C and mahtabin A

1.6.4 Khanbabee's pedunculagin (2,3,4,6-HHDP) total synthesis

The methodology developed by Khanbabee allowed the synthesis of pedunculagin (**8**) [87] in only two steps, against the 9 steps of the first total synthesis reported by Feldman in 1994[74]) (Scheme 21).

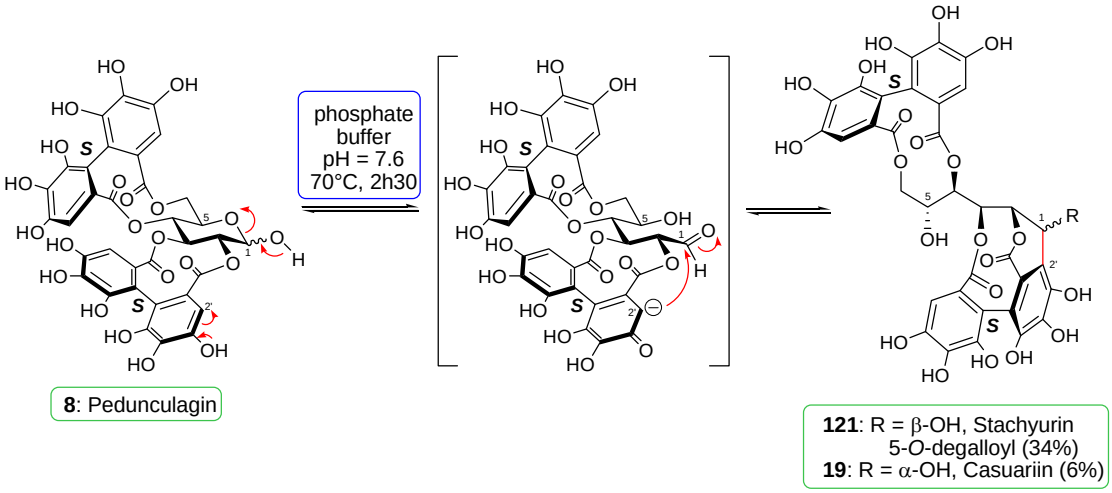


Scheme 21. Total synthesis of pedunculagin by Kanbabee

The compound (*S*,*S*)-**120** was purified with a good yield of 60%. A complex mixture of not purifiable polar compounds was also obtained. The hydrogenolysis of **120** led to pedunculagin **9** with an overall yield of 39%.

1.7 Hemisynthesis of a C-arylglucosidic ellagitannin

No member of this sub-class of ellagitannins has never been ssubmitted to a total synthesis. An only report is present in the literature concerning the *C*-arylglucosidic bond formation. Tanaka *et coll.*[117] who managed to convert the glucopyranosyl pedunculagin (**8**) into the *C*-arylglucosidic ellagitannin casuariin (**19**) and its C-1 epimer (1**8**) (Scheme 22).



Scheme 22. Hemysynthesis of casuariin *via* *C*-arylglucosidation of pedunculagin

According to the proposed mechanism, the reaction proceeds *via* the opening of the sugar with formation of the aldehydic form (as liquibambin **29** in the biosynthetic pathway) which undergoes nucleophilic attack to give casuariin (**19**) and its epimer (**121**) stachyirin degalloylated at the 5 position.

The predominance of β-OH was considered to be due to the nucleophilic attack of the pyrogallol ring on the glucose C-1 aldehyde from the lower side of the glucose.

Chapter 2

Retrosynthetic Analysis and Precursors Synthesis

The practice of total synthesis demands the following virtues from, and cultivates the best in, those who practice it: ingenuity, artistic taste, experimental skill, persistence, and character.
Nicolau K. C.

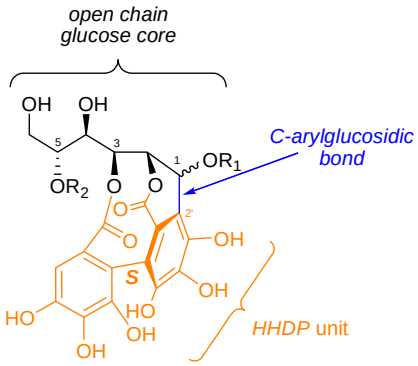
The research group directed by Prof. Stéphane Quideau at the European Institut of Chemistry and Biology in Bordeaux is at the moment one of the most active and experienced in the studies of chemistry and biological activities of *C*-arylglucosidic ellagitannins. Prof. Quideau has recently published a number of articles in highly reputed journals relating his group's initial investigations of the chemical activities of these compounds, and he also edited the first book focusing on the chemistry and biology of ellagitannins.

The present thesis work is part of a very ambitious project aimed to the development of *C*-arylglucosidic ellagitannins as chemoterapeutic agents against cancer. The *C*-arylglucosidic ellagitannins present the structural particularity of having a highly characteristic C–C linkage between the C-1 atom of an open-chain glucose core and a galloyl-derived unit that is either part of an HHDP (hexahydroxydiphenoyl) ester group bridging the 2- and 3-positions of the glucose core, as exemplified in the structures of punicacortein A (**23**) or part of a terarilic nonahydroxyterphenoyl (NHTP) variant that is attached via three ester bonds to the 2-, 3- and 5-positions of the glucose core, as exemplified in the structures of vescalin (**25**) (Figure 16).
Preliminary studies conducted by Quideau *et coll.*[50] have indicated that some of these ellagitannins are highly potent inhibitors of human DNA topoisomerase II, enzyme being a current target of anticancer chemotherapies.

The specific objective of this PhD project was the development of general approaches to the compounds of this class. The punicacortein A (**23a**) and its C-1 epimer epipunicacortein A (**23b**) were the first objective of our synthetic efforts, as simplest structures of this class of natural compounds.
Towards this aim it was necessary to develop novel methodologies related to sugar chemistry, to install the *C*-arylglucosidic bond on an open chain glucose core.
A significant part of this objective, that it's important to emphasize, was the development of an improved purification method for such polar and reactive compounds.

It is possible to identify three key issues that must be addressed in order to accomplish the synthesis of *C*-arylglucosidic ellagitannins:

- Opening of the sugar
- *C*-arylglucosidation reaction
- Atroposelective intramolecular biaryl coupling for the HHDP construction (Figure 16)



23a: R_1 = α-OH; R_2 = G punicacortein A
23b: R_1 = β-OH; R_2 = G epi-punicacortein A
24a: R_1 = α-OH; R_2 = H degalloyl punicacortein A
24b: R_1 = β-OH; R_2 = H degalloyl epipunicacortein A

Figure 16. Key structural elements of *C*-arylglucosidic ellagitannins

2.1 Retrosynthetic analysis

The retrosynthetic plan, depicted in Scheme 23, reflects our wish to develop a biomimetic route to Punicacortein A (**23**).

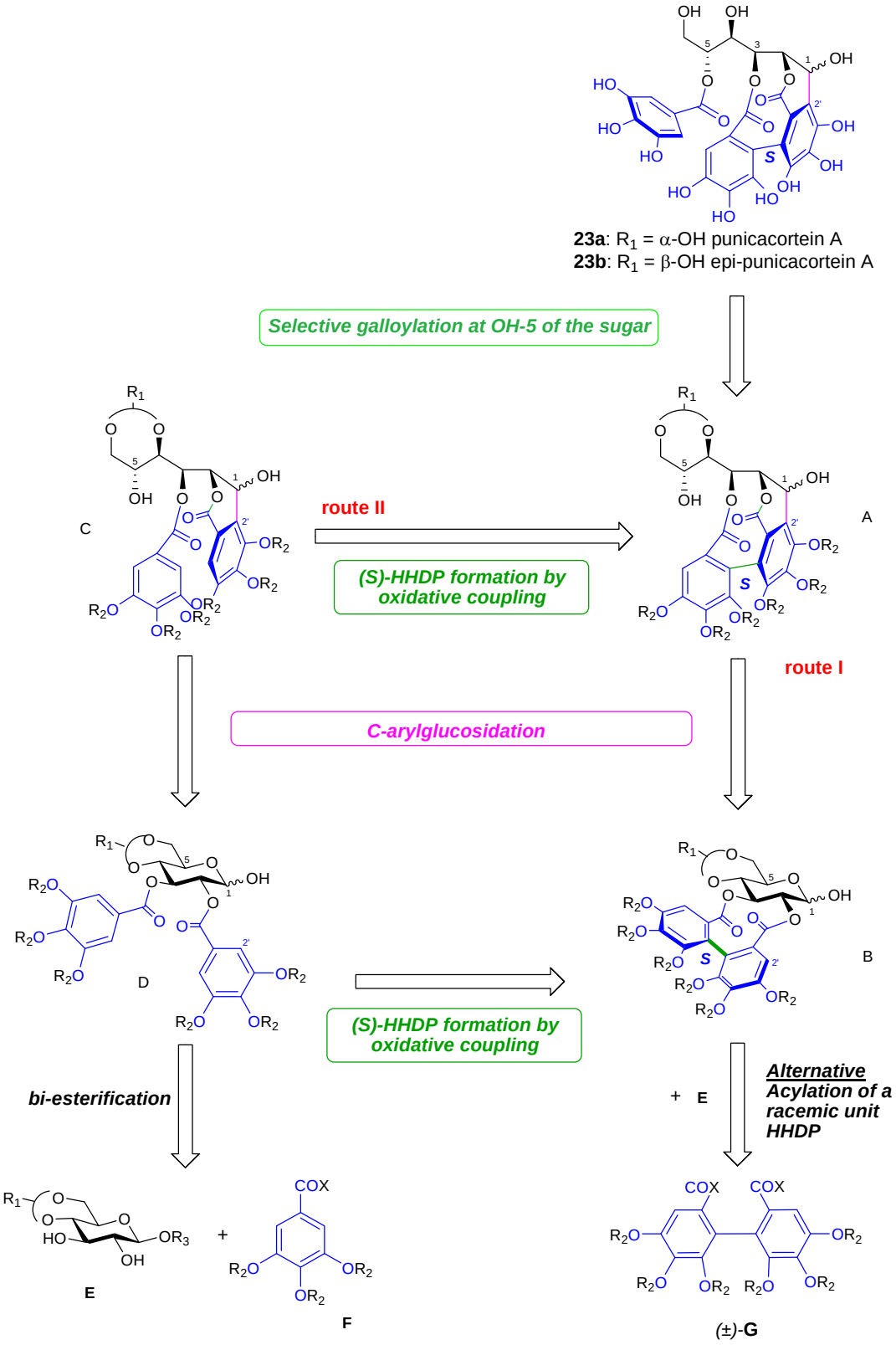
The choice of the synthons has been made in order to allow: *(i)* to get information about the reactivity of these structures, *(ii)* to give access to lead-compounds for the synthesis of scaffolds of molecules for the structure-activity relationship studies, *(iii)* to furnish information about the biosynthetic pathway of *C*-arylglucosidic ellagitannins proposed in the literature (Scheme 23).

In this vein, two possible synthetic strategies can be considered. For both, the access to punicacortein A **23** is done by a sequence of "selective galloylation/*C*-arylglucosidation" on the sugar derivatives **B** (substituted with an HHDP unit) or **C** (substituted with two galloyl units) that are the most important intermediates of the two retrosynthetic routes. The following step of *C*-arylglucosidation is carried out on the intermediate were the HHDP is already present on the sugar (route I) or alternatively on the architecture **C** with the two galloyl units not coupled (route II).

This transformation is the really most innovative and crucial step of the synthesis. It involves opening of the glucopyranosyl ring with concomitant formation of the *C*-arylglucosidic bond. Although both routes have been followed, our guess was from the beginning that the formation of the key *C*-arylglucosidic bond would be facilitated in the case of the conformationally-constrained HHDP-bearing intermediate **B**, in accordance with current biosynthetic hypothesis.
In any event these synthesis permitted to evaluate both alternatives in the context of their relevance to the biogenesis of the target compounds.

According to our strategy punicacortein A **23** is obtained *via* selective esterification of the secondary alcohol in position 5 of the sugar derivatives **A** with a galloyl unit **F** conveniently protected and at the same time activated on the carbonylic function. Several condition will be taken into account at this staid to ensure selective galloylation of the more nucleophilic secondary alcohol without affecting the phenolates.
The intermediate **B** (route I), bearing the (*S*)-HHBP unit, can be prepared (*i*) *via* esterification of a glucopyranosic derivative 1,4,6-*O*-protected **E** with a racemic HHBP (±)-**G** unit or (*ii*) *via* an oxidative coupling, from the intermediate **D**, shared between the two retrosynthetic routes.

Evidently, the choice of the protecting group is of paramount importance for the success of the synthesis. R_1, R_2 and R_3 must be orthogonal and removable in mild conditions applicable to such complexes intermediates.
The value of appropriate protecting groups becomes all the more obvious when manipulation of the end products are considered. The well documented difficulties associated with purification and isolation of the perhydroxylated natural products themselves highlights the absolute necessity of preparing a readily purifiable penultimate synthetic precursor which, upon simple deprotection, will deliver ellagitannin product free of impurities. Thus, the protecting groups not only must modulate the reactivity of the attached phenolic rings but also must provide “handles” compatible with delicate chromatographic purification at the end of the synthesis.[29]



Scheme 23. Retrosynthetic approach to punicacortein A

2.2 Synthesis of intermediate D

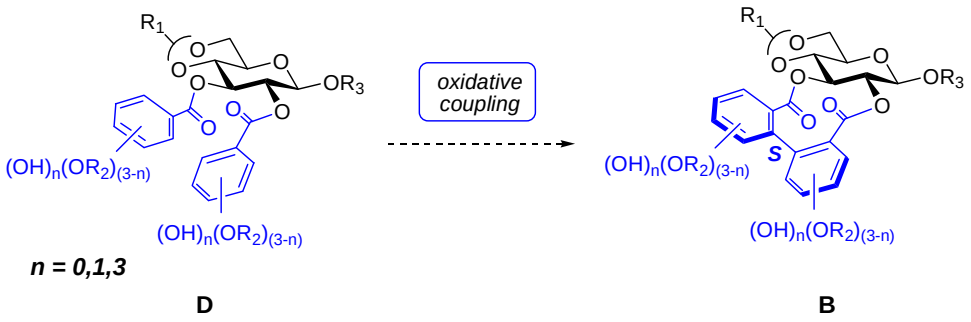
The architecture **D** is shared by the two retrosynthetic routes, it was employed for the *C*-arylglucosidation reaction (route II) and also for the construction of the intermediate **B** of route I.

With this aim a family of eight related digalloyl substrates (**135a-e**, **148**, **149a**, **149b**) with different oxidation potential was synthesized:

- Intermediate D_0, n=0 : completely protected intermediate

-Intermediate D_2, n=2 : *para*-protected galloyl units (reactivity phenols like, *Yamada type*)

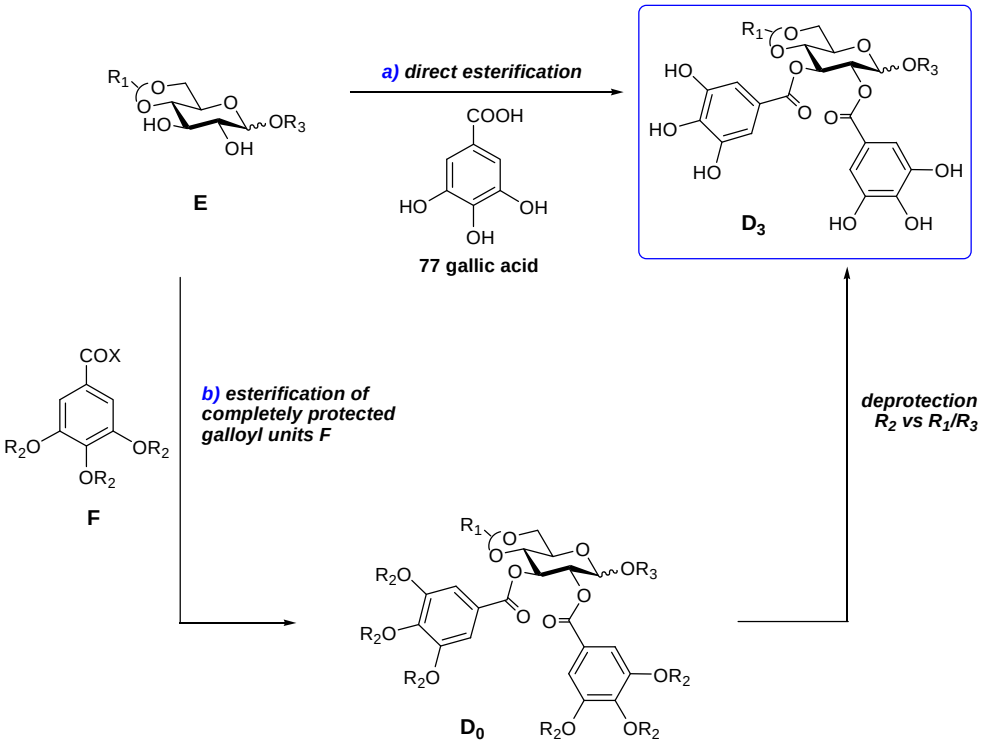
- Intermediate D_3, n=3 : completely deprotected galloyl units (reactivity pyrogallol like, *Feldman type*)



Scheme 24. Compounds D for the intramolecular oxidative coupling

2.2.1 Synthesis of polyhydroxylated intermediate D_3

The precursor D_3 can be synthesized by two ways (Scheme 25): a) *via* esterification of gallic acid **77** on a glucopyranosic 1,4,6-*O*-triprotected derivative **E** ; b) *via* esterification of the same sugar derivative **E** with gallic units completely protected **F**. The desired compound **D_3** is then obtained after an orthogonal deprotection R_2 vs R_1/R_3 of **D_0**.



Scheme 25. Two alternative ways for accessing to the intermediates polyhydroxylated D_3

2.2.2. Synthesis of sugar E

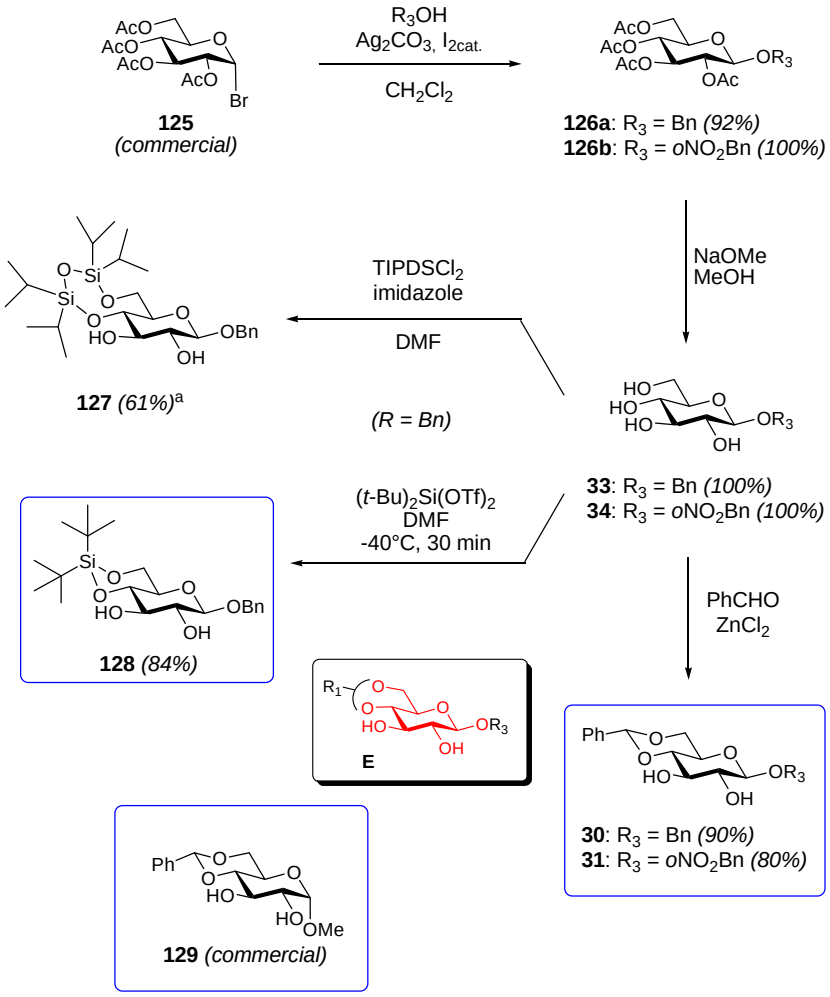
Several sugars **E** were synthesized with different protecting groups at the anomeric position (R_3 = methyle (Me), benzyl group (Bn) and *o*-nitrobenzyl group (*o*NO_2Bn)) (Scheme 26).

The compound **129** (R_3 = α-methyl) is commercially available. As the methyl group at the anomeric position is difficult to remove, this compound was employed for model studies.

The protecting group benzyl (removable by hydrogenolysis) and *o*-nitrobenzyl (oNO_2Bn, removable by photolysis) were chosen as they are cleaved under very mild conditions.
The protecting groups cleavable by irradiation as *ortho*-nitrobenzyl moiety -the most employed-[127] furnish a valid alternative to the conventional protecting group.[128,129] It is stable under several condition and can be selectively removed for irradiation at 300 nm.[73,130]
Moreover both Bn and *o*NO_2Bn can be introduced easily and in *quasi* identical conditions. The starting compound acetobromo-α-D-glucose **125** is commercially available. The intermediates **126a-b** are obtained easily via Koenigs-Knorr reaction[131] with the alcohol R_3OH in presence of silver carbonate and iodine in dichloromethane. A classical deacetylation reaction[131] gives the sugars **33** and **34** in quantitative yields.

The sugar derivatives obtained can be regioselectively protected in 4,6-positions by a benzilydene group (removable in acid conditions) or a 1,1,3,3-tetraisopropyldisiloxan-1,3-diyl (TIPS, selectively and softly removable by reaction with fluoride ion), both orthogonal to the group R_3 at the anomeric position, previously installed (Scheme 26).

The benzylidene group is already present on the commercially available sugar **129**. It can be easily installed on the sugars **33** and **34** by reaction with zinc chloride and benzaldehyde to give the sugars **30** and **31**, both largely employed in the total synthesis of ellagitannins.



[a] *not repeatable yields.*

Scheme 26. Synthesis of sugars E **(4,6-*O*-protected D-glucopyranoside derivative)**

The group R_1 = TIPDS was introduced on the sugar **33** by treating with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxan ($TIPDSCl_2$) in dimethylformamide (DMF) in the presence of imidazole to give **127** with a chemical yield of 61%.[132]

This protection step was characterized by not reproducible yields so it was tried as alternative protecting group R_1 = di-*t*-butylsilyl (DTBD). In this case, the resulting 6-membered cycle is thermodynamically more stable than the 8 membered cycle obtained with TIPDS. Moreover, it is simple to install as diols protecting group, and it results to be very stable to both acid and basic conditions. The reaction conditions introduced by Seeberger[133] were applied on the compound **33** and the sugar **128** was obtained with a reproducible chemical yield of 84%.

The sugar precursors **E** synthesized were so employed in the following reaction of esterification with the opportunely protected galloyl unit **F** (Scheme 25).

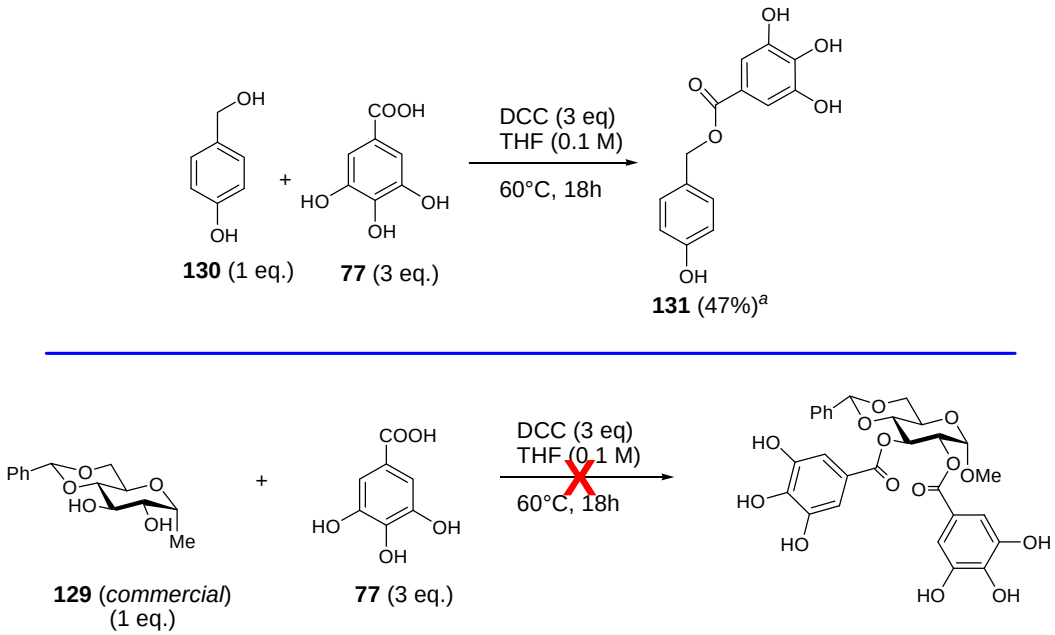
2.2.3. "Biomimetic" approach to the D_3 synthesis: esterification of the sugar E with gallic acid

At first, we considered the possibility to perform the esterification in a direct way, without protecting the gallic acid **77**.

Even if the galloylation of a sugar derivative is a classical reaction in the ellagitannins chemistry, the only conditions at today optimized are the Steglich conditions[107,108] employable to completely protected galloyl units **F**.

The difficulty consists in the fact that the free phenols on the gallic acid **77** can compete with the secondary alcohols of **E** in the esterification. According to the classical Steglich conditions, the esterification is performed in presence of carbodiimide in basic conditions. These are not the best conditions to favor the reactivity of the alcohol against the phenol. The use of an nitrogenated basis (DMAP, pyridine…) causes the deprotonation of the phenols that become more nucleophilic than the aliphatic alcohol.
The most employed methodology to favor the nucleophilicity of an alcohol on a phenol is the one proposed by Mitsunobu and applied by Appendino to the synthesis of gallic acid esters.[134] The Mitsunobu esterification is exploitable on a wide variety of substrates with several functional group. The major inconvenient is due to the inversion of configuration at the substitution center.
The alternative is to promote the reaction with DCC without the basis in order to obtain an activation of the alcohol in neutral conditions. In these conditions, the aliphatic alcohols, more nucleophile that the phenols, can react preferentially.[135,136]

Preliminary promising results were obtained on a model compound, the *para*-hydroxybenzylic acid **130** (Scheme 27).



[a] *Not optimized conditions. Not complete consumption of the starting material. Esterification on the phenolic function not observed.*

Scheme 27. Direct esterification of gallic acid

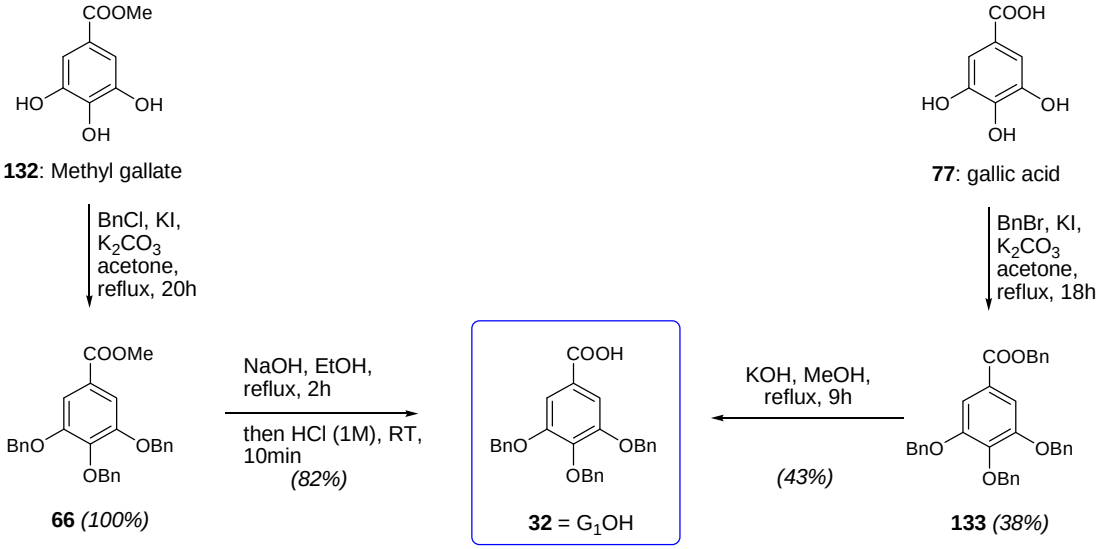
These results encouraged us to apply the same conditions on the commercially available sugar **129** as model system, prior to venturing toward the actual synthesis. In this case, even after prolonged reaction time, and variing the reaction conditions (stochiometry of DCC, temperature, concentrations) any consumption of the starting compounds was observed. The secondary alcohols on **129** are maybe less accessible than in **130**, this could be an explication of the experimental finding.

Even if other strategy could be tried (i.e. utilization of a chloride of the acid or an anhydride), or other catalyst, we preferred to continue the synthesis by employing a fully protected derivative of the gallic acid, under the classical Steglich conditions.

2.2.4 Synthesis of completely protected galloyl units F_0

A protecting benzyl group (R_2 = OBn), easy to introduce on the phenols of gallic acid, has been chosen.

The perbenzylated **F_0** unit was synthesized under Chen conditions[137] from the methyl gallate **132** (Scheme 28). The benzylation was carried out in acetone with benzyl chloride in presence of potassium iodide and potassium carbonate. The perbenzylated compound obtained was then hydrolyzed in presence of sodium hydroxide in ethanol to give the compound **32** with a global yield of 82%.



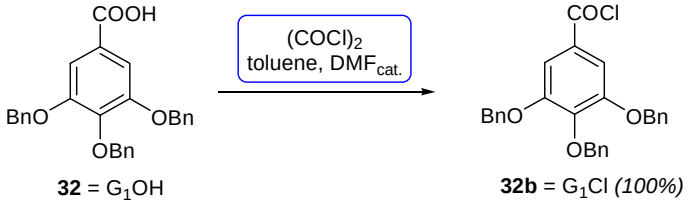
Scheme 28. Syntesis of F_0 –unit

An alternative way leading to the compound **32** is a perbenzylation of gallic acid **77** promoted by benzyl bromide in acetone followed by hydrolysis in methanol with sodium hydroxide.[138] The overall yield in this case was lower than 20%, so the first way was preferred.

The next step of esterification can demand the preparation of the acyl chloride in order to improve the chemical yields.

The preparation of **F_0** chloride of was performed by using oxalyl chloride in toluene in the presence of a catalytic amount of DMF.[137]

The chloride obtained has been employed directly in the following esterification reaction.



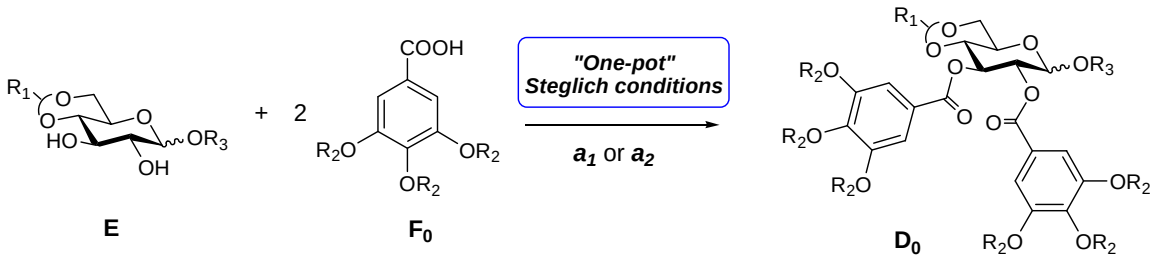
32 = G_1OH **32b** = G_1Cl *(100%)*

Scheme 29. Synthesis of F_1-Cl unit

2.2.5 Preparation of intermediates D_0

The previously synthesized $\mathbf{F_0}$ unit was introduced on the sugar **E** in the classical Steglich conditions,[107,108] that are also the most employed in ellagitannins synthesis.

The reaction was carried out in dichloromethane in presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give the esterified sugars $\mathbf{D_0}$ (Scheme 30).



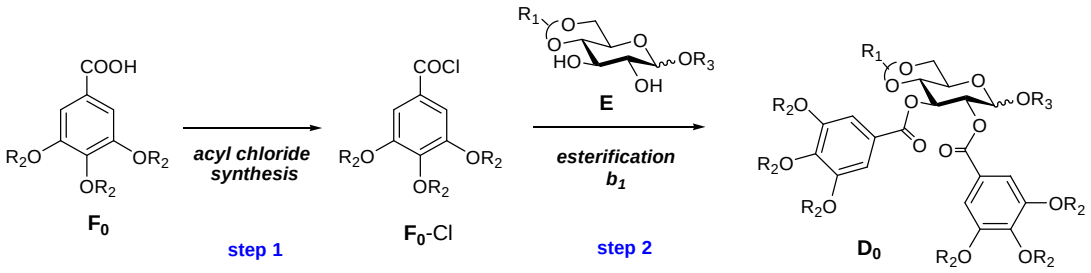
E **F_0** **D_0**

a_1: **E** (1 eq.), $\mathbf{F_1}$ (2.2 eq.), DCC (4.4 eq.), DMAP (2.2 eq.), CH_2Cl_2 (0.025 M), ta ou Δ, 16-48h
a_2: **E** (1 eq.), $\mathbf{F_1}$ (2.2 eq.), DCC (2.2 eq.), DMAP (0.5 eq.), DMAP.HCl (0.5 eq.), CH_2Cl_2 (0.025 M), Δ, 5 -24h

Scheme 30. « one-pot » esterification conditions

The conditions a_2 are the Keck[107] modified Steglich conditions. The addition of an hydrochloride amine, DMAP·HCl, permits to favor the proton transfer needed for the esterification, and reduce the formation of *N*-acylurea, secondary and undesired product of the esterification DCC-promoted (see annex 1).

As the a_1 and a_2 conditions, that can be defined « one-pot », gave not reproducible chemical yields, a two steps strategy was developed as alternative. It consists in the formation of the acyl chloride $\mathbf{F_1}$-Cl of the gallic acid derivative, then bi-esterification of **E** with an excess of chloride (Scheme 31).



***b*$_1$**: **E** (1 eq.),**F$_1$-Cl** (2.4 eq.), DMAP (3 eq.), CH_2Cl_2 (0.025 M), RT, 16-22h

Scheme 31. « Two-steps » esterification conditions

This “two-steps” strategy is rarely utilized in the ellagitannins synthesis; even if it adds another step to the synthesis, it is easy to realize as the acyl chloride intermediate is directly involved in the esterification without any purification.

The results are synthesized in the Table 2.

Entry	Galloyl unit			Sugar			Products	Conditions[a]	Yields[b]
	F$_0$	**F$_0$**-Cl	R_2	**E**	R_1	R_3	**D$_0$**		
1	**32**	**32b**	Bn	**129**	PhCH	α-Me	**134a**	a_2 b_1	97% 80%
2				**30**	PhCH	β-Bn	**134b**	a_2	56%[c]
3				**31**	PhCH	β-*o*NO_2Bn	**134c**[d]	a_2	100%
4				**128**	DTBS	β-Bn	**134e**[d]	a_1 b_1	20%[c,d] 30%[c]

[a] ***a*** *= conditions « one-pot » ;* ***b*** *= conditions « two-steps ».* [b] *Chemical yield after silica gel column chromatography purification.* [c] *Not optimized yields.* [d] *product monogalloylated obtained.* [d]*Product synthesized by G. Malik. Characterization not detailed in the experimental section.*

Table 2. Results of the esterification of F$_0$ units

2.2.6 Preparation of the itermediates D$_3$ via orthogonal deprotection of precursors D$_0$

The orthogonal deprotection of D_0 intermediates was carried out *via* two ways:

- hydrogenolysis of benzyl groups;
- photolysis of the *ortho*-nitrobenzyl group at the anomeric position.

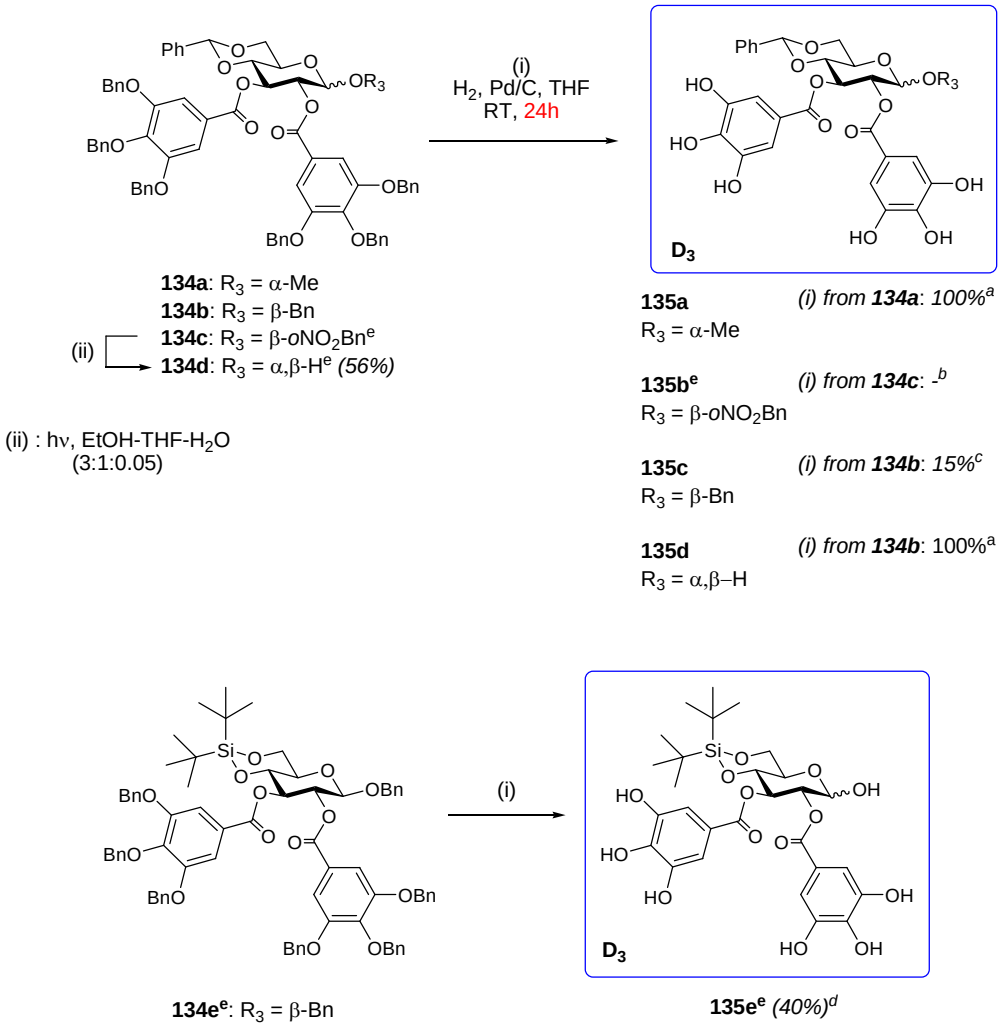
It is important to highlight that the polyhydroxylated products of deprotection are very polar compounds and very sensitive to oxidation. For these reasons, the deprotection steps must

be easy and fast in the work-up and in the purification. Sometimes a reverse phase column chromatography was employed for the purification and in all cases important lost of mass were observed.

The hydrogenation gave the best conditions: a simple filtration on celite in the end of the reaction allowed the obtention of pure final compound.

The purity of the starting material and the following of the reaction appeared extremely important factors to get compounds **135a-e** as pure as possible.

In certain cases, we got a partially deprotected product. As the benzyl group on the phenols in **134b** is easier to remove than the benzyl group at the anomeric position, compound **135c** was obtained. It needed to make addition of new catalyst in order to complete the reaction.



*[a] Yield basisd on ^{1}H-NMR of the crude ; [b] not-purificable complexe mixture of products was formed; any observation of expected product formation ; [c] Reaction not complete; chemical yields after column chromatography purification ; products obtained **135d** (40%) and partially deprotected product **135c** (15%). [d] Chemical yields after C_{18} – reverse phase column chromatography; [e] Product synthesized by G. Malik. Characterization not detailed in the experimental section.*

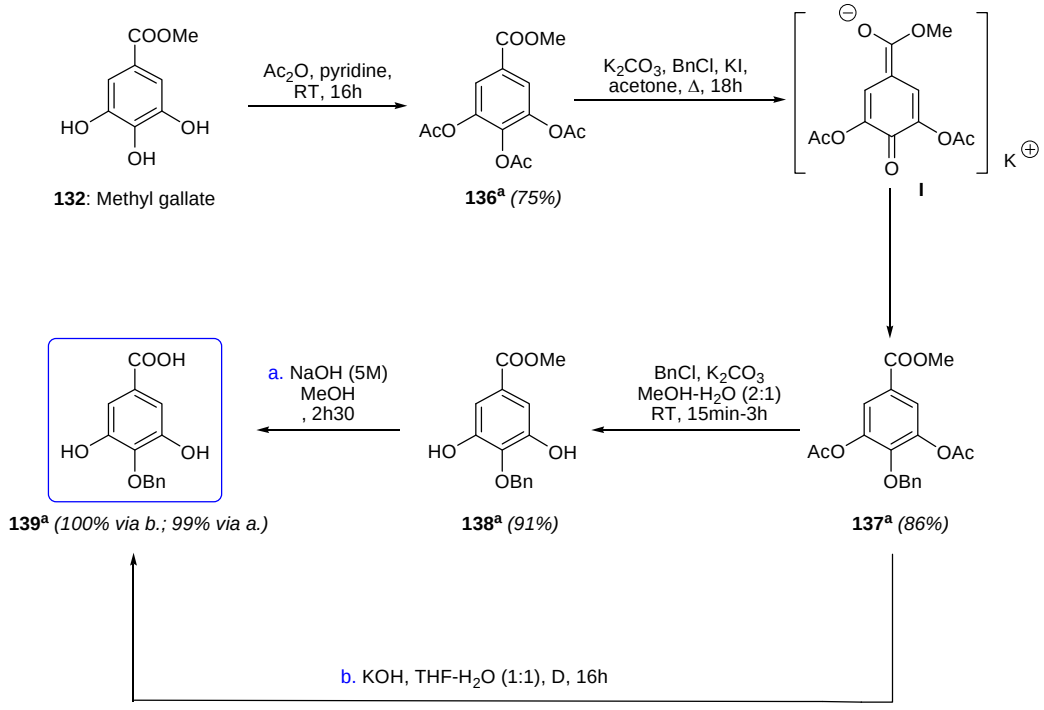
Scheme 32. D_3 orthogonal deprotection

The hydrogenolysis conditions on the perbenzylated compounds **134c** and **135b**, with an *ortho*-nitrobenzyl group at the anomeric position, led to the formation of a complex mixture of products difficult to purify and characterize. To go over this problem the deprotection of the *ortho*-nitrobenzyl group of **134c** was carried out at first *via* photolytic reaction at 365 nm (too much slow at 312 nm), to give the compound **134d** with a chemical yield of 56%, the following hydrogenolysis gave the compound **135d** (48% of chemical yield on two steps, lower than the quantitative yield obtained for the hydrolysis of **134b**).

The intermediates **D** so synthesized with the pyrogallol functions were directly employed in (*i*) the synthesis of the intermediates **B** *via* oxidative coupling and (*ii*) for the studies towards the development of a methodology for the *C*-arylglucosidic bond formation (route II of the retrosynthesis; Scheme 23).

2.2.7 Synthesis of *para*-protected galloyl units F_2

For accessing to such galloyl units **F_2** it was chosen a protecting group R_2 = Bn (cleavable *via* hydrogenolysis).[139]



132: Methyl gallate

136[a] *(75%)*

I

137[a] *(86%)*

138[a] *(91%)*

139[a] *(100% via b.; 99% via a.)*

[a]*Products characterization not detailed in the experimental section.*

Scheme 33. Synthesis of *para*-protected galloyl units F_2

The peracetylated intermediate **137** was synthesized in two steps according to the procedures described by Pearson[140] and Zhu[141] with a global yield of 65%. The selective introduction of an alkyl group on the *para*-position is maybe due to the presence of the ester that led to the intermediate **I**.[141] Finally, the selective hydrolysis of the acetate groups in weakly basic conditions led to methyl ester.

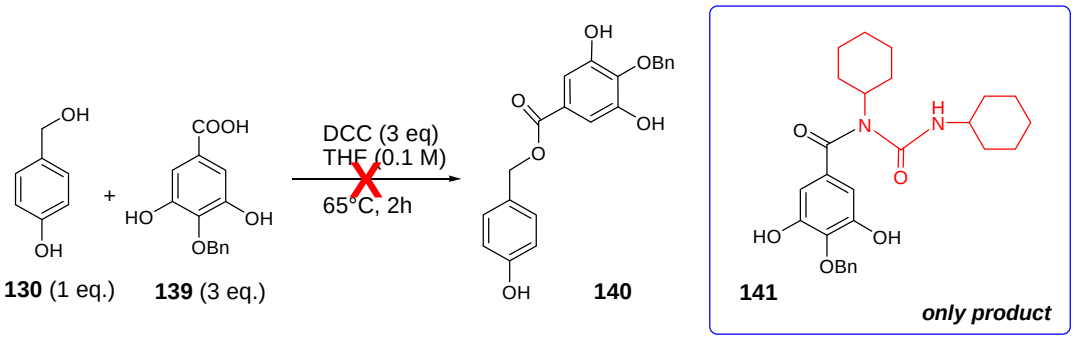
The acid function was then deprotected *via* basic hydrolysis of the intermediate **138** or through the pathway *b* (Scheme 33) consisting in a one step esters hydrolysis.

2.2.8 Preparation of intermediates D_2

Drawing from biomimetic esterification of gallic acid **77** with sugar **E** to get polyhydroxylated precursors $\mathbf{D_3}$, direct esterifications were attempted on galloyl unit $\mathbf{F_2}$ featuring a 3-5 hydroxyl pattern.

Preliminary results were obtained on the model compound *para*-hydroxybenzylic alcohol **130**. The same conditions working on the gallic acid conducted in this case to the non-reactive *N*-acylurea,deriving from the rearrangement of the *O*-acylurea (see annex 1).

In spite of the number of different reaction conditions carried out (different solvents and carbodiimide concentration), only the formation of the secondary undesired product was observed.

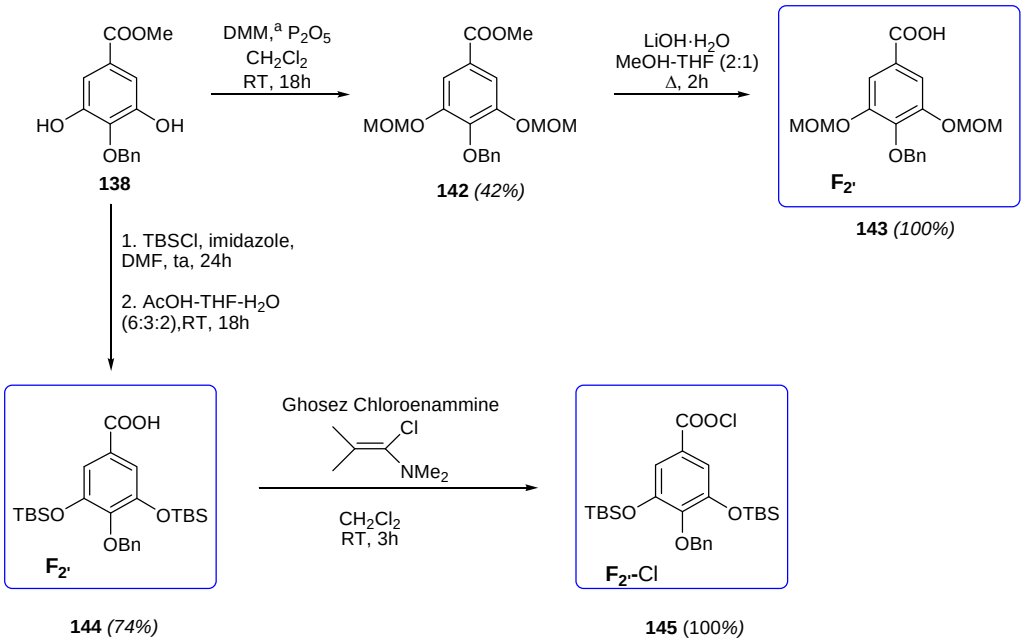


Scheme 34. Direct esterification of F_2

It was decided to protect again the phenolic functions for the following esterification.

2.2.9 Protection of F_2 units

$R_{2'}$ = MOM (methoxymethyl group, removable in acidic conditions) or TBS (removable *via* reaction with fluoro) were chosen as protecting group of the meta phenolic functions on **F_2**.
Three different **$F_{2'}$** galloyl units were so synthesized (Scheme 35).
The methoxymethylation step was not realized in the classical conditions (MOMCl, NaH, DMF).[92]



Products synthesized by G. Malik, their characterization is not detailed in the experimental section.

Scheme 35. F_2 units protection

Milder conditions were carried out on the methyl ester **138**. Compound **142** was obtained with a not-optimized yield of 42%.[142,143] The basic hydrolysis of this compounds gave the galloyl unit **$F_{2'}$**-(**143**) with a global yield of 25% on 5 steps.

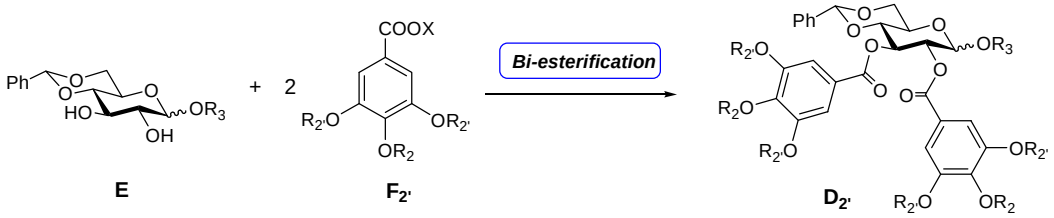
The acid **138** was also protected via trisylilation in classical conditions. Selective deprotection of TBS groups on the acid[72,144] gave the galloyl units **$F_{2'}$** (**144**) (Scheme 35).

The acyl chloride **145** was synthesized *via* reaction with the Ghosez's chloroenamine on the compound **144** with a quantitative yield. It was employed in the following step of esterification without further purification.

2.2.10 Preparation of intermediates $D_{2'}$

Our first attempts of esterifications were performed in THF with dicyclohexylurea (DCC). Also in this case, this essay led to the only formation of the *N*-acylurea.

The classical conditions “one pot” (a) and “two-steps” (b) were so exploited with the following results:



E **$F_{2'}$** **$D_{2'}$**

.

Entry	Galloyl unit				Sugar			Products	Conditions[a]	Yields[b]
	F_2	$F_{2'}$-Cl	R_2	$R_{2'}$	E	R_1	R_3			
1	**143**	-	Bn	MOM	**129**	PhCH	α-Me	**146**	a_3[c]	90%
2	**144**	**145**	Bn	TBS	**31**	PhCH	*o*NO_2Bn	**147**	a_1	24%
									a_3[c]	80%
									b_1	25%[d]

Products synthesized by G. Malik. Their characterization is not detailed in the experimental section
*[a] **a** = conditions « one-pot » ; **b** = conditions « two-steps ». [b] Chemical yield after silica gel column chromatography purification. [c] Conditions **a_3** = **E** (1 eq.), **$F_{2'}$** (2.5 eq.), EDCI (5 eq.), DMAP (7 eq.), CH_2Cl_2 (0.025M), RT, 8-18h ; [d] Partial consumption of starting compound, monogalloylated product isolated.*

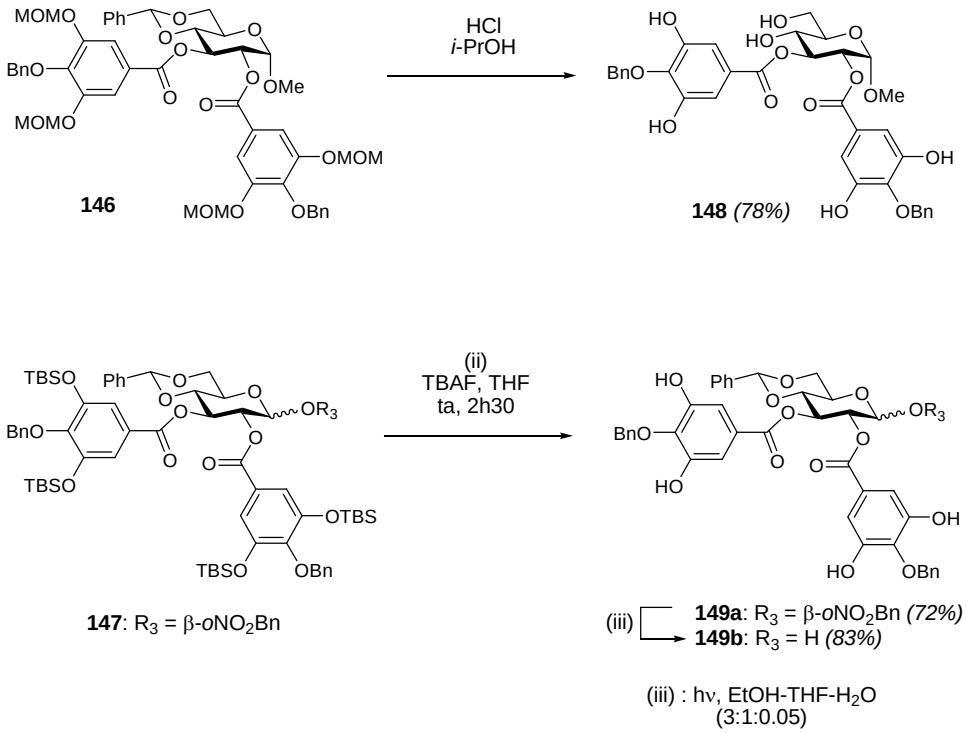
Table 3. bi-esterification of galloyl units $F_{2'}$

The classical conditions a_1 and b_1 applied on the combination sugar **31** and galloyl **144** led to low yields (24 and 25% respectively).

As an alternative the 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, conditions a_3) allowed to reach a good yields for the compound **147**. The by-products obtained in the reaction EDCI promoted, are easily removed by an acid work up.

2.2.11 Preparation of the intermediates D_2 via orthogonal deprotection of $D_{2'}$

The methoxymethyl groups (MOM) of **146** can be cleaved in acid conditions. These conditions are not orthogonal to the benzylidene protecting group. The compounds **148** was so obtained with a yield of 78% for reaction with HCl in isopropanol (Scheme 36).



Products synthesized by G. Malik. Their characterization is not detailed in the experimental section.

Scheme 36. D_2 synthesis *via* orthogonal cleavage of $R_{2'}$

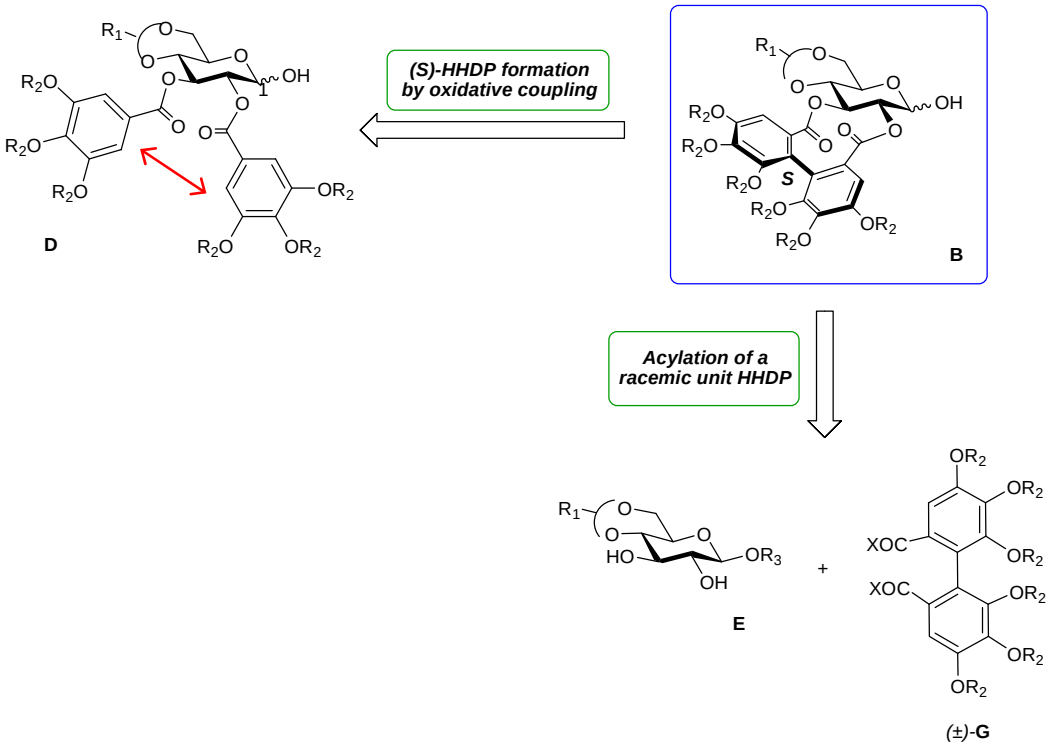
The silyl groups were so preferred as removable in an orthogonal manner. Compounds **149a** was so obtained from **147** in a 72% chemical yield.

The cleavage of the photolabile *ortho*-nitrobenzyl group was successfully achieved on the compound **149a** leading to the compound **149b**.

2.3 Synthesis of inetrmediates B

As showed in the retrosynthetic plan (Scheme 23) the synthons **B** can be obtained by two ways: (*i*) *via* an oxidative intramolecular coupling starting from D-type intermediates or (*ii*) *via* acetylation of the sugar **E** with a racemic mixture (±)-**G**.

Beyond featuring a biomimetic inspiration way, (i) also allows a straightforward rout from punicacortein A (**23**) to NHTP bearing ellagitannins.



Scheme 37. Retrosynthetic approaches to synthons B

2.4 Intermediates B via Biarylic oxidative coupling

This section will focus on the results obtained form the oxidative-coupling studies aimed to develop an efficient methodology to generate the teraryl- (NHTP) type unit in an atropoisomerically controlled manner. Beyond possessing an intrinsic synthetic value, this approach, basisd on the coupling between suitably protected galloyl units attached to a glucose core, will give information about the biosynthetic construction of these characteristical structural elements of ellagitannin molecules.
In particular, the results here exposed were obtained by Gaelle Malik, a PhD student in the Quideau's group, who addressed the development of a synthetic strategy towards the NHTP-unit construction.
The presentation of some of her results may help to outline the framework in wich the C-*arylglucosidation of the architecture **B** was addressed.*

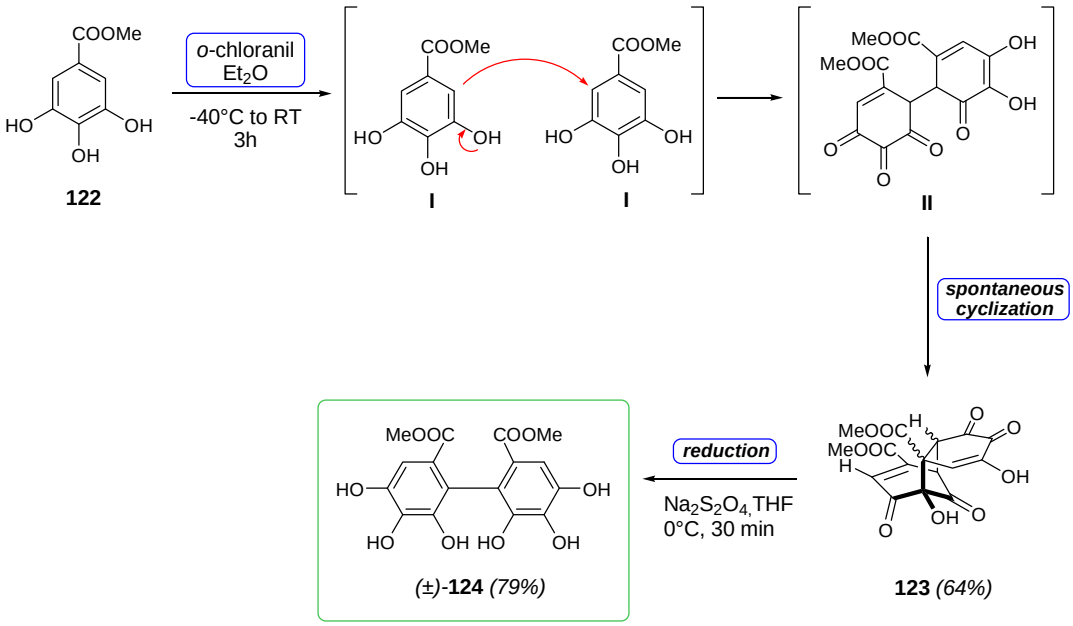
A family of eight related digalloyl substrates (**135a-e**, **148**, **149a**, **149b**) of varying oxidation potential was crossed with several common oxidants to forge the biaryl HHDP core.
Two of the oxidant systems exploited are herein discussed:
- (i) *o*-chloranil mediated oxidative coupling on substrates with pyrogallol-like reactivity (n=3) (on polyhydroxylated compounds **135a-d**);
- (ii) $CuCl_2$-amine complexes mediate oxidative coupling requiring a phenol-like reactivity (n=1) (on compounds **148** and **149a-b**).

2.4.1. *o*-chloranil mediated intramolecular biarylic oxidative coupling

The first reported HHDP construction towards ellagitannins synthesis was achieved by Feldman *et coll.* and was centered around the use of a $Pb(OAc)_4$ mediated intramolecular oxidative coupling of diphenylmethylene-protected gallates attached on a glucopyranose core.[72] This coupling step generated the desired (*S*)-atropoisomer of the HHDP group. Free hydroxyl groups in the gallic acid moieties were required to facilitate the cyclization; this necessitated the introduction of additional protection/deprotection steps in the synthesis. Overall the complete reaction pathway suffered from somewhat moderate yields, reflecting the complexity of targeted molecules. Moreover, this method provides a mixture of regioisomers due to the asymmetry of the protecting groups.

Our aim was to develop a new methodology of oxidative coupling on completely deprotected galloyl units that allows a reduction of protection/deprotection steps number.

o-chloranil was already employed by Feldman for the intermolecular coupling between two methyl gallate units **122** to give a poly-hydroxylated *HHDP* unit (±)-**124** (Scheme 38).[145]

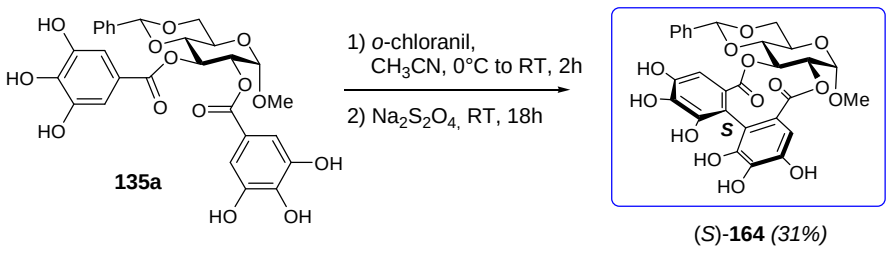


Scheme 38. Intermolecular o-chloranil-mediated oxidative coupling of methyl gallate units

A model system study was deemed appropriate prior to venturing toward the actual synthesis. So the coupling was carried out on the compound **135a** (obtained easily in three steps from the commercially available sugar **129**) under Feldman's conditions.

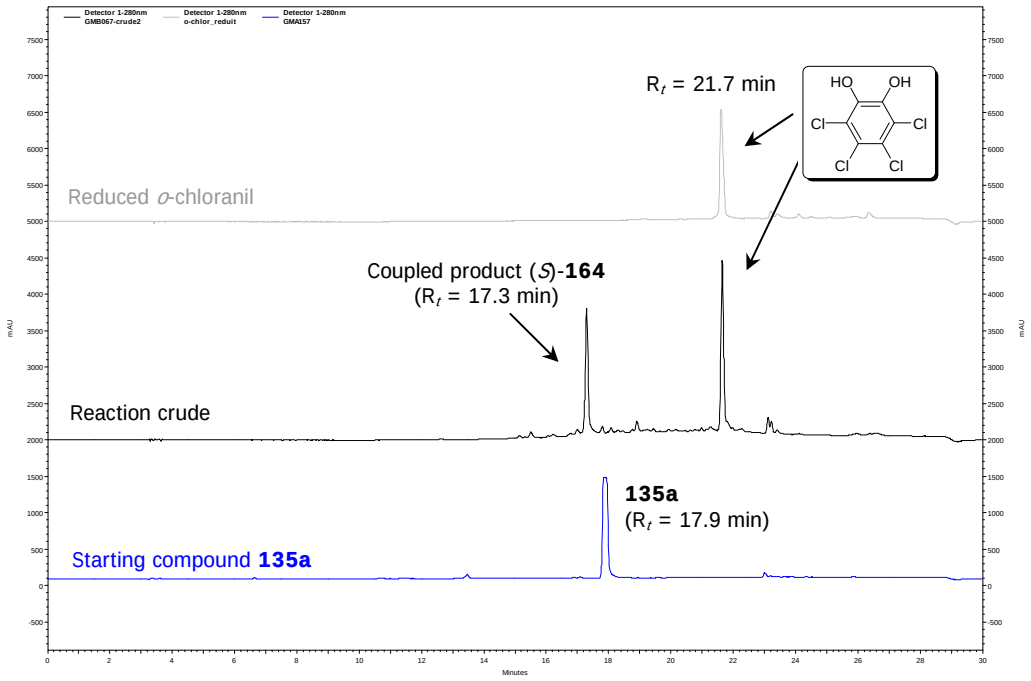
The reaction was monitored by analytic RP-C18 HPLC Varian Pursuit C18 (250 x 4,6 mm) (Eluents H_2O:MeOH gradient from 1:0 to 0:1 in 20 min, flow 1 mL/min) because the starting compounds and the products reactions are poorly resolved by thin layer chromatography.

The reaction (Scheme 39) was carried out in acetonitrile and the starting compound **135a** was added at 0°C to the *o*-chloranil solution. The temperature was let to go to 25°C and after 2h, 8 equivalents of sodium dithionite were added with a catalytic amount of water.



Scheme 39. Intramolecular *o*-chloranil-mediated oxidative coupling of 135a

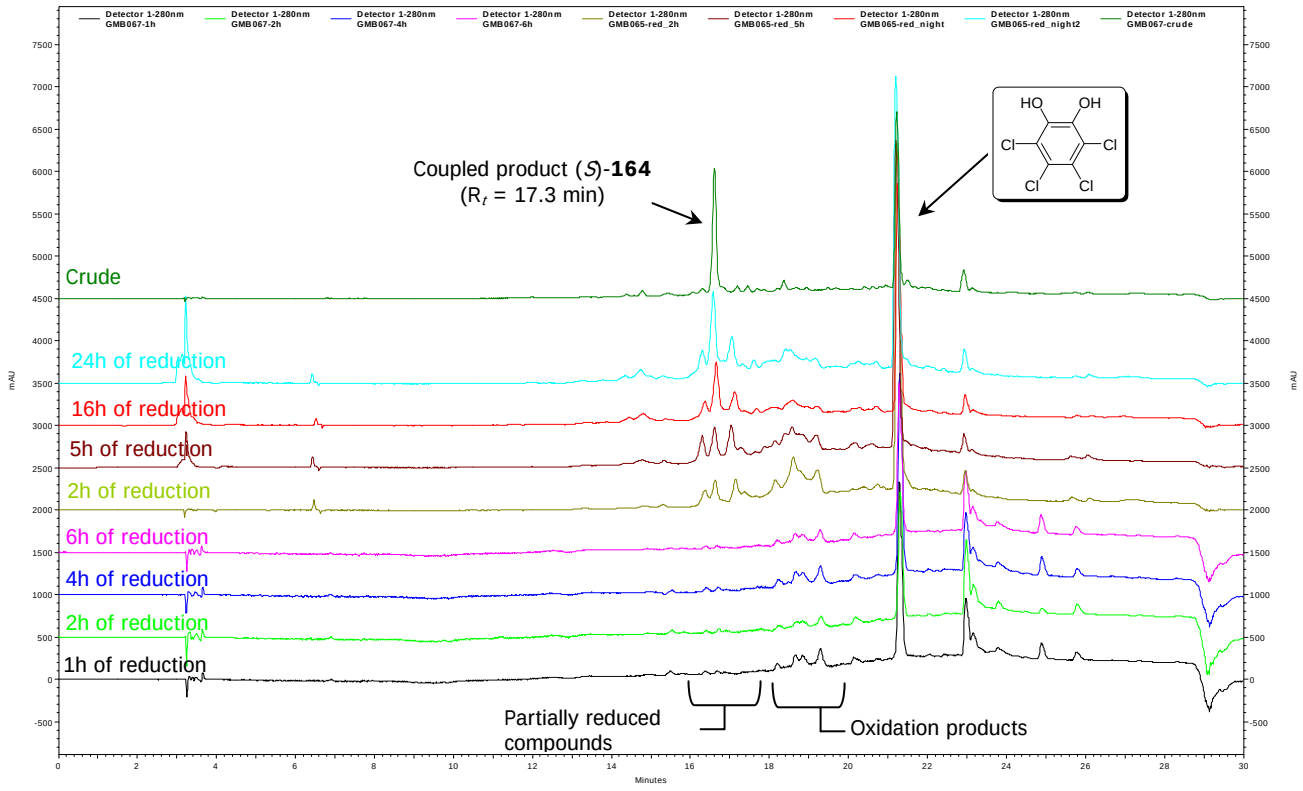
The reaction mixture was then stirred at RT for 18h. The HPLC profile (Figure 17) showed the consumption of the starting compound and the formation of two new products. The less polar between them (R_t = 21.7 min) was identified as the tetrachlorocathecol (the reduced form of *o*-chloranil) on the basis of the comparison with a standard obtained from *o*-chloranil reduction. An LC/MS analysis showed that the other compound at 17.3 min was the coupling product, as confirmed by comparison with the compound (*S*)-**162**, obtained from hydrogenolysis of (*S*)-**153** (Scheme 53). Accordingly with the Schmidt and Haslam postulate, the only S atropoisomer was obtained.



Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

Figure 17. HPLC profile of the oxidative coupling of 135a

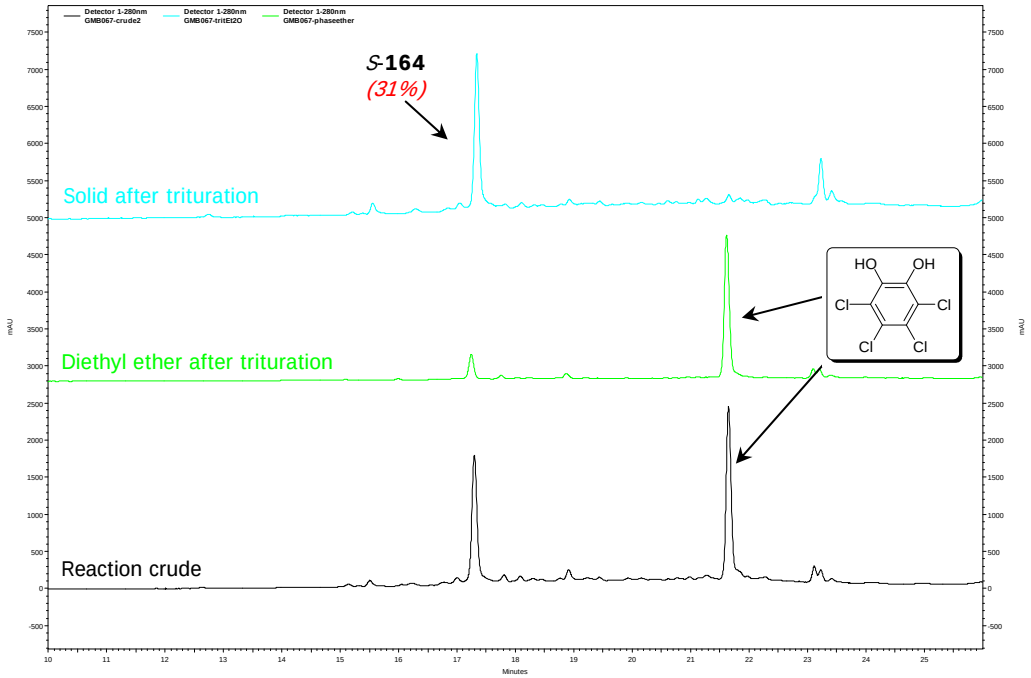
The HPLC monitoring of the reaction showed that the oxidation was a very fast process that resulted completed after 1h and gave rise to a mixture of products. The following reduction step demanded longer reaction time. It needed 24h to be completed. During the reduction several partially reduced compounds are formed.



Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

Figure 18. HPLC profile of the oxidative coupling of 135a

The reaction crude was tritured with diethyl eter. This work-up allowed the removal of the reduced form of *o*-chloranil. The HPLC profile in Figure 19 shows that the totality of tetra chlorocatechol was removed by trituration.



Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

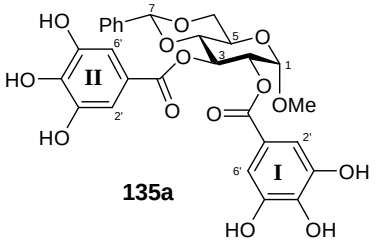
Figure 19. HPLC profile of the work-up of the oxidative coupling of 135a

The ^{1}H-NMR of the product obtained after purification allowed the confirmation of its structure. In Figure 20, the comparison between the proton NMR spectra of compounds *S*-**164** and the starting material **135a** is shown.

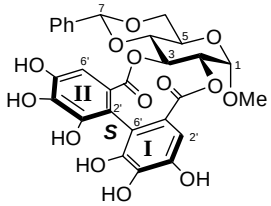
The most important differences are :

- H-3 of the sugar is shielded of 0.4 ppm in the coupling product with respect to the starting compound;

- The aromatic protons on the galloyl moieties (2'$_I$, 6'$_I$, 2'$_{II}$, 6'$_{II}$) are upfield (0.4 ppm of difference) and their integration is halved (corresponding to the lost of two protons).

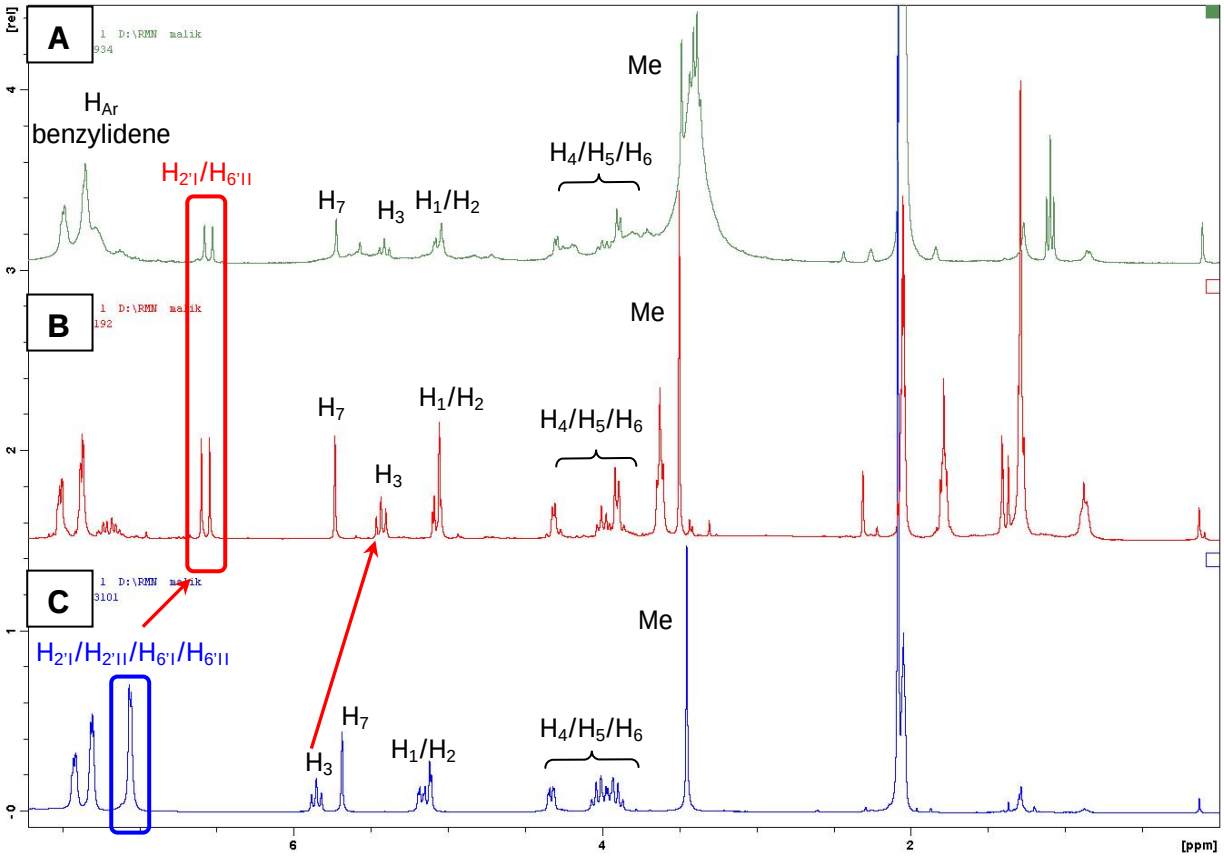


135a



(*S*)-**164**

The spectra A and B are exactly the same. The only difference is the lower resolution obtained for the coupled product. A further purification step resulted necessary. The only envisageable method was the inversed phased preparative HPLC.



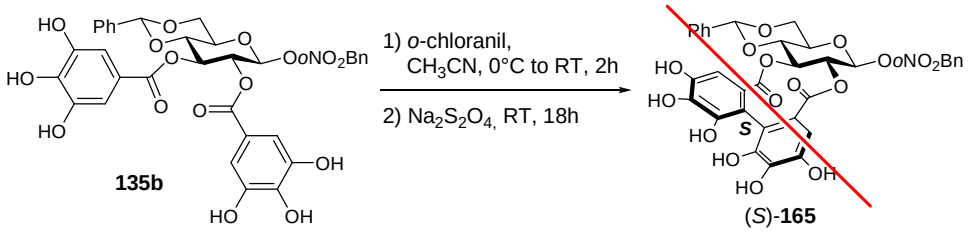
A : ^{1}*H-NMR (acetone-d$_6$) compound (S)-**164** obtained from o-chloranil coupling*
B : ^{1}*H-NMR (acetone-d$_6$) compound (S)-**162** obtained from hydrogenolysis of (S)-**135a***
C: ^{1}*H-NMR (acetone-d$_6$) compound **135a** starting compound of the oxidative coupling*

Figure 20. Comparison of ^{1}H-NMR spectra of compounds (*S*)-164**,** (*S*)-162 **and** 135a

It was tried to remove the methoxy-protecting group at the anomeric position by reaction with trityl-tetrafluoroborate (Ph_3CBF_4), as described by Vankar.[146] The strategy appeared not compatible with the complex structure of (*S*)-**164**.

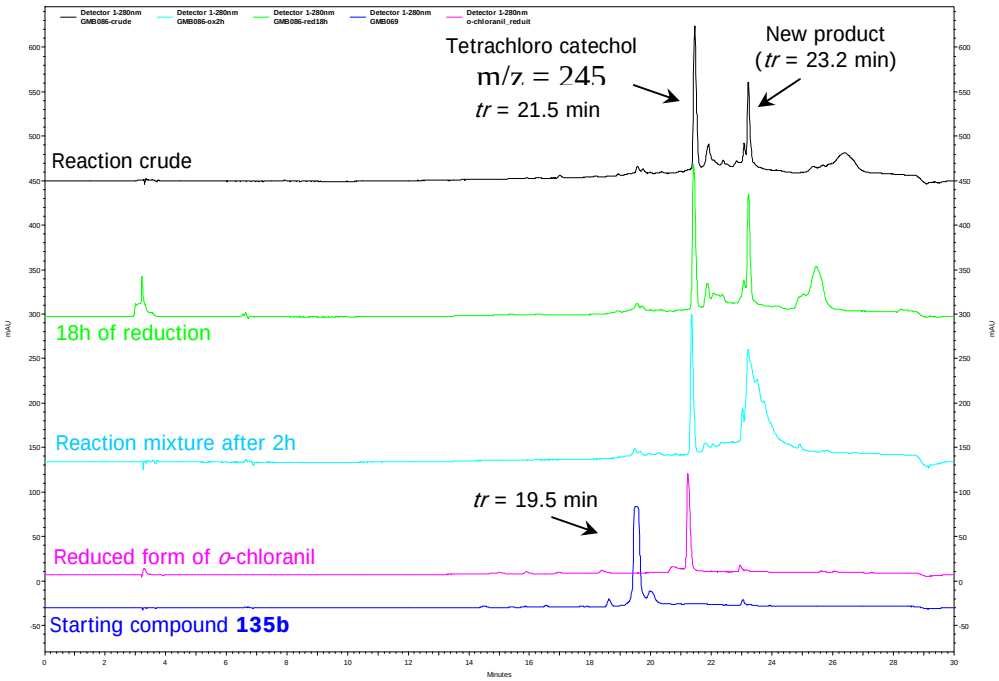
2.4.2 *o*-chloranil mediated oxidative coupling of 135b

The same conditions were so applied on **135b**, with an *ortho*-nitrobenzyl protecting group removable under milder conditions (Scheme 40).



Scheme 40. *o*-chloranil mediated oxidative coupling of 135b

In these conditions, a product (R_t = 23.2 min, Figure 21) less polar than the tetra-chlorocatechol was formed. It was impossible to characterize this new compound, but we could affirm with certitude that it was not the coupling product. As already reported, the C-1 protecting group affect the efficiency of the oxidative coupling, possibly through an inductive effect. An electron-deficient moiety (e.g., *o*-nitrobenzyl) at this position appeared to reduce the yield of the coupled product compared to its more electron-rich counterparts.[29]



Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

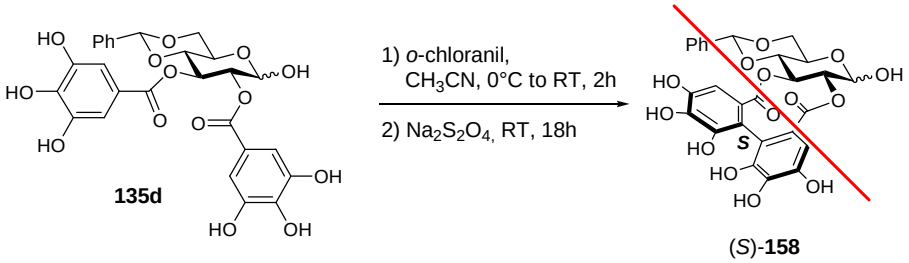
Figure 21. HPLC profile of the oxidative coupling of 135b ***o*-chloranil mediated**

The LC/MS analysis of the reaction crude showed the presence of three products with an isotopic pattern characteristic of the presence of chloro atoms.

After RP-C18 column chromatography a too little amount of product was obtained so it resulted impossible to purse the complete characterization.

2.4.3 *o*-chloranil mediated oxidative coupling of 135d

The Feldman's conditions were so carried out directly on the reducing sugar **135d**.



Scheme 41. *o*-chloranil mediated oxidative coupling of 135d

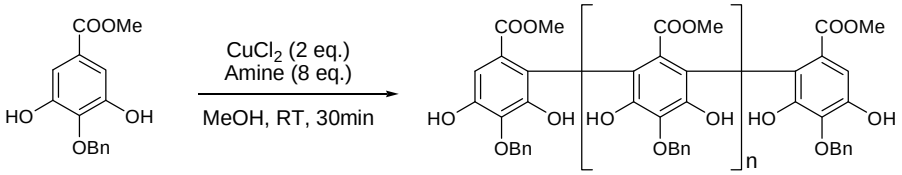
Even after 3h of oxidation the starting compound was only partially consumed. It was necessary to add three further equivalents of o-chloranil. The formation of several new products was observed by HPLC as in the case of the oxidation on **135a.**

The reaction products were so purified by preparative HPLC, but it resulted impossible to complete the characterization because of the too little amount obtained. As in the case of **135b** the coupling product was not obtained.

2.4.4 Cu(II)-amine complex promoted intramolecular biarylic oxidative coupling

An alternative synthetic method for the HHDP group construction was applied by Yamada to the corilagin total synthesis.[92] Symmetrically designed methyl 4-*O*-benzylgallate were applied in the phenol coupling methods employing $CuCl_2$-amine complex.

The feasibility of this synthetic approach towards the HHDP construction was investigated by Yamada[92] at first on methyl 4-*O*-benzyl gallate unit **138** (Scheme 42).



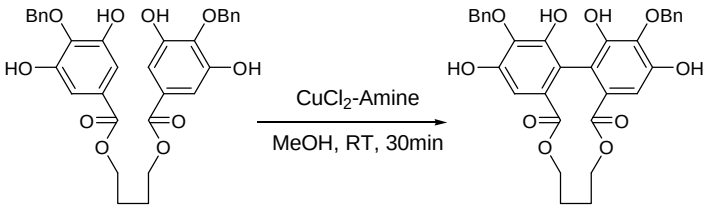
138

169a: n = 0 *(35 to 49%)*
169b: n = 1 *(5 to 8%)*
169c-d: n = 2 and 3 *(traces)*

Scheme 42. Coupling of 4-*O*-Benzylgallates by $CuCl_2$ amine complex

The coupling of **138** was successful when using not only ethylamine ($EtNH_2$), but also *n*-butyl- (*n*-$BuNH_2$) and *n*-hexylamines (*n*-$HexNH_2$) to give the corresponding dimer. It is worth of note the fact that also the trimer is obtained in this conditions. That means that this method could be employed to the construction of the (*S*,*S*)-NHTP unit of vescalin.

The same reaction conditions were then applied by Yamada *et coll.* to the intramolecular cases with a digallate **170** in which the four-carbon-linker corresponded to the 3- to 6-positions of glucose. The yields in the intramolecular coupling were even better than those on the intermolecular cases providing **171** in 77-85% yield.



170

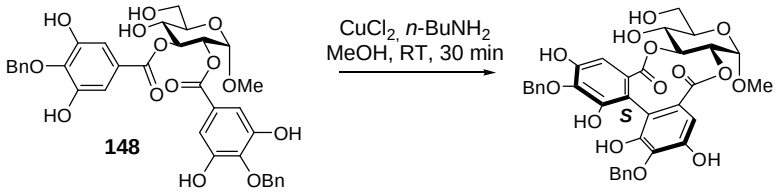
171 *(77 to 85%)*

Scheme 43. Intramolecular oxidative coupling of 4-*O*-Benzylgallates by $CuCl_2$ amine complex

These results afforded to the total synthesis of corilagin accomplished by Yamada *et coll.* in 2008.[92]

The same conditions were applied on our **D** architectures with *para*-protected galloyl units. As already mentioned above the p*ara*-protection - as in the case of the polyhydroxylated employed in the biomimetic *o*-chloranil coupling - presents the advantage to avoid the formation of several regioisomers.

The Yamada conditions were at first experimented on the model compound **148**



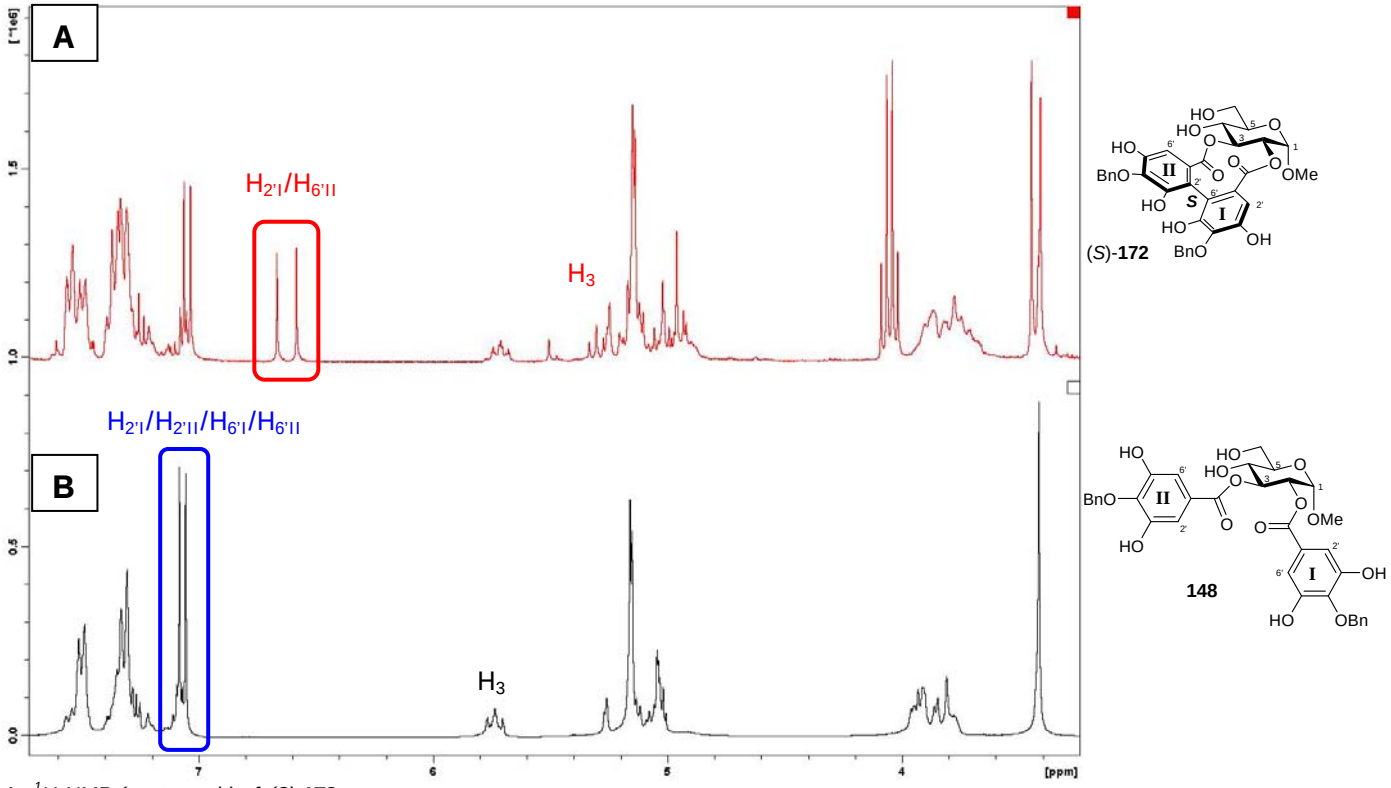
Products synthesized by G. Malik. Their characterization is not detailed in the experimental section.

Scheme 44. $CuCl_2$ amine complex mediated oxidative coupling of 4-*O*-Benzylgallates functionalized compound 148

The coupled product (*S*)-**172** was obtained from the *para*-benzylated product after 30 minutes of reaction.

The ^{1}H-NMR of the crude reaction showed the presence of the coupling product and the starting compound in a ratio of 1:1.

Diagnostic feature in the ^{1}H-NMR spectra of the formation of the coupling product is the shielding of the H-3 protons (5.76 ppm for **148** ; 5.31 ppm for (*S*)-**172**).



*A : ^{1}H-NMR (acetone-d_6) of (S)-**172***
*B: ^{1}H-NMR (acetone-d_6) of compound **148** starting compound of the oxidative coupling*

Figure 22. Comparison of ^{1}H-NMR of reaction product (*S*)-172 **and starting compound** 148

The compound (*S*)-**172** was purified by preparative HPLC and obtained with a yield of 56%. The atropoisomery was established on the basis of the comparison with the NMR proton spectra of compounds previously synthesized (Figure 23).

It is worthing to note that the aromatic protons characteristic of the coupled product (*S*)-**172** integrate for two protons and possess a chemical shift comparable to the compound (*S*)-**162**. The other atropoisomer (*R*)-**162** presents two broad singlets for the aromatic protons.
From this observation, it was possible to be sure that the atropoisomer obtained was the *S* accordingly with the Schmidt and Haslam postulate.

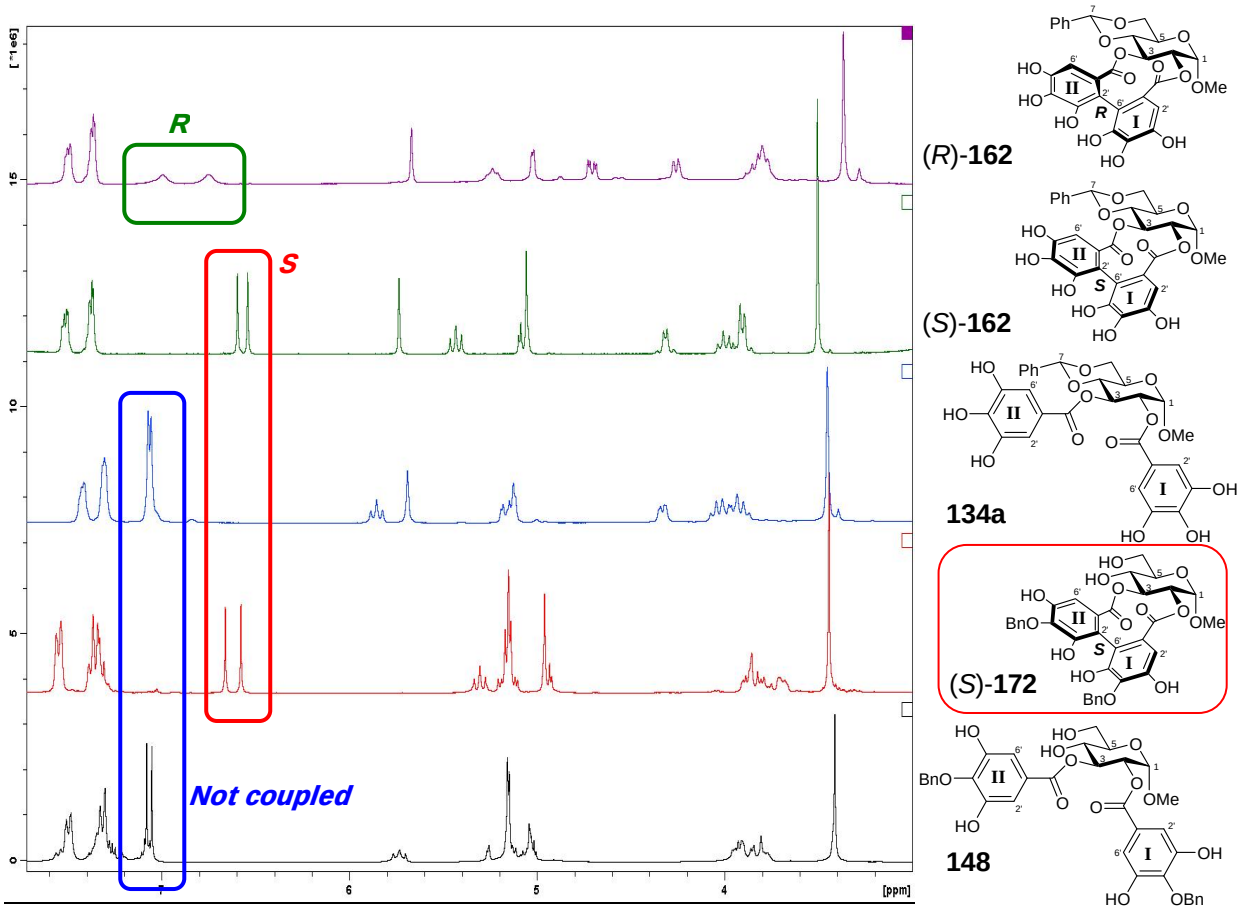
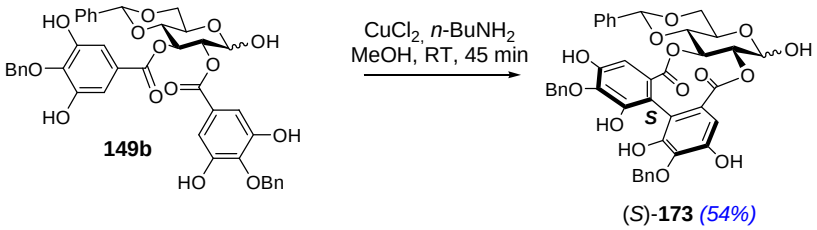


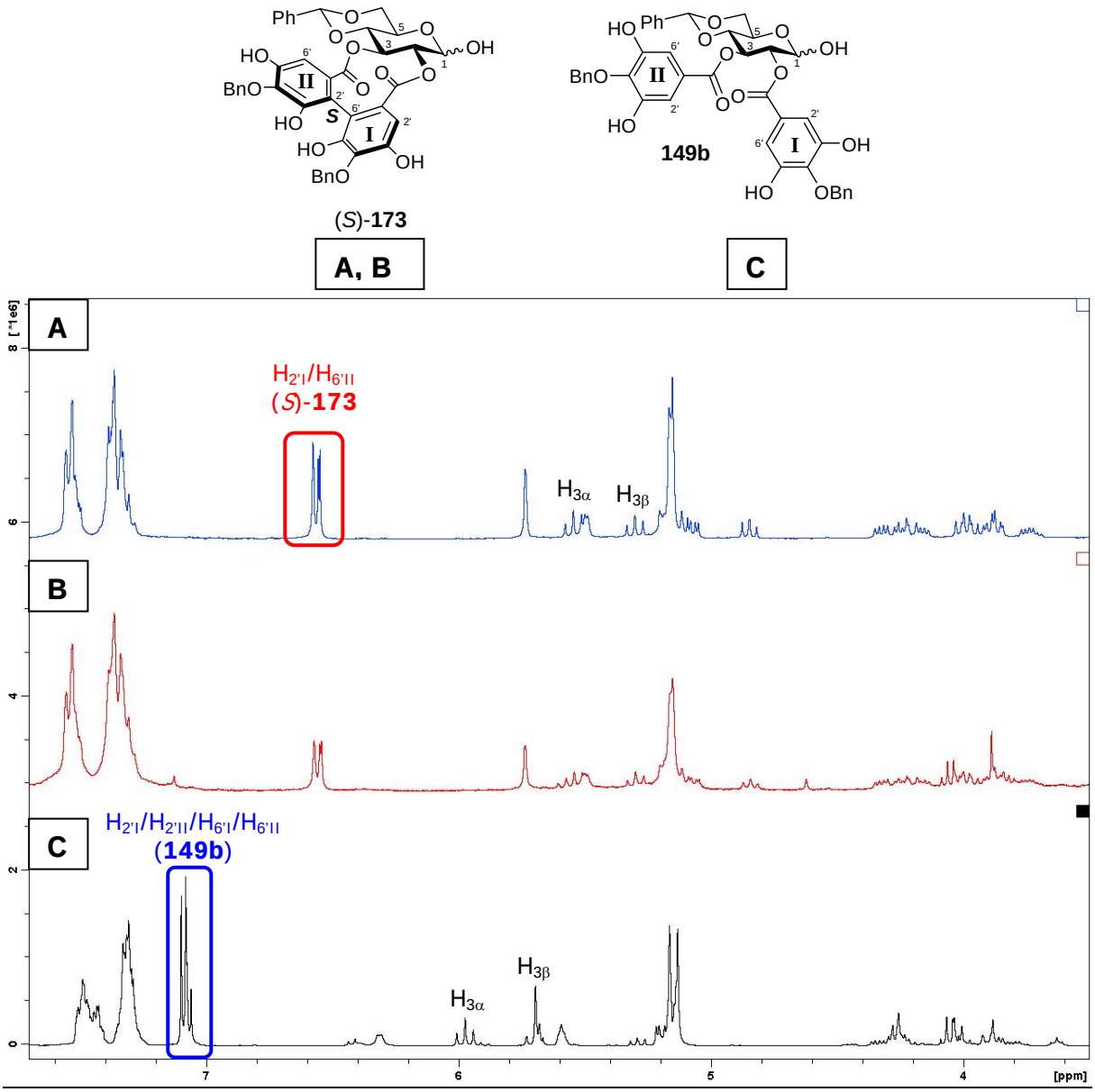
Figure 23. ^{1}H-NMR spectra comparison among not coupled compounds (148 **and** 134a**) and coupled ones (**162 **and** (*S*)-172**)**

2.4.5 Cu(II)-amine complex mediate oxidative coupling of 149b

The same conditions were so carried out on the compound **149b** (Scheme 45).



Scheme 45. $CuCl_2$ amine complex mediated oxidative coupling of 4-*O*-Benzylgallates functionalized compound 149b



*A : ^{1}H-NMR (acetone-d_6) of compound (S)-**173** obtained after purification by column chromatography*
B : ^{1}H-NMR (acetone-d_6) of reaction crude after 45 min
*C : ^{1}H-NMR (acetone-d_6) of starting compound **149b***

Figure 24. ^{1}H-NMR comparison between the reaction crude and the starting compound

The crude ^{1}H-NMR spectra showed that after 45 min, the starting compound was completely consumed.

The reaction time resulted strictly dependent on the reaction scale, i.e. for n = 0.265 mmol (200 mg) of starting compound it needs 45 min, for n = 0.771 mmol (580 mg) of starting compound 2h are needed.

The product (*S*)-**173** was obtained with a yield of 54% even if the spectra of the crude reaction let expect better yields. Important lost of material were caused by the purification step.

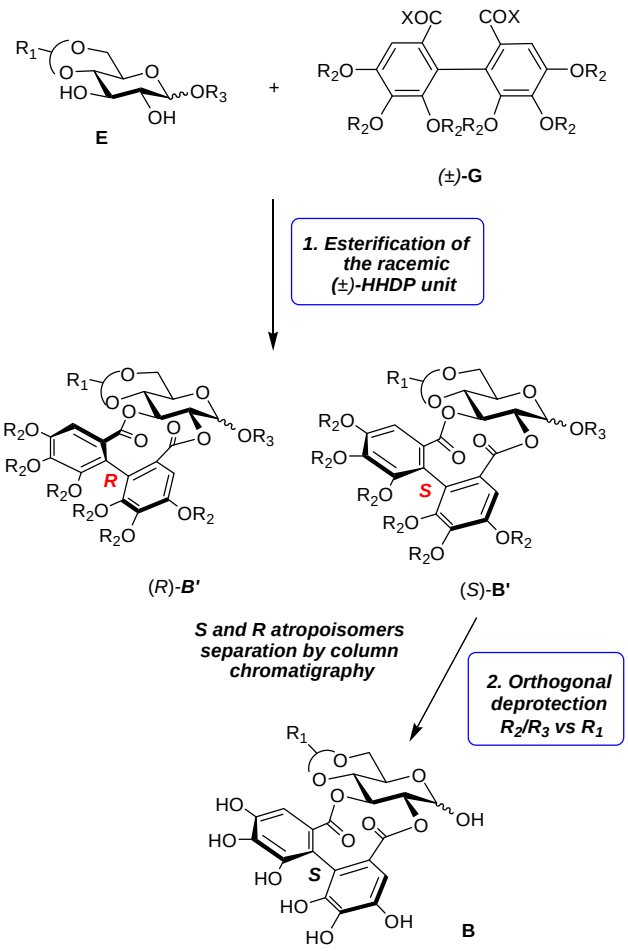
2.5 Intermediates B via acetylation of a racemic unit (±)-HHDP

This strategy was inspired by the work already reported by Khanbabee on the kinetic resolution of a racemic mixture of (±)-*HHDP* unit.[75]

As showed in Scheme 46, the esterification of (±)-*HHDP* on the sugar **E** gives rise to two atropoisomers (*R*)-**B'** and (*S*)-**B'**. The atropoisomer of interest (*S*) can be involved in an orthogonal deprotection step to give the most important synthon of our synthetic strategy. This product is in fact the direct precursor of the *C*-arylglucosidation step.

The starting point of this alternative synthesis is the preparation of the racemic unit (±)-**G**. Then its introduction on the sugar **E** will be detailed.

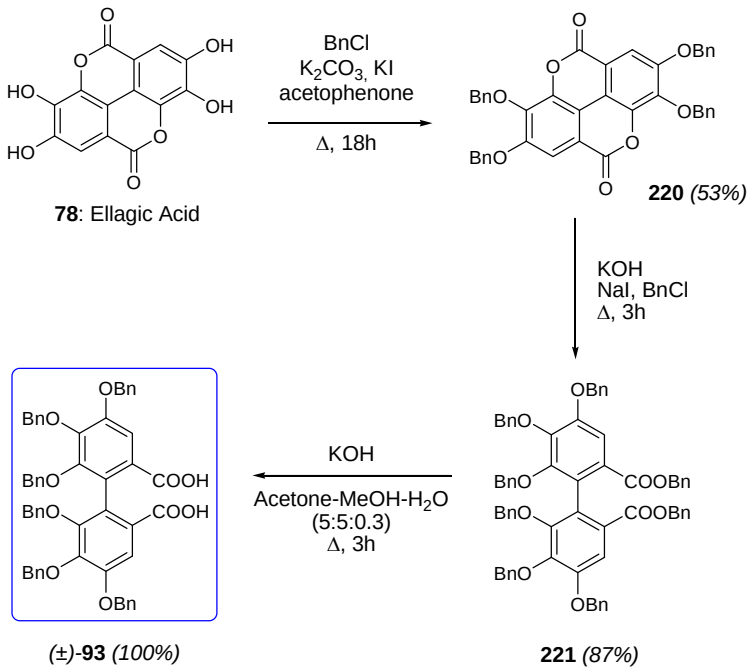
A benzyl group was chosen as $R_{2'}$ as cleavable at the same time than the anomeric protecting group.



Scheme 46. Kinetic resolution of a racemic HHDP mixture

2.5.1 Synthesis of the racemic *(±)*-HHDP

The racemic mixture (±)-**G** was synthsized according to the procedure reported by Schmidt[116,118,119] and successively optimized by Kashiwada,[147] that was already applied to the ellagitannins synthesis by Khanbabee and Itoh.



Scheme 47. Synthesis of perbenzylated (±)-HHDP

At first, the ellagic acid **78** was perbenzylated by reaction with benzyl chloride in acetophenone in the presence of potassium carbonate and potassium iodide. The yield of 53% resulted difficult to reproduce because of insolubility of ellagic acid. Rigorous anhydrous conditions resulted extremely important to the obtention of this yield even modest for a protection step. The presence of water lead to the introduction of benzyl moiety in *ortho* of the esters bond as collateral reaction.[148]

The product **220** was then involved in a « one-pot » sequence of basic hydrolysis/benzylation of the esters and phenols leading to **221**. The following of the reaction by TLC was of paramount importance because several regioisomers of partial hydrolysis were obtained. The least esters hydrolysis was carried out in a mixture acetone/methanol/water to give the racemic mixture of perbenylated (±)-**93** with a global yield of 44% in three steps.

Another method for the synthesis of the racemic HHDP unit was reported by Feldman.[145]

This methodology is easier to get under way and also the chemical yields are higher, but at least two more steps (protection of the phenolic functions; methyl esters hydrolysis) are needed to address our target compound.

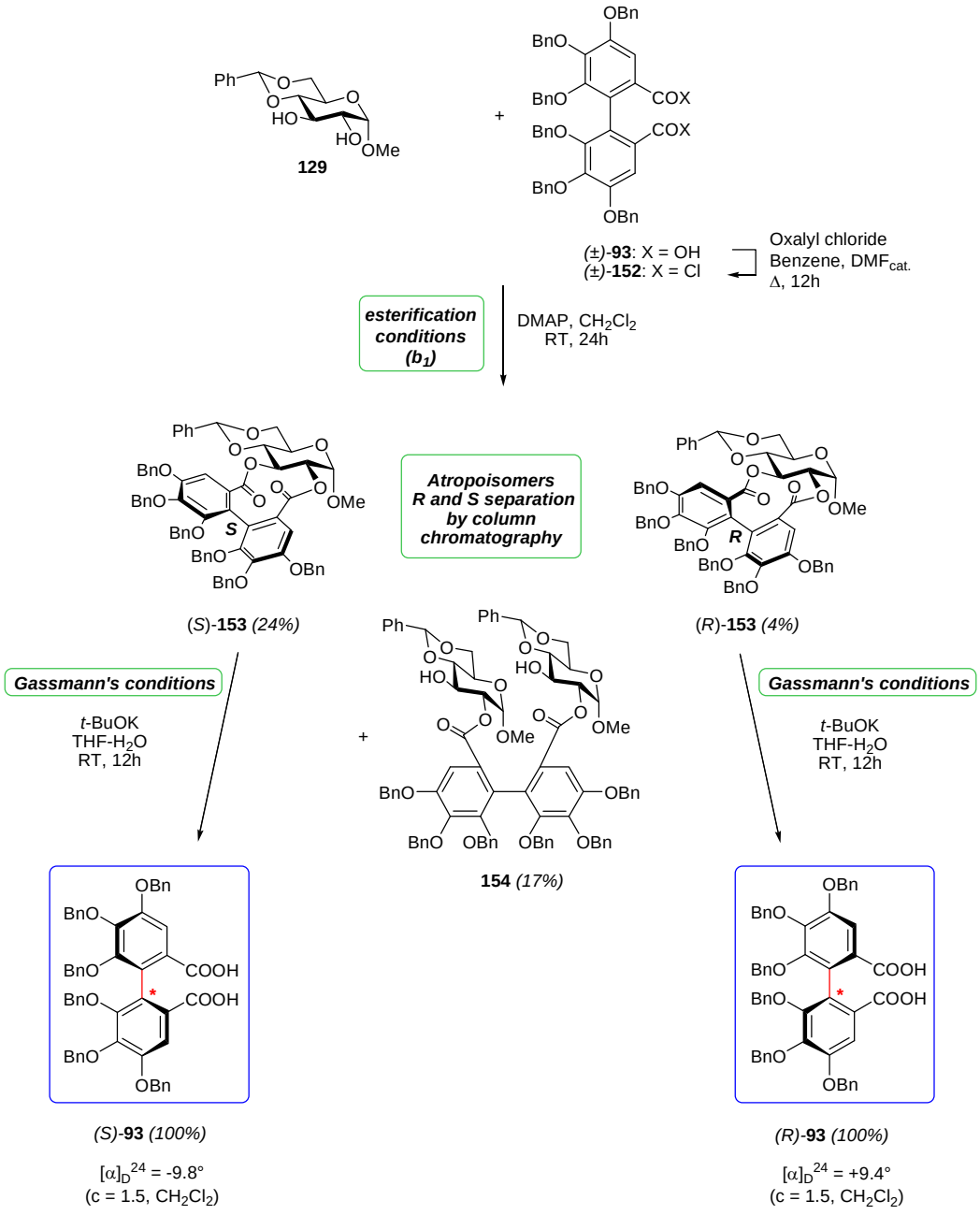
2.5.2 Installation of the HHDP unit on the sugar E

As reported in the literature for the ellagitannins synthesis, the installation of the racemic unit (±)-**G** is mainly carried out under classical esterification conditions (Steglich or *via* acyl chloride).
In our studies, we first attempted the reaction in the conditions described by Itoh[95,115] on the commercial sugar **129**.
After activation of the acid (±)-**93** as acyl chloride (±)-**152**, the bi-esterification was carried out in the presence of DMAP (b_1 conditions) to give the desired atropoisomer (*S*)-**153** with a satisfactory yield of 24%. In agreement with what reported by Itoh, the atropoisomer (*R*)-**153** (4% yield) and the dimer **154**[a] were also obtained.

The desired *S* atropoisomer was obtained as main product. Several reaction conditions were tested changing solvent and concentration of reactants without any improvements in the yields. In any case it was obtained an improvement in the yield of the atropoisomer *R* and the diastereoselectivity resulted to be worse.

HHDP units (S)-**93** and (R)-**93** were obtained in pure form after hydrolysis[114] of (S)-**153** and (R)-**153** respectively. It was so possible to make a full characterization. The optical activities of the so obtained compounds were in agreement with the values reported by Schmidt.[119]

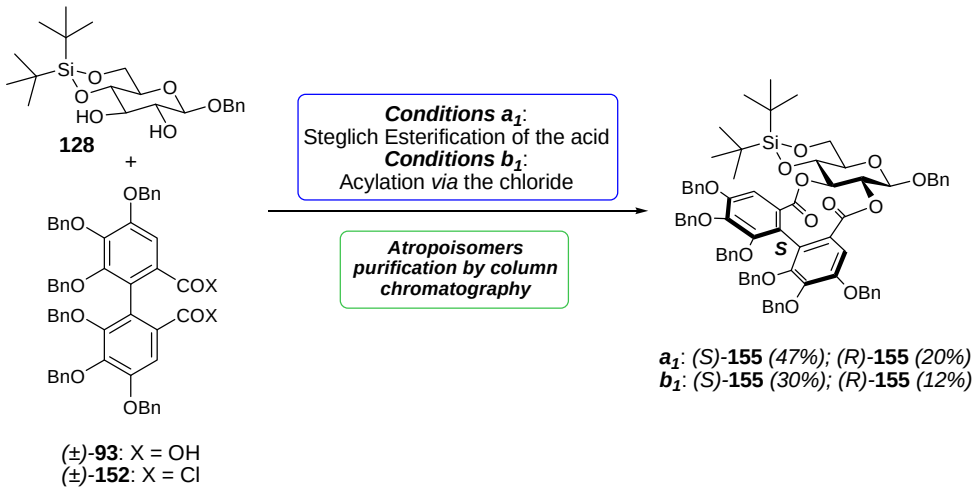
[a] *The product was obtained as a complex mixture with other products so it was impossible to make a full characterization. It was characterized on the basis of the comparison of the NMR data with what reported in the literature.113. Arisawa, M. et al. An unexpected intermolecular chiral biaryl coupling reaction induced by hypervalent iodine (III) reagent : synthesis of potential precursor for ellagitannin. Chem. Commun., 469-470 (1999), 115. Itoh, T. & Chika, J. New method for kinetic resolution of axially chiral biaryl compounds using a sugar template. J. Org. Chem.* ***60****, 4968-4969 (1995).*



Scheme 48. Kinetic resolution of (±)-93

We applied then the same conditions on the sugar **E** with a cleavable protecting group at the anomeric position.

The esterification was carried out on the sugar **128** in the classical Steglich conditions (conditions a_1) and *via* the chloride (±)-**152**.



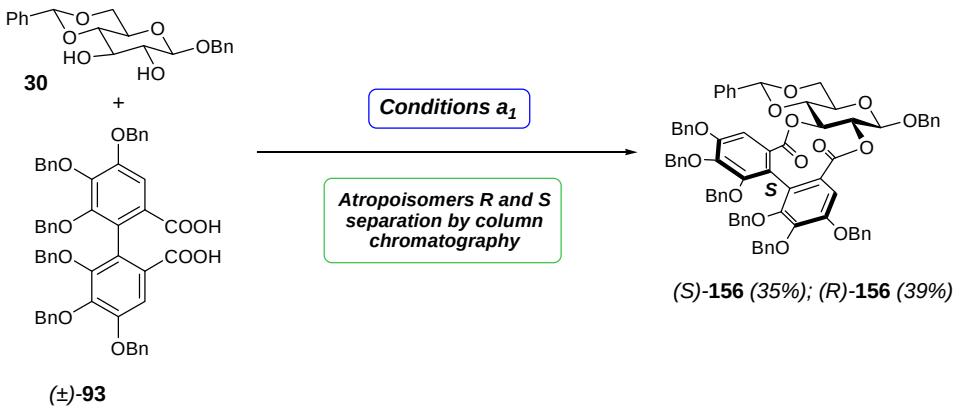
Products characterization is not detailed in the experimental section.

Scheme 49. Bi-esterification HHDP unit on the sylilated sugar

The atropoisomers of interest (S)-**155** was obtained with a 30% yield on two steps in the b_1 conditions, and 47% yield in the a_1 conditions.

The last conditions (a_1) were the most satisfying even better than with the commercial sugar.

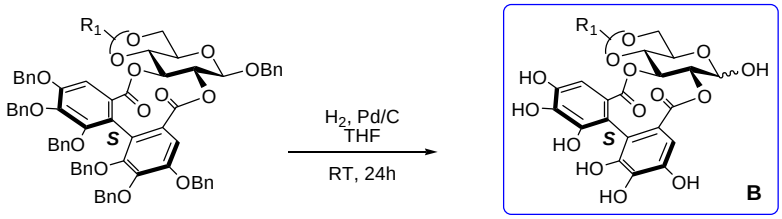
These conditions were also applied on the sugar **30** (Scheme 50) with still good results, even if the stereo-control of the reaction resulted less efficacious (the atropoisomers *S* and *R* were obtained with comparable yields). We were not interested to isolate the dimer in these conditions.



a_1: **E** (1 eq.), **F_1** (2.2 eq.), DCC (4.4 eq.), DMAP (2.2 eq.), CH_2Cl_2 (0.025 M), RT or Δ, 16-48h

Scheme 50. Bi-esterification of the HHDP unit on the sugar 30

The compounds **155-156** so synthesized were subject to hydrogenolysis reaction to give the key intermediates of our synthetic plain (Scheme 51).



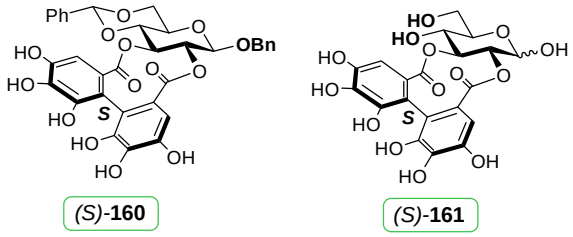
(S)-**155**: R_1 = Si(*i*-Pr)$_2$
(S)-**156**: R_1 = CHPh

(S)-**157**: R_1 = Si(*i*-Pr)$_2$ *(100%)*[a]
(S)-**158**: R_1 = CHPh *(57%)*[b]

[a] *Chemical yields after reverse phase column chromatography purification* [b] *Yield basisd on reaction crude.*

Scheme 51. Hydrogenolysis of compounds (S)-155 **and** (S)-156

The hydrogenolysis reaction revealed to be more difficult than expected. The products **(S)-159**-**(S)-160** of partial deprotection were also obtained together with the completely deprotected product **(S)-161**.

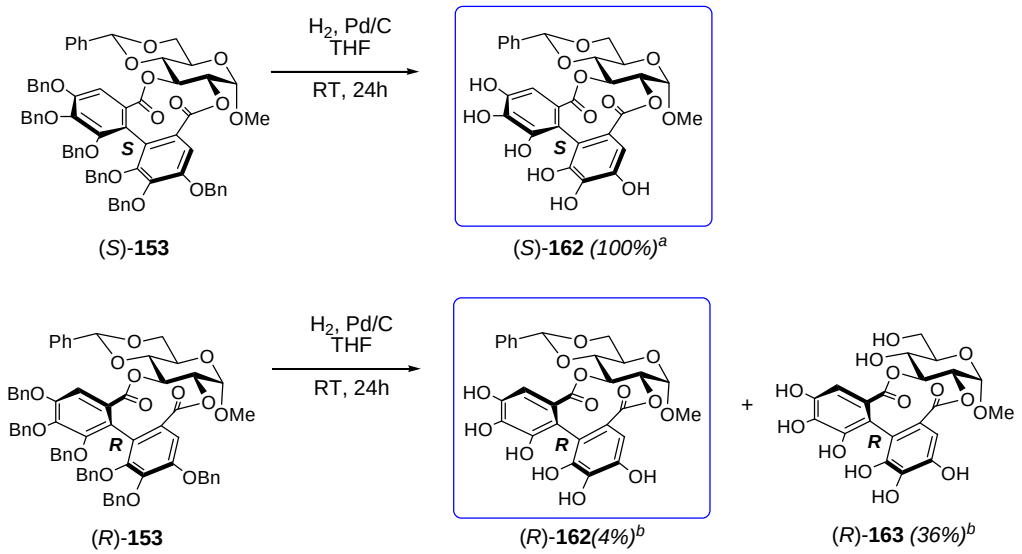


(S)-**160**

(S)-**161**

Scheme 52. By-products of hydrogenolysis

This deprotection reaction was also performed on the compounds **153** in order to have references for the studies of oxidative coupling.



[a] Chemical yield basisd on crude reaction. [b] Chemical yield after reverse phase C_{18} column chromatography. Products synthesized by G.Malik. Their characterization is not detailed in the experimental section.

Scheme 53. Hydrogenolysis of compounds S- **and** R-153

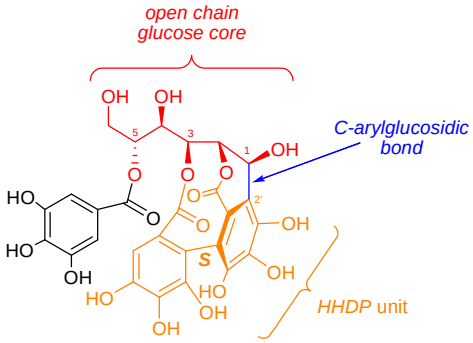
With all these compound in hands, we focused our synthetic effort towards the development of a procedure for the *C*-arylglucosydation reaction.

Chapter 3
C-arylglucosidation Step

Nature does nothing uselessly.
Aristotele, *Politics*, I.1253a8

3.1 The key step of *C*-arylglucosidation

First described by Mayer in the late 1960s, *C*-arylglucosidic ellagitannins are natural compounds characterized by the particularity, unique among the natural products, of featuring an open-chain glucose core and a carbon–carbon (C–C) linkage between an aromatic aglycon and the C-1 of the attached carbohydrate.



23: punicacortein A

This unique *C*-arylglucosidic structure is embodied in a variety of biologically important natural products and confers remarkable stability to both enzymatic and/or chemical hydrolysis. Moreover – maybe as a consequence of the rigidity of their bicyclic structure - these unusual natural products exhibit a diverse range of biological activities as antibacterial, antiviral and antitumor activity.[149,150]

3.1.1. Synthetic approaches to *C*-arylglucosidation

Due to their significant biological activities and the inherent novel architectures, the *C*-arylglucosidic natural products present unique challenges for contemporary total synthesis.

Before starting a discussion on the developed strategies towards the *C*-arylglucosidic bond formation, it is important to make a precisation.

Formally a *glucoside* (more generally a *glycoside*, if we want extend the discussion to any sugar different from glucose) is any molecule in which a glucose group is bounded through its anomeric carbon to another group *via* a *glucosidic* bond.

Glycosides can be linked by an O (*O*-glycosides), N (*N*-glycosides), S (thioglycosides) or C (*C*-glycosides) glycosidic bond (Figure 25). (The given definition is the one used by IUPAC).

The glycone part of a glycoside consists of a single sugar group (monosaccharide) or several sugar groups (oligosaccharide).

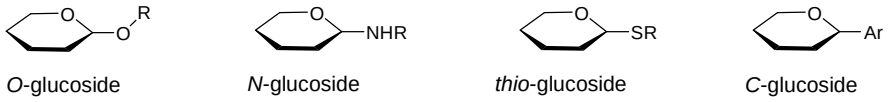
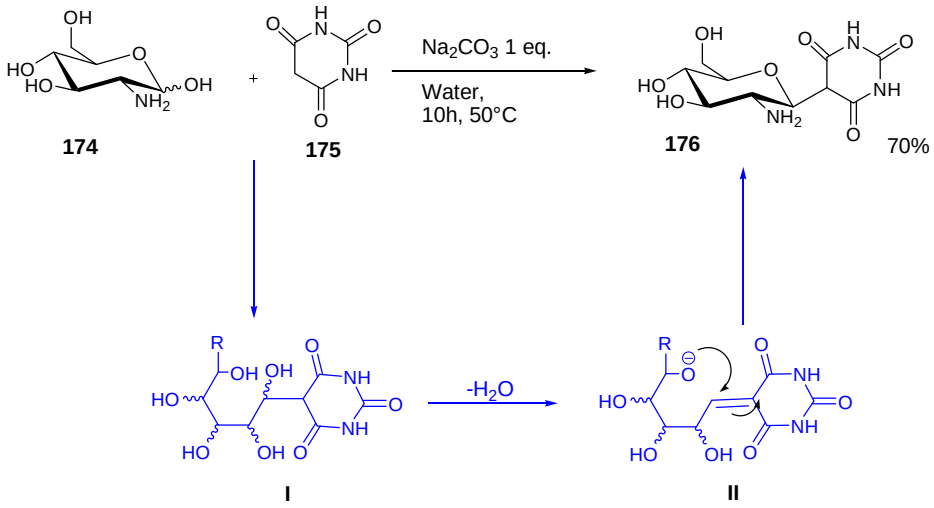


Figure 25. Glucosidic structures

In this light, the definition of *C*-arylglucosidic ellagitannins could not be completely appropriate. However, the scientific community continues to name these molecule as *C*-glucosides.

Numerous specifically methods for *C*-arylglucosidation reaction have been developed in the last years[151] but any of these resulted relevant to our purposes, because in any case the sugar of the final compound is in open chain.

Only one report for convertion of reducing monosaccharides into *C*-glucosidic derivatives exploiting the reactivity of the aldehydic form of the sugar was reported in 1986 by Gonzalez *et coll*.[152] They developed a general methodology for the synthesis of pyrimidine *C*-nucleosides involving a one step reaction of aldohexose and aldopentose with barbituric acids in a water solution of sodium carbonate at 50°C (Scheme 54).

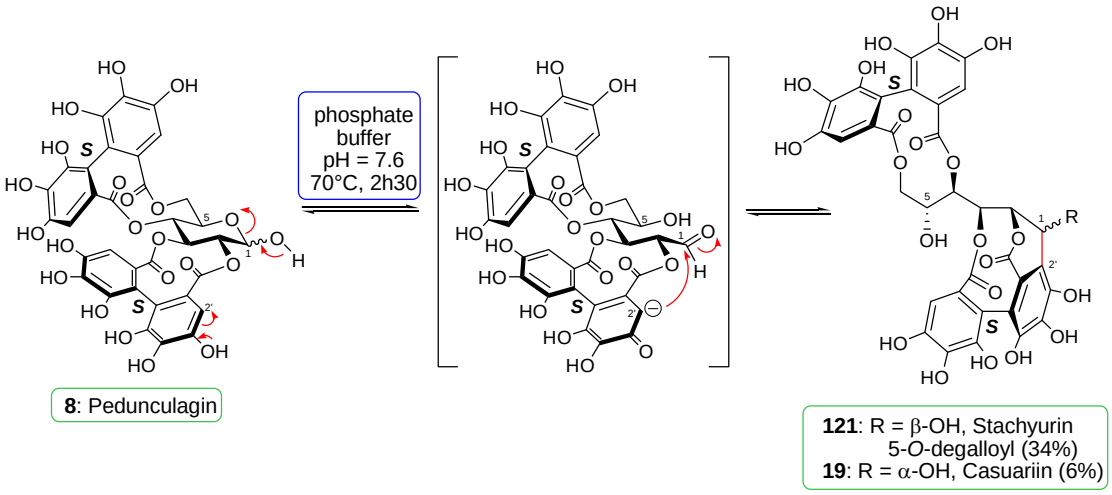


Scheme 54. *C*-glucosylbarbiturates synthesis under physiological conditions and proposed reaction mechanism

In Scheme 54 it is showed the guest mechanism for this transformation. From the pK_a values of the barbituric acid **175** (about 4) it is reasonable to suppose that this compound can react

as nucleophile even in absence of a strong basis. One can guest that the initial adduct **I** undergoes a β-elimination of water to give the unsaturated intermediate **II**, which, as in similar reactions from noncarbohydrate aldehydes[153] can be attacked by another nucleophile. The most probable is the intermolecular reaction with the oxygen six position.

This work was of inspiration for Tanaka *et coll.*[117] who managed to convert the glucopyranosyl pedunculagin (**8**) into the *C*-arylglucosidic ellagitannin casuariin (**19**) and its C-1 epimer (**121**) (Scheme 55) under biomimetic conditions.



Scheme 55. Hemisynthesis of casuariin *via* *C*-arylglucosidation of pedunculagin and proposed mechanism for the *C*-arylglucosidic bond formation

Accordingly to the Gonzalez's proposition, the reaction mechanism is though to be an aldol-type condensation on the aldehydic form of the sugar. The predominance of β-OH was considered by Tanaka *et coll.* to be due to the nucleophilic attack of the pyrogallol ring on the glucose C-1 aldehyde from the lower side of the glucose.

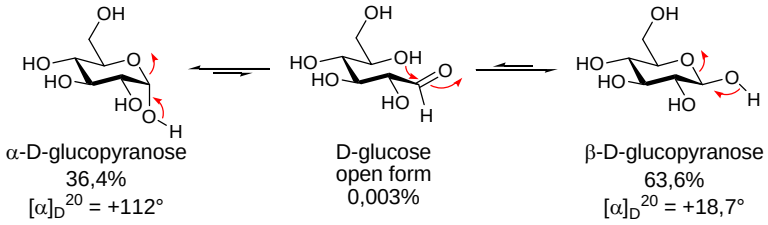
3.2 Our approach to *C*-arylglucosidation

According to the mechanism proposed by Tanaka, one can assume that an opening of the sugar is the first key event that opens up the door to the *C*-glucosidic ellagitannins. Then follows the intramolecuar aldol-type nucleophilic addition to the aldehyde function giving rise to a *C*-glucosidic bond. This hypotesis was supported by the isolation of the open-chain aldehyde liquidambin (**29**)[58] that can be considered as a molecular quoin for the passage from glucopyranosic to *C*-glucosidic ellagitannins.

3.2.A The mutarotation

We know that aldehydes and ketones undergo a rapid and reversible nucleophilic addition reaction with alcohols to form hemiacetals.

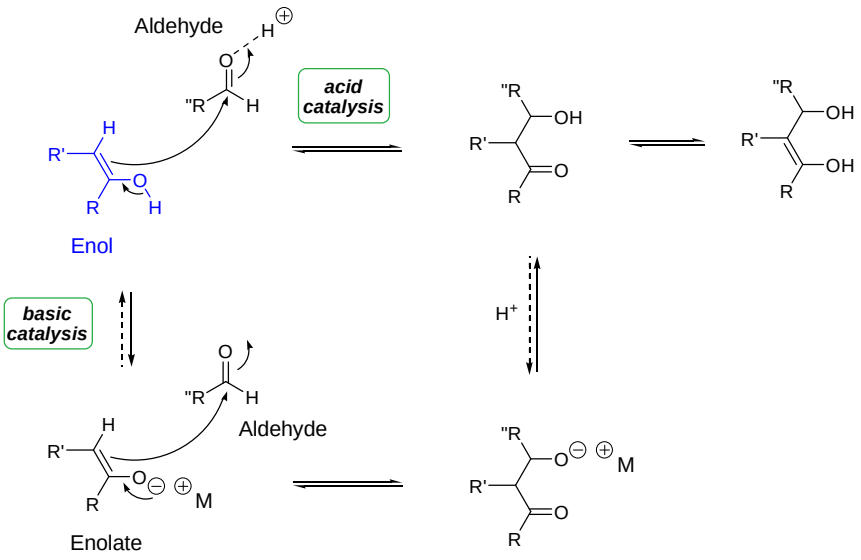
If the carbonyl and the hydroxyl group are in the same molecule, an intramolecular nucleophilic addition can take place leading to the formation of a cyclic hemiacetal.



Five- and six-membered cyclic hemiacetals are particularly stable, and many carbohydrates therefore exist in an equilibrium between open-chain and cyclic forms. When an open chain monosaccaride cyclizes to a pyranose or furanose form, a new chirality center is generated at the former carbonyl carbon. The two diastereoisomers produced are called α,β-anomers, and the hemiacetal carbon is referred to as the anomeric center. When a sample of either pure anomer is dissolved in water its optical rotation slowly changes and ultimately reaches a constant value. This change in optical rotation is called mutarotation and it is due to the slow conversion of the pure anomer into an equilibrium mixture. Altought equilibration is possible at neutral pH, it is catalyzed by both acid and basis.

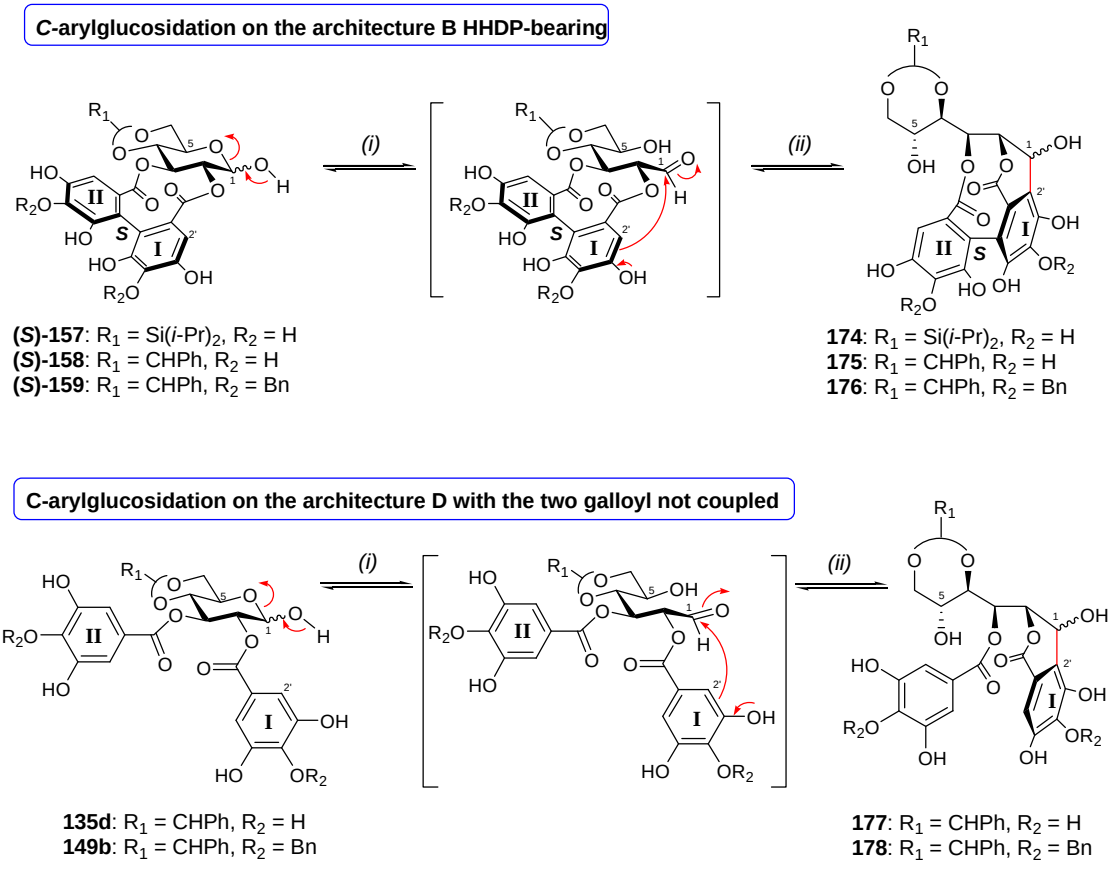
3.2.B The aldolic condensation

Aldol reactions like other carbonyl condensations occur by nucleophilic addition of an enolate ion of the donor molecule to the carbonyl group of the acceptor molecule, and give rise to the formation of a new C-C bond. The reaction is normally basis catalyzed, as in this condition the enol nucleophilicity is more accentuated. However an acidic catalysis is possible and consists in the activation of the carbonylic carbon after protonation of the oxygen.



Scheme 56. Aldolic condensation mechanisms

The success of our approach stays in the choice of the reaction conditions, that must favor both (i) the mutarotation of the sugar derivatives **B** or **D** and (ii) the aldolic condensation between the C_1 and $C_{2'I}$ (Scheme 57).



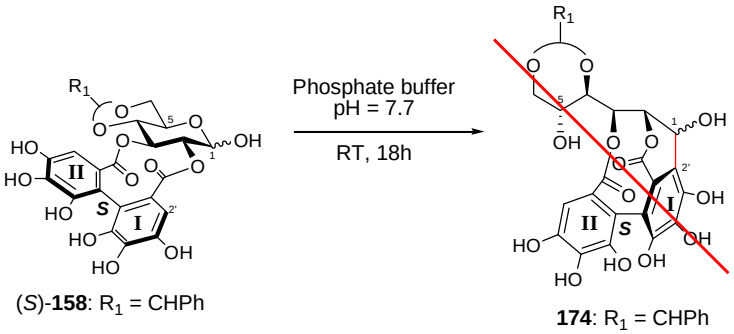
Scheme 57. *C*-arylglucosidation step

All reactions were followed by reverse phase analytic HPLC (column Pursuit C-18 15cm or 25 cm; eluting system CH_3CN-H_2O-0.1% COOH), and by RP C-18 TLC (CH_3CN-H_2O =7:3) using $FeCl_3$ to reveal the catecholic hydroxyl groups. In the general procedure, the starting material is dissolved in the solvent and stirred at the indicated temperature.

3.3 First *C*-arylglucosidation attempts: Tanaka's conditions

3.3.1 *C*-arylglucosidation on the architecture B (HHDP-bearing)

Our attemps of *C*-arylglucosidation were at first carried out on the coupled compound (*S*)-**158**. We first attempted the *C*-arylglucosidation reaction in weakly basic condition[117] were both the mutarotation and the aldolic condensation are well favored.

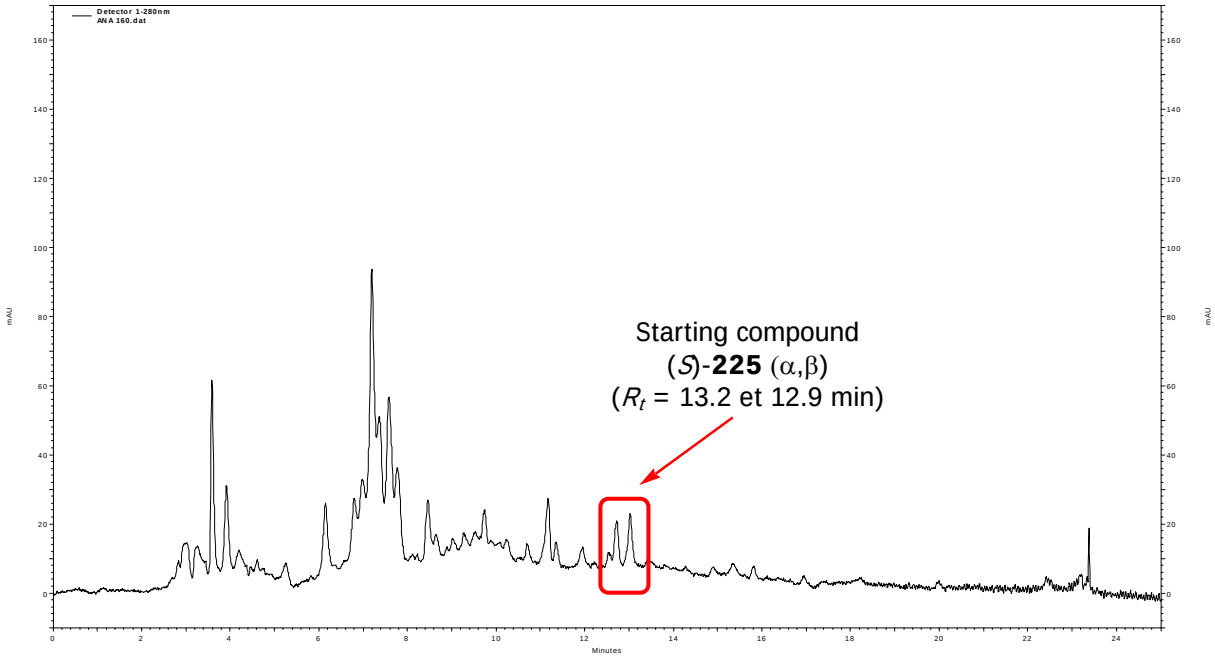


Scheme 58. *C*-arylglucosidation in the Tanaka's conditions on compound (*S*)-158

The starting compound was dissolved in water at RT and in two hours the formation of several products was observed by HPLC. To the consumption of the starting compound it corresponded the formation of a complex mixture of products deriving undoubtedly from the degradation of the starting material. It is known that the degradation due to oxidation of *ortho* catechol function is favored in basic conditions.[154]

Any improvement was obtained when the reaction was performed in a strictly inert atmosphere.

It is interesting to observe the different reactivity of our compounds and pedunculagin (**8**). Even if the yield reported by Tanaka are very low (40% total yield for *C*-arylglyucosidation products) the presence of a second HHDP unit at 4,6- position of the glucose seems to give major stability to the molecule, that resist to the weakly basic condition.



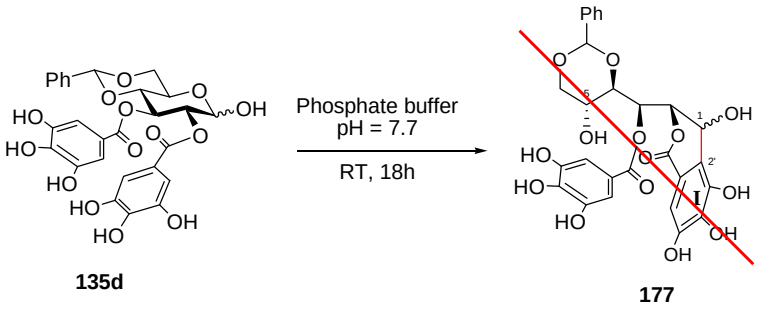
Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 30 to 100% of B in 25 min, Flow : 1mL/min, Detector UV (280nm).

Figure 26. HPLC profile *C*-arylglucosidation at pH = 7.7 on compound (*S*)-158

The same HPLC profile was obtained in the successive experiment where the reaction was carried out in water using Na_2CO_3 as basis (pH = 7/8) at room temperature.[152] A changing in the color of the reaction mixture, from yellow to dark violet through green accompanied from degradation of the starting material was observed, as for the previous essays.

3.3.2 *C*-arylglucosidation on the architecture D (two galloyl not coupled)

The same conditions were applied on compound **135d** with two pending galloyl unit attached to the glucopyranose core (Scheme 59).



135d **177**

Scheme 59. *C*—arylglucosidation in the Tanaka's conditions on compound 135d

The HPLC following of the reaction showed the rapid consumption of the starting compound and the formation of a complex mixture of products, as in the case of the HHDP-bearing intermediate.

3.4 *C*-arylglucosidation attempts in organic solvents

Having in mind the mechanism proposed by Tanaka for the *C*-arylglucosidic bond formation (Scheme 55), reaction conditions which were expected to drive the aldol-type reaction equilibrium toward the desired product were tested. It was tried to perform the reaction in organic solvents using nitrogen basiss of several strength and nature. The general procedure consisted in the addition of the basis to a solution of the starting compound in the organic solvent.

The organic basiss were chosen on the basis of their pK_a values.

Nitrogen-containing basiss were employed both without and with the solvent (generally THF) and concerning the potassium *tert*-butyloxide (*t*-BuOK) it was employed in *tert*-butanol.

Organic basiss	pK_a (acidity in DMSO)[a]
Pyridine	5
NEt_3	9-10
DBU	11-12
t-BuOK	20

[a] *http://www.chem.wisc.edu/areas/reich/pkatable/*

Table 4. pK_a values of the basiss used for the *C*-arylglucosidic reaction in organic medium

In another series of experiments the reaction was carried out in presence of carbonate (pK_a about 10) of several cations (Li_2CO_3, K_2CO_3 and Cs_2CO_3) in polar solvent as acetone or trifluoroethanol, in which the opening of the sugar is favored. By this way it was tryied to activate the carbonyl group of the aldehydic form towards nucleophilic attack via oxygen coordination.

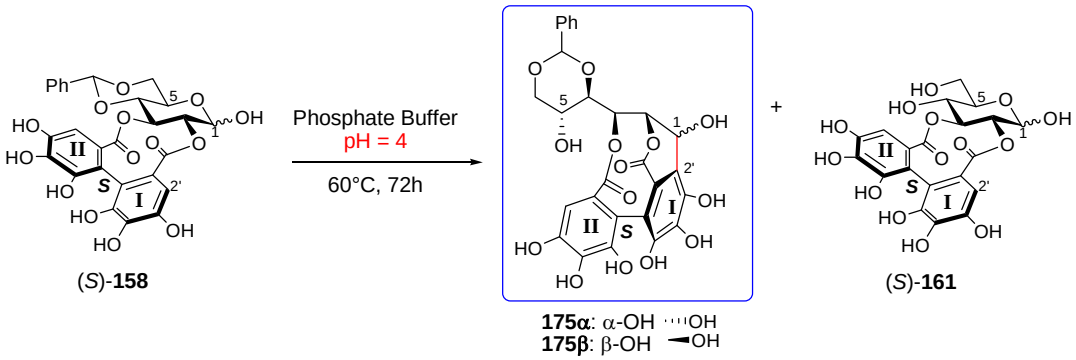
In spite of the number of different reaction condition carried out we didn't succeed in the realization of the *C*-arylglucosidic bond in this basic conditions: any consumption of the starting material was observed when weak basiss were utilized (even after prolonged reaction time 10 days), degradation of the starting material in presence of strong basiss was observed.

3.5 *C*-arylglucosidation attempts in acid conditions on the architecture B

As the essays in organic solvents were not satisfactory we came back to the aqueous medium, that is the best solvent to favor the mutarotation.

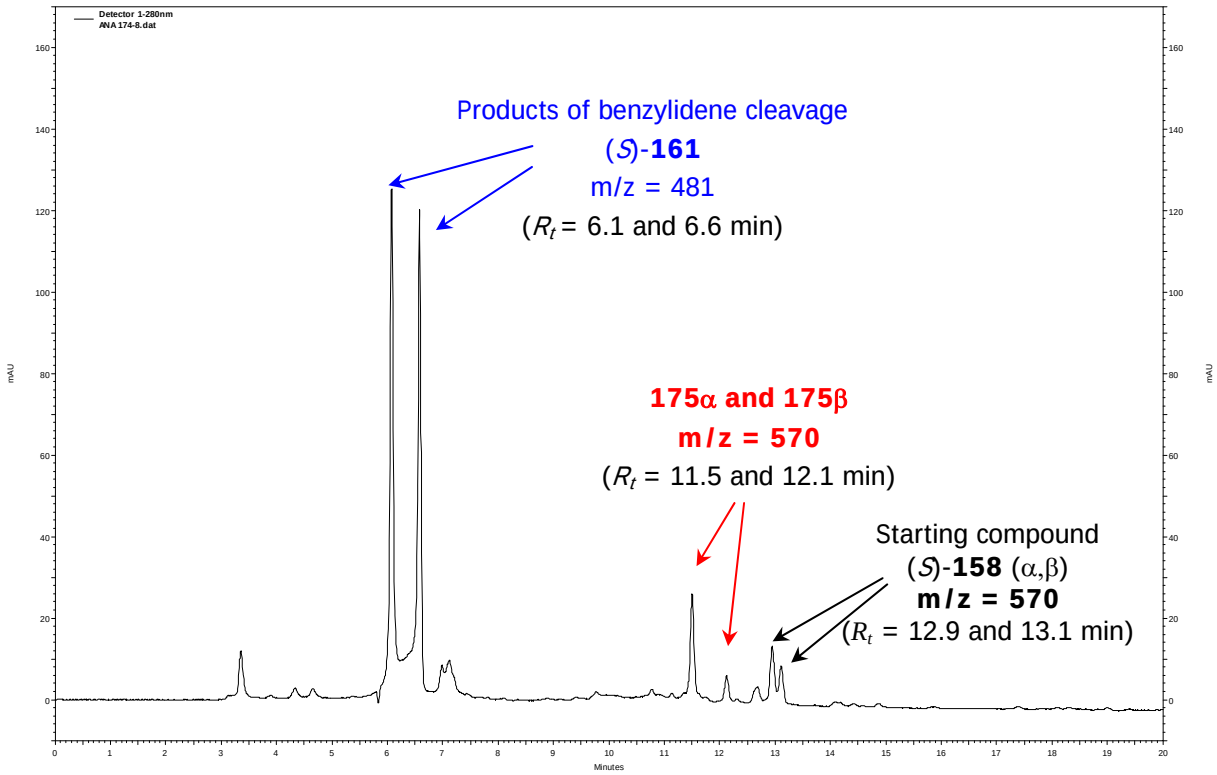
As the opening of the glucose necessary for the *C*-arylglucosidic reaction could be catalyzed in basic but also in acidic conditions, we decided to carry out the reaction in acidic condition. In these conditions the nucleofilicity of the enol -masked by the aromatic system- is less important than in basic conditions but the nucleophilic attack on the aldehydic form of the sugar is nevertheless favored by the carbonylic oxygen protonation. Moreover the oxidative processes responsible of the degradation of the starting material are less favored in acid conditions.

The first attempt was carried out on the compound (*S*)-**158** in phosphate buffer at pH = 4 under argon atmosphere (Scheme 60).



Scheme 60 : *C*-arylglucosidation in phosphate buffer at pH = 4 on compound (*S*)-158

After 1h stirring at 60°C, the HPLC profile showed a partial consumption of the starting compound and the formation of 4 new products. After three days the starting compound was almost completely consumed. The molecular masses of the reaction product (m/z) were obtained by an LC-MS analysis.



Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

Figure 27. HPLC profile *C*-arylglucosidation at pH = 4 on compound (*S*)-158 **after three days**

An ESI(-) LC-MS analysis showed for two of the new products (R_t = 11.5 and 12.1 min) masse values m/z = 570 (ion $[M-H]^-$), identical to the starting compound as expected for the *C*-arylglucosiditation epimeric products **175α** and **β**. The other pair of compounds (R_t = 6.1 et 6.6 min, m/z $[M-H]^-$ = 481) derived from the benzylidene hydrolysis in acid condition (*S*)-**161**.

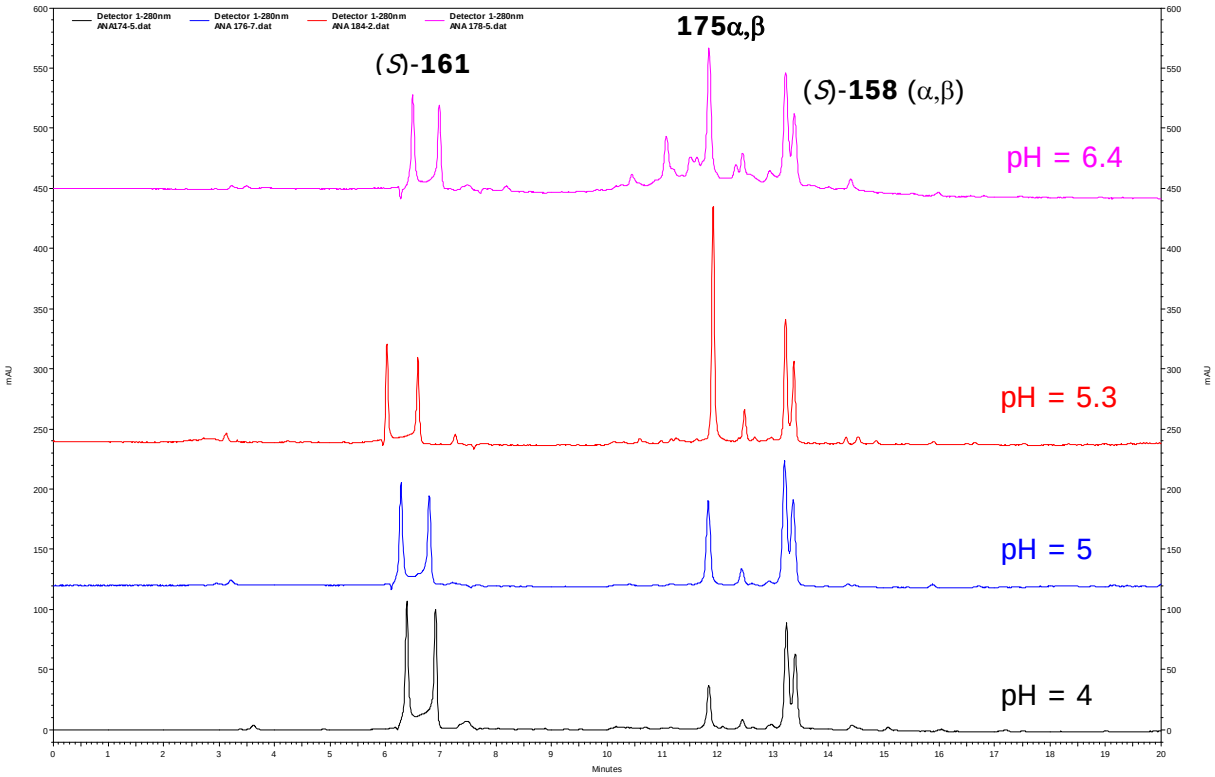
It is interesting to highlight that the *C*-arylglucosidation products without the benzylidene group are not formed in these conditions. On the basis of this observation one can deduce that the compound (*S*)-**161** is not involved in the *C*-arylglucosidation. Moreover another important information can be deduced: once the *C*-arylglucosidic bond is formed the benzylidene cleavage doesn't take place (the two epimers **175α** and **175β** do not undergo the benzylidene cleavage).

The epimer **175β** is largely favored than the other. This is in agreement with the Tanaka results and it is likely due to a preferential attack of the nucleophil on the lower side of the aldehyde.

As it is possible to see from the HPLC-UV trace (Figure 28) the major product at pH = 4 is the product of deprotection (*S*)-**161**.

Further experiments have been carried out at several pH in order to reduce the entity of the deprotection reaction in favor of the *C*-arylglucosylation reaction (Figure 28).

A wide range of pH was exploited and it was found that the more basic is the pH, minor is the benzylidene cleavage, faster is the *C*-arylglucosidation reaction but degradation also occurs. In acid conditions the conversion of the starting compound is slower and to a lesser extent but cleaner.



Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

Figure 28 : HPLC-UV *C*-aryl glucosydation in phosphate buffer at several pH after 48 h stirring at 60°C

The best conditions were found to be between pH 5 and 6. The reaction was then carried out at pH 5.3 on larger scale.

3.6 The *C*-arylglucosidation step

3.6.1 Reaction on (*S*)-158 work-up and products purification

(*S*)-**158** was dissolved in the phosphate buffer at pH = 5.3 and the resulting solution was stirred at 65°C for two days. Then the reaction mixture was concentrated *in vacuum* and purified by semipreparative reverse phase HPLC (Microsorb C18, 250 x 41.4 mm).

An acid was added to the HPLC eluent in order to avoid ionization of the phenols, unless the peaks are considerably flattened and no reproducible retention times are obtained.

After lyophilization of collected fractions the compounds **175α**, **175β** and (*S*)-**161** were obtained with a yield of 9%, 20% and 15%. The starting compound was also recovered (25%).

These value were obtained on a scale of 20 mg of starting compound and are reproducible on analytical scale even if problems appeared when reaction was carried on a preparative scale.

When the reaction was carried out on a scale of 300 mg of (*S*)-**158** the purification became cumbersome (the maximum amount of 20 mg was injectable on semipreparative column to have a good separation) and the amount of solvent huge.

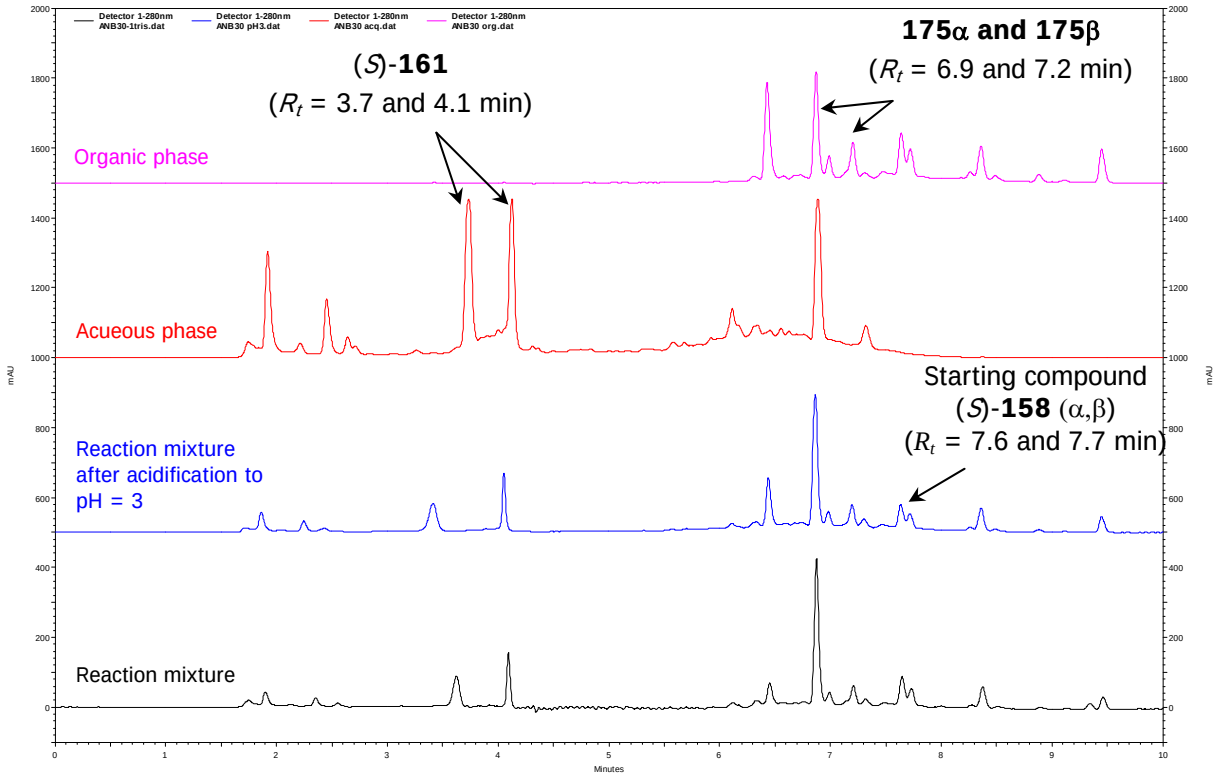
Two preliminar work-up have been tested in order to semplify the reaction mixture by remotion of phosphate salts before the purification by HPLC:

- reverse phase C-18 silica gel filtration
- liquid-liquid extraction of the aqueous phase with an organic solvent

The silica gel filtration on C-18 allowed to remove all the inorganic compounds that are not retained by the C-18 chain, fixed on the silica. The reaction product were after eluted with an organic solvent. The drawback of this method was that the total mass recovered in the end was never bigger than 75% and mostly constitued of degradation compounds.

The liquid-liquid extraction with an organic solvent seemed to be the best solution. The ethyl acetate was chosen as organic solvent for its high polarity and because the reaction product were soluble in it. The acidification to pH = 2-3 of water by addition of a solution of hydrochloridric acid (2M) allowed the protonation all the species in the reaction mixture making the extraction more efficacious.

In the Figure 29 it is showed the monitoring of the acidification and extraction in the end of the reaction.



Analysis conditions : Column : Pursuit 3 C18 (150 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 10 min, Flow : 1mL/min, Detector UV (280nm).

Figure 29. HPLC profile of the work-up of the *C*-arylglucosidation of (*S*)-158

As it is possible to see the acidification did not change the HPLC profile (any change in the product ratio is observed neither degradation). After three extractions with ethyl acetate the crude reaction mass after solvent evaporation corresponded almost to the 90% of the initial mass engaged in the reaction.

After evaporation of all the organic phase the solid crude was very difficult to solubilize in water for the subsequent HPLC purification. A large amount of water was necessary to dissolve the solid and this lead to a big augmentation of injection numbers.

Moreover a precipitate of ellagic acid was formed after evaporation, due to esters hydrolysis.

In order to overcome this problem it was tried to not dry completely the crude by addition of some water to the ethyl acetate after extraction. Again a degradation of products was observed.

It was realized that the reaction products are very sensible to any treatment and we decided to purify directly the reaction mixture without any work-up by HPLC. In order to reduce the purification time the reaction was carried out at higher concentration.

The chemical yield of the reaction is relatively small compared with what was expected on the basis of the crude proton NMR. That could be explained by the fact that the chemical yield depends not only on the initial concentration of the compounds in the raw material, but also on the degradation and dispersion compounds in several injections for the purification.

3.6.2 Products 175α and β characterization

The two epimeric compounds **175α** and **175β** (Figure 30) were obtained pure after HPLC purification. The minor compound was difficult to obtain in a pure form.

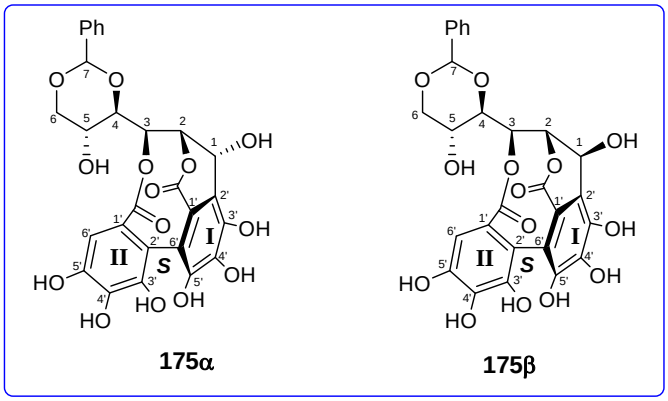


Figure 30. Epimeric products 175α **and** β **from *C*-arylglucosidation on** (*S*)-158

For the main compound **175β** the considerations about the formation of the new C-C bond was done on the basis of the comparison with the specra of the starting material (*S*)-**158**.

The chemical shift and the coupling patterns of the open-chain glucose core protons were assigned by ^{1}H-^{1}H COSY experiments: from H-2 to H-5 in the zone 3-5 ppm, with the H-6 characteristic for the coupling $^{1}J_{C\text{-}H}$ HMQC with the only secondary carbon C-6.

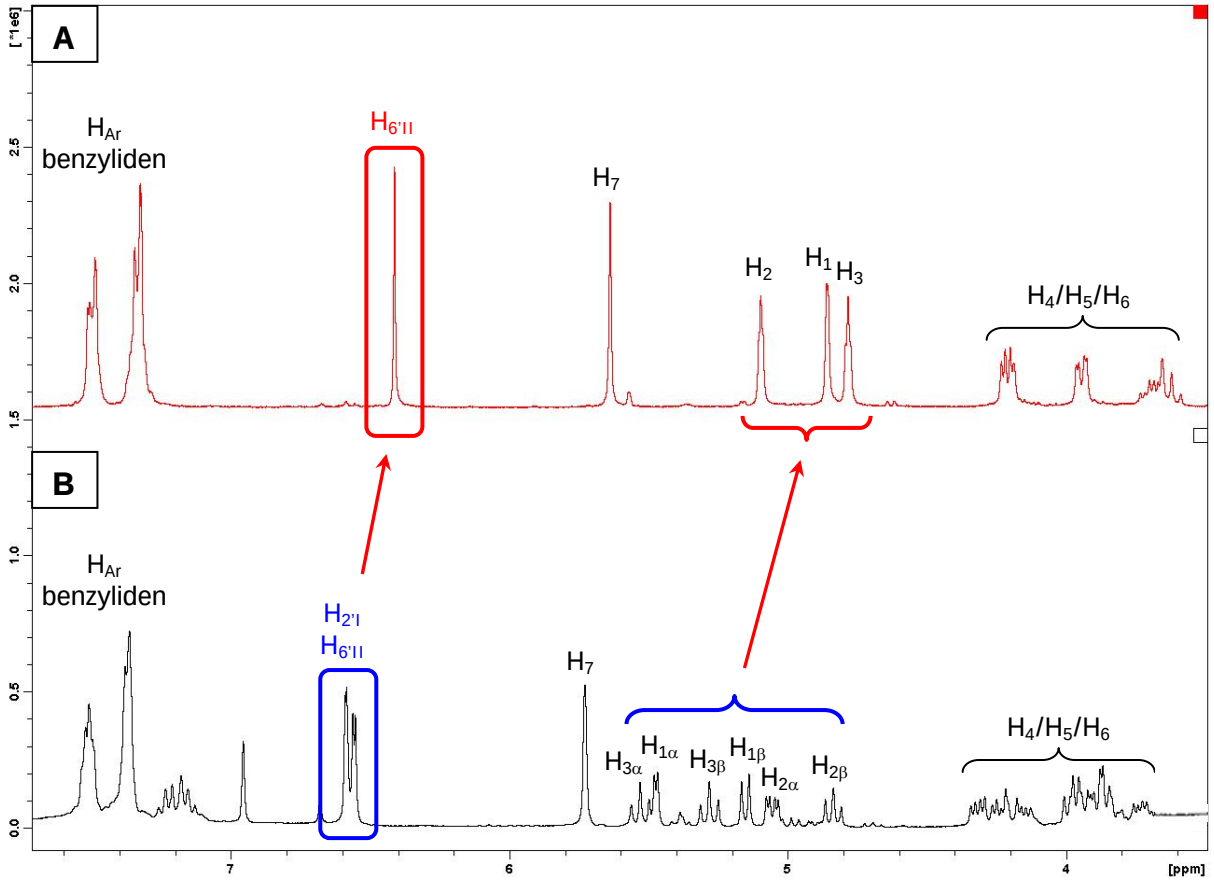
	H-1	H-2	H-3	H-4	H-5	H-6
H-1		X				
H-2			X			
H-3		X		X		
H-4			X		X	
H-5				X		X
H-6					X	X

Table 5. ^{1}H-^{1}H COSY correlation of compound 175β

Diagnostic features in the ^{1}H-NMR spectra (Figure 31) was the presence of only one of the two isolated proton singlets at 6.5 attributable to the HHDP moiety ($H_{6'II}$, *red marked*).

The corresponding aromatic protons in the starting material (*S*)-**158**, integrate for 4H (2H for the α anomer and 2H for the β) and were 4 singlets in the region between 6.55 and 6.59 ppm (*blue marked*).

The sugar protons H_1, H_2 and H_3 of the reaction product resulted shielded in the region between 4.77 and 5.10 ppm and the coupling constants varying between 2.1 and 2.8 Hz. These little values for the coupling constants are different from the characteristic constants of glucopyranose (generally ^{3}J = 8-9 Hz for $H_{1\beta}$, H_2 and H_3 and $^{3}J \approx 3.5$ Hz for $H_{1\alpha}$) and are typical of an open chain glucose.



A : ^{1}*H-NMR (acetone-d$_6$) compound* ***175β*** *major product of C-arylglucosidation*
B : ^{1}*H-NMR (acetone-d$_6$) compound (S)-**158** (mixture of anomers α:β = 1:1) starting material of C-arylglucosidation*

Figure 31. ^{1}H-NMR spectra of the main product compared with the starting compound

The carbon chemical shift were assigned on the basis of DEPT and HMQC experiments.

In a DEPT-^{13}C (distortionless enhancement of polarisation transfer) experiment, a sequence of pulses with various delay times are used to create the DEPT spectra where -CH3 and CH peaks appear as normal and -CH2- peaks appear inverted. Quaternary C are not usually seen. By this way the number of H attached to C can usually be deduced.

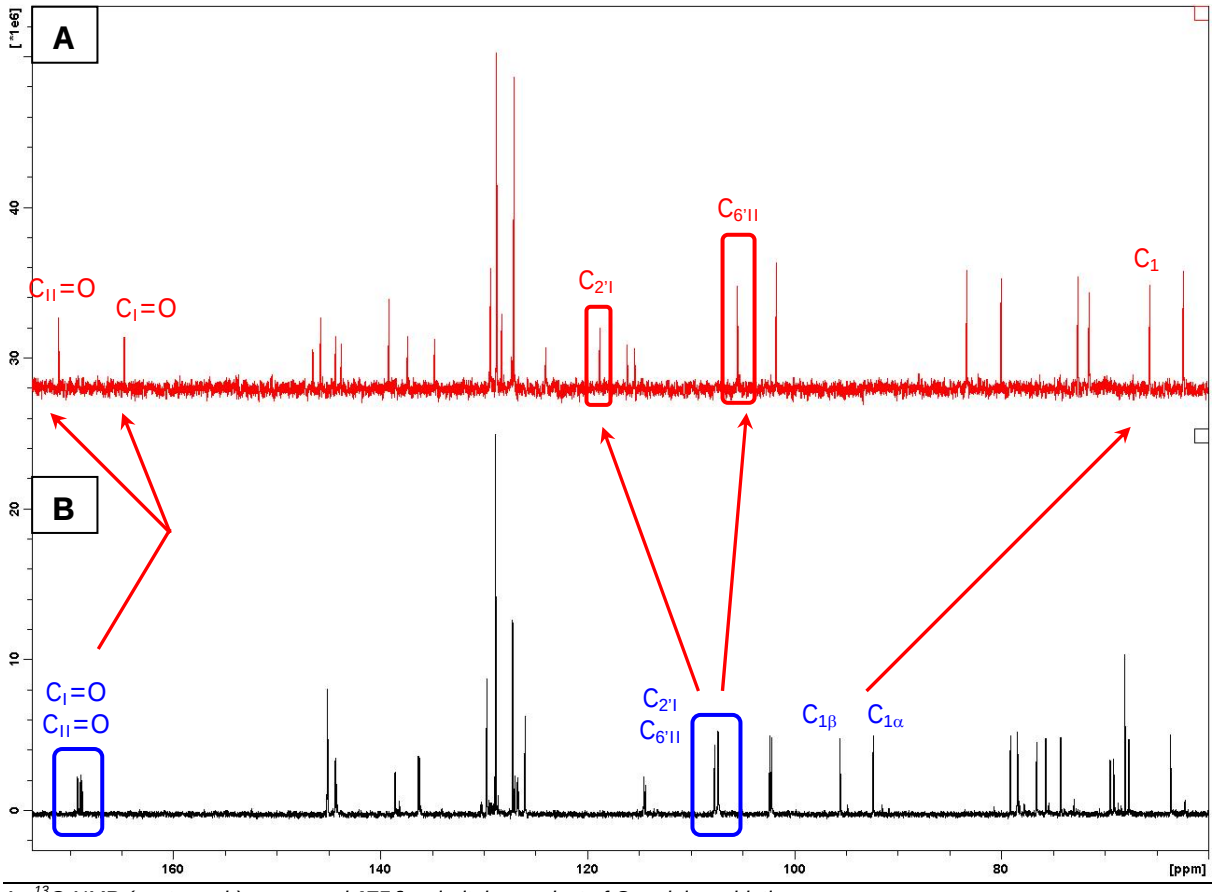
The 2D-NMR experiment through the short distance C-H correlations (HMQC) allows to associate the proton signals to the signals on the DEPT of the carbon to whom they are linked.

The appearance of six aliphatic carbon signals (region 62.4 and 83.3 ppm) indicated that compound **175β** possessed a C-6 polyalchol core. The absence of an anomeric signal in the ^{13}C spectra (Figure 32) in the region 92-96 ppm (characteristic of α and β anomeric carbon of a glucopyranose) indicated that the glucose core was in an open-chain conformation. The upfield of C-1 signal as respect to the starting material (65,7 vs 92,4/95,6) was indicative of a C-C bond formed.

Two further information were deduced from the ^{13}C-NMR spectra to support the guest structure.

- the two carbons $C_{2'I}$ and $C_{6'II}$ belonging to the HHDP unit had a very different chemical shift (118.8 and 105.4 ppm respectively) as respect to the starting material and a DEPT experiment allowed the assignation of their multeplicity: $C_{2'I}$ resulted to be a quaternary carbon whereas $C_{6'II}$ tertiary; further sign of the *C*-arylglucosidic bond formation.

- the carbonyl carbon on the cycle noted I (C_I=O) involved in the new formed *C*-arylglucosidic bond was shielded at 164.6 ppm whereas the carbonylic carbon on the cycle II (C_{II}=O) is deshielded at 171.0 ppm (the carbonylic carbons on the starting material occur between 168.5 and 169.0 for the two anomers α and β)



A : ^{13}*C-NMR (acetone-d$_6$) compound* ***175β*** *majoritaire product of C-arylglucosidation*
B : ^{13}*C-NMR (acetone-d$_6$) compound (S)-****158*** *(mixture of anomers* α*:*β *= 1:1) starting material of C-arylglucosidation*

Figure 32. ^{13}C-NMR spectra of the major epimer compared compared with the starting compound

A correlation HMBC[b] (Figure 33) with H-1 and H-2 and the quaternary carbon $C_{2'I}$ involved in the new C-C bond gave further confirmation of the structure.

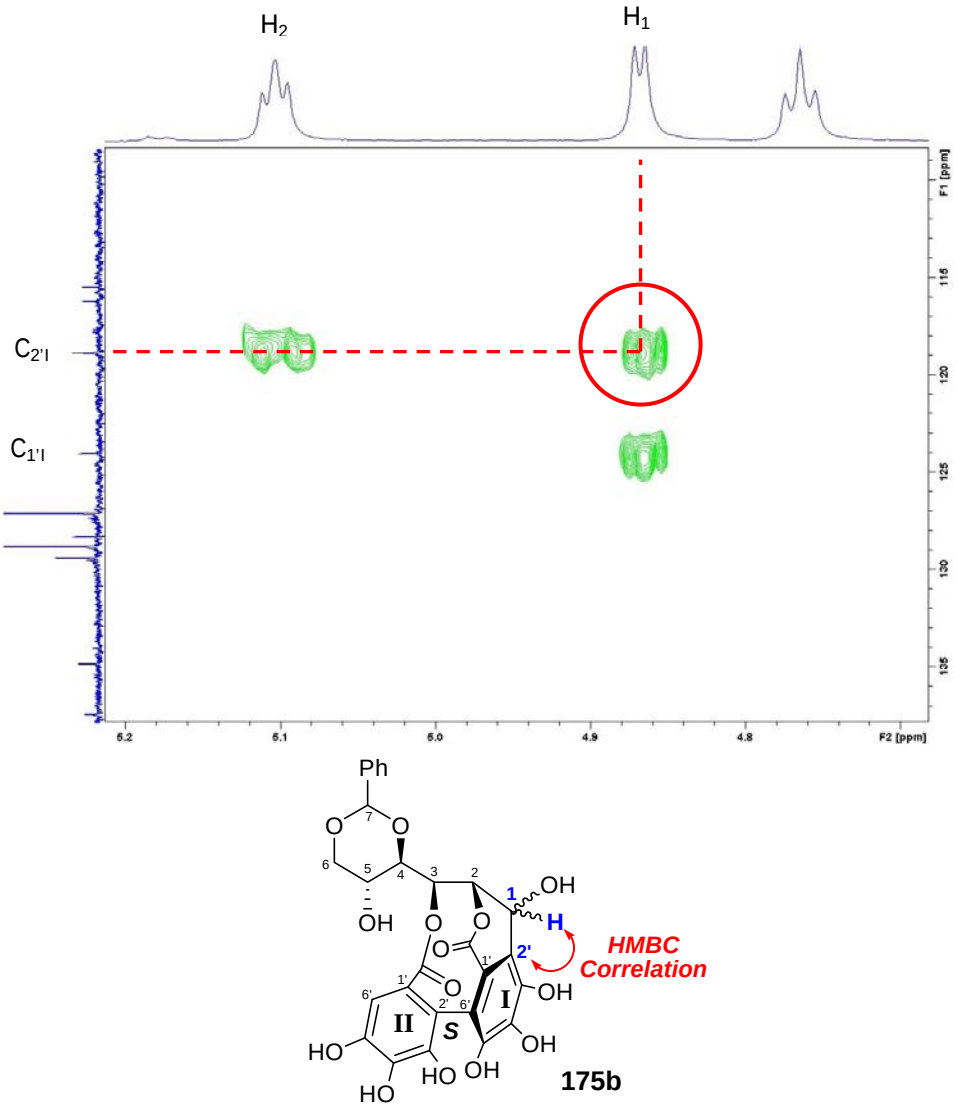
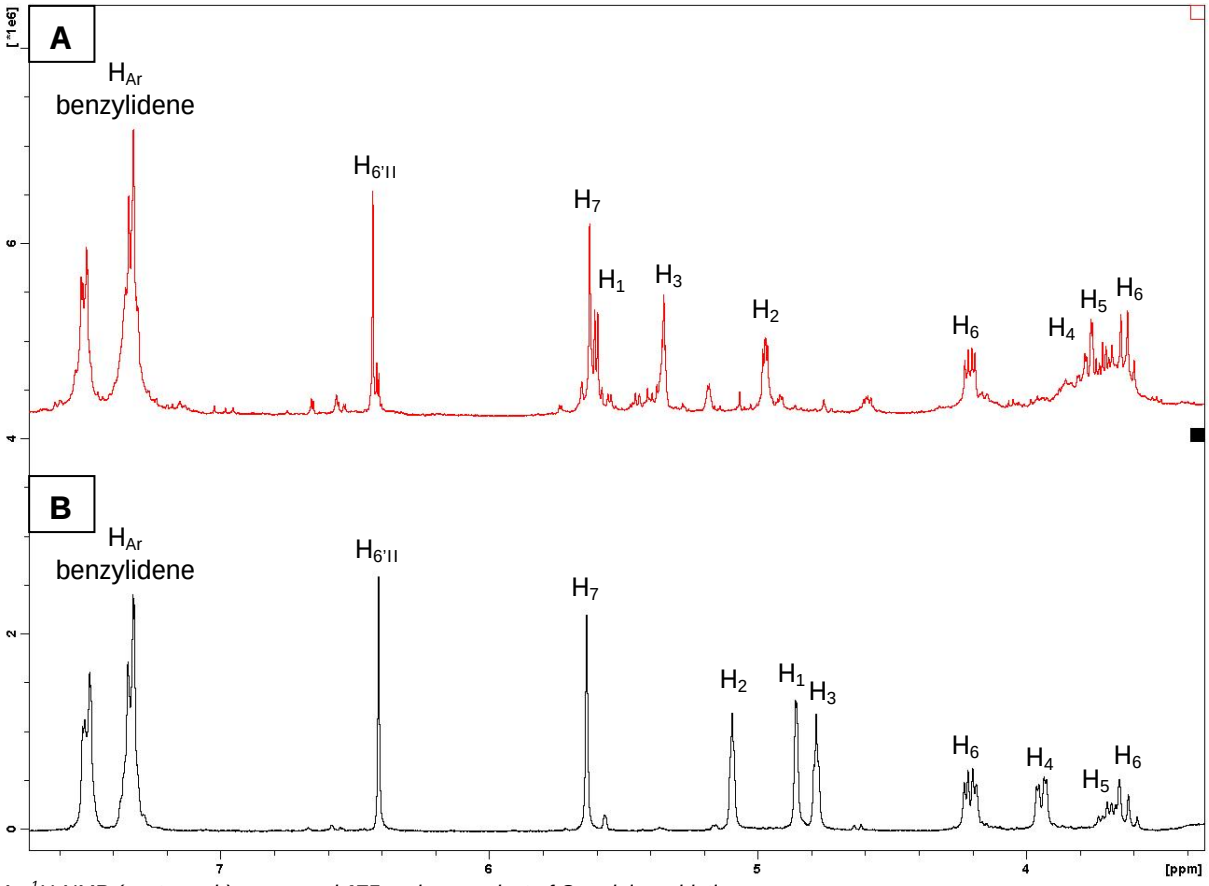


Figure 33. HMBC experiment on compound 175β

[b] Heteronuclear Multiple Bond Correlation is an experiment that identifies proton nuclei with carbon nuclei that are separated by more than one bond

For the minor product **175α** the ^{1}H-NMR analysis allowed to confirm that this second compound was the second diastereoisomer at the C_1 deriving from the *C*-arylglucosidation.

The ^{1}H-NMR spectra presented the same number of signals than the β epimer. The chemical shift and the coupling patterns of the open-chain glucose core protons were assigned on the basis of ^{1}H-^{1}H COSY experiments



*A : ^{1}H-NMR (acetone-d_6) compound **175α** minor product of C-arylglucosidation*
*B : ^{1}H-NMR (acetone-d_6) compound **175β** major product of C-arylglucosidation*

Figure 34. Comparison between the ^{1}H-NMR spectra of the two epimers 175

3.6.3 C-1 configuration determination

The C-arylglucosylation reaction corresponds formally to an intramolecular aldol-type nucleophilic addition of the 2,3-HHBP unit to the aldehyde function generated during the mutarotation of the sugar. The two epimers at the C-1 position of the glucose are then obtained after the attack to the carbonylic carbon.

The C-1 configuration of the products obtained can be determined on the basis of two-dimensional nuclear Overhauser effect (NOE) spectroscopy and NOE difference spectroscopy.

An examination of the Dreiding models revealed in fact that there is no marked difference in the dihedral angles of the two C-1 epimers (the angle is, in all cases, ca. 60°), so their configuration cannot be assigned with certitude on the basis of the coupling constant values. In the course of their studies, Nonaka[25] found that the NOESY of vescalagin (β configuration) showed a cross peak between the H-1 and the H-3, whereas in castalagin (α configuration), this cross peak was not observed.

Likewise we carried ROESY experiments in order to assign the C-1 configurations of the two diasteroisomers obtained. Unfortunately, the expected correlation were not evident. However the C-1 configuration can be tentatively assigned on the basis of the value of the coupling constants of the H-1 signals. In 1990, on the basis of the accumulated data on several complex tannins as appropriate model compounds, Nonaka G. *et coll*.[25] concluded that in the *C*-glucosidic hydrolyzable tannins, a small coupling constant (0-2 Hz) of the H-1 signal corresponds to the β-linkage of the substituent, whereas a larger coupling constant (ca.5 Hz) indicates the α–linkage.

The C-1 configuration of our products was so determined on the basis of the comparison between the coupling constant for the H1 proton between the two products obtained **175α** and **175β** with that reported in literature for other epimeric pairs punicacortein A/epipunicacortein A (**23a-b**) and the castalin/vescalin (**26/27**) (Table 6).[42,155,156]

	Castalin	Vescalin	Punicacortein A	Epi-punicacortein A
H-1	d J=3.5	d J=1.5	d J=5	d J=4.4
H-2	brs	d J=1.5	dd J=2, 5	m
H-3	d J=7.8	d J=1.5	brs	brs
C-1	α	β	α	β

Table 6. H-1, H-2 and H-3 coupling constants reported in literature for *C*-arylglucosidic ellagitannins epimeric pairs

So it was assigned the β configuration to the C-1 of the main product. It presented a coupling constant $^{3}J_{H1\text{-}H2}$ of 2.1 Hz, similar to vescalin **27** and epi-punicacortein A **23b**. While to the minor product, with a $^{3}J_{H1\text{-}H2}$ of 4.6 Hz, it was assigned an α C-1 configuration (Table 7).

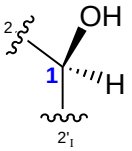
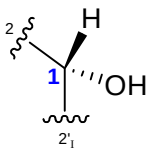
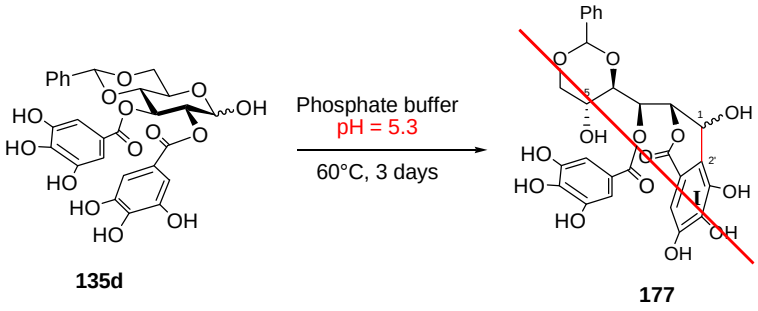
	major product 175β	minor product 175α
H-1	d *J* = 2.1	d *J* = 4.6
H-2	t *J* = 2.5	dd *J* = 2.8, 4.5
H-3	t *J* = 2.8	t *J* = 2.6
C-1 configuration	 β	 α

Table 7. C-1 configuration of the *C*-arylglucosidation products on the basis of their coupling constants

3.7 *C*-arylglucosidation on the architecture D

The same reaction conditions were carried out on the 2,3-digalloylated reducing glucose **135d** (Scheme 61).

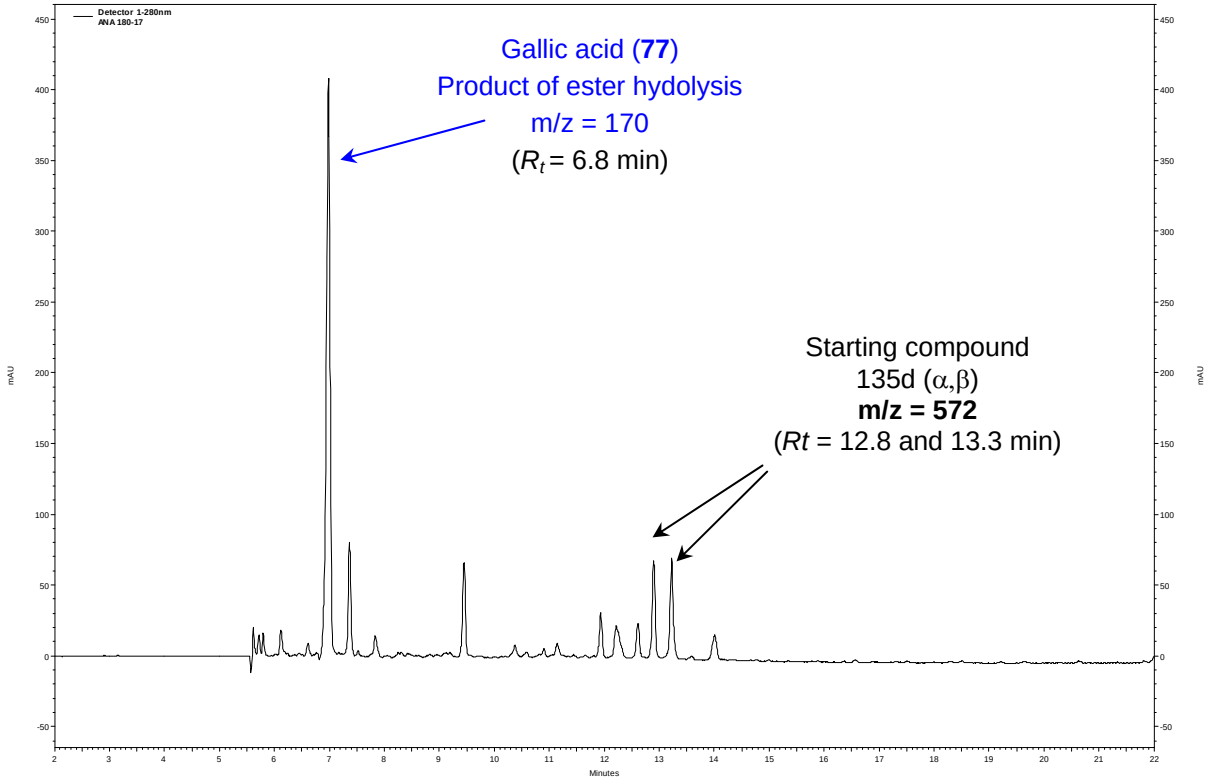


135d **177**

Scheme 61. *C*-arylglucosidation in phosphate buffer at pH = 5.3 on compound 135d

It is worth noting the different reactivity and solubility determined by the presence of the HHDP. The compound **135d** resulted less soluble than the HHDP-bearing intermediate (*S*)-**158**, so it was necessary to add some acetonitrile to obtain its complete solubilization. After 1h stirring at 60°C the starting compound was almost completely consumed giving place to

the formation of a new major product (Figure 35). An LC/MS analysis allowed the attribution of this signal to gallic acid **77** generated from esters hydrolysis in **135d**.



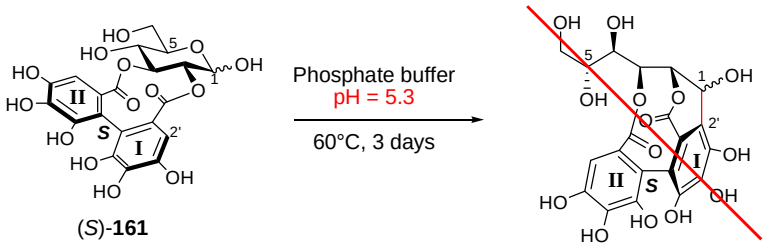
Analysis conditions : Column : Pursuit 5 C18 (250 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 0 to 100% of B in 20 min, Flow : 1mL/min, Detector UV (280nm).

Figure 35. HPLC profile *C*-arylglucosidation at pH = 5.3 on compound 135d

Evidently the formation of the key *C*-arylglucosidic bond is made possible from the conformational constraint in the HHDP-bearing architecture **B**. This experimental observation invalidated our alternative retrosynthetic approach (route II) but furnished an important support to the current biosynthetic hypotheses:[13] the HHDP formation is anterior to the *C*-arylglucosidation.

3.8 *C*-arylglucosidation attempts in acid conditions on a completely deprotected intermediate

The reaction conditions optimized on compound (*S*)-**158** leading to the *C*-arylglucosidic bond formation were also applied on the compound (*S*)-**161** (Scheme 62).



(*S*)-**161**

Scheme 62. *C*-arylglucosidation in phosphate buffer at pH = 5.3 on compound (*S*)-161

Even after prolonged reaction time (6 days), no conversion of the starting compound was observed by HPLC analysis of the reaction mixture.
The starting compound was recovered with a 95% yield after filtration of the reaction mixture on LH-20 Sephadex (100% water to 100% MeOH).

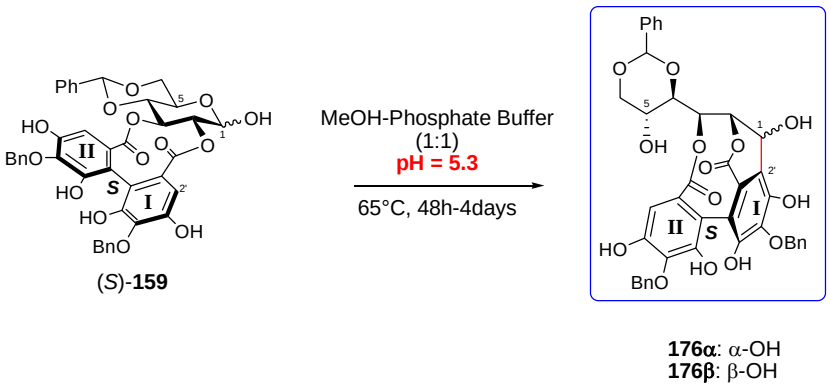
The presence of the benzylidene group at the O-4 and O-6 appears to be mandatory for the formation of the *C*-arylglucosidic bond. Pherhaps it may induce a structural strain on conformation favoring bond formation.

3.9 Towards the NHTP-unit constuction: *C*-arylglucosidation on the *para*-protected compound (S)-159

In the section **2.4** reporting coupling studies, it has been showed the unfeasibility of a synthetic strategy involving C-C-biaryl bond formation on the perhydroxylated precursor. *O*-chloranil did work on methyl glycosides but not on a reducing sugar and furthemore the coupling proved not easily reproducible.
As an alternate route, the Yamada conditions - which required the preparation of a precursor featuring a *para* protected gallic units – were adapted to our substrates. By this way, it was possible to obtain the precursor (*S*)-**159** for the *C*-arylglucosidic reaction which will be applied in the building of the NHTP unit.

The *para*-benzylated compound (*S*)-**159** resulted not soluble in water so several non-nucleophilic co-solvents were tested to get the conditions most similar to previously adopted for the *C*-arylglucosidation reaction on the polyhydroxylated intermediate. The methanol resulted to be the best choice.

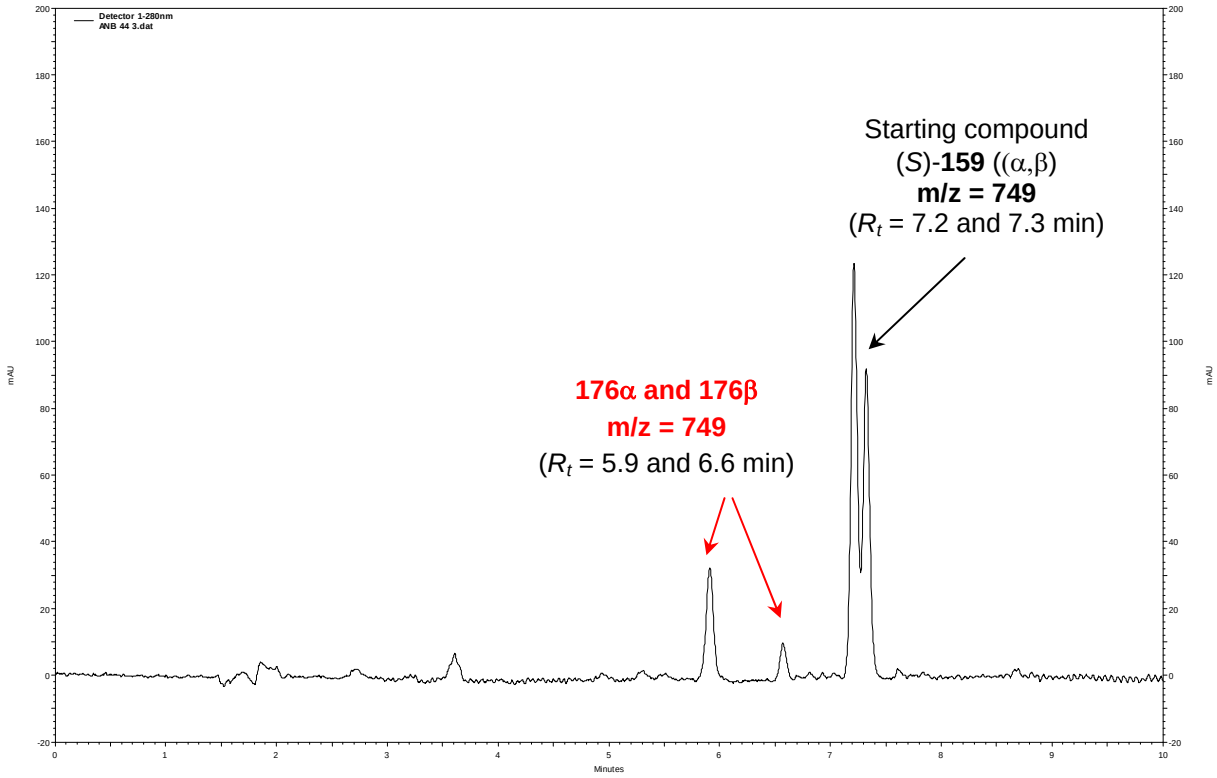
The *C*-arylglucosidation reaction was at first carried out in methanol and phosphate buffer at pH = 5.3 under argon atmosphere (Figure 36). After 48 h stirring at 65°C, the starting compound (*S*)-**159** was poorly consumed and the formation of little amounts of two more polar new compounds was observed. The two new products (R_t = 5.9 and 6.6 min) were identified by LC-MS analysis of the reaction mixture as the epimeric pairs of expected *C*-arylglucosidation products (*S*)-**159**.



(*S*)-**159**

176α: α-OH
176β: β-OH

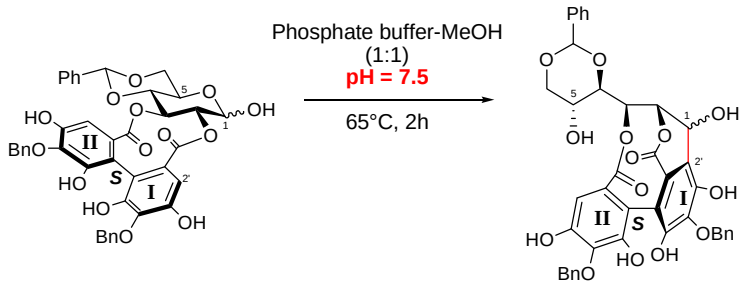
Scheme 63 : *C*-arylglucosidation in phosphate buffer at pH = 5.3 on compound (*S*)-159



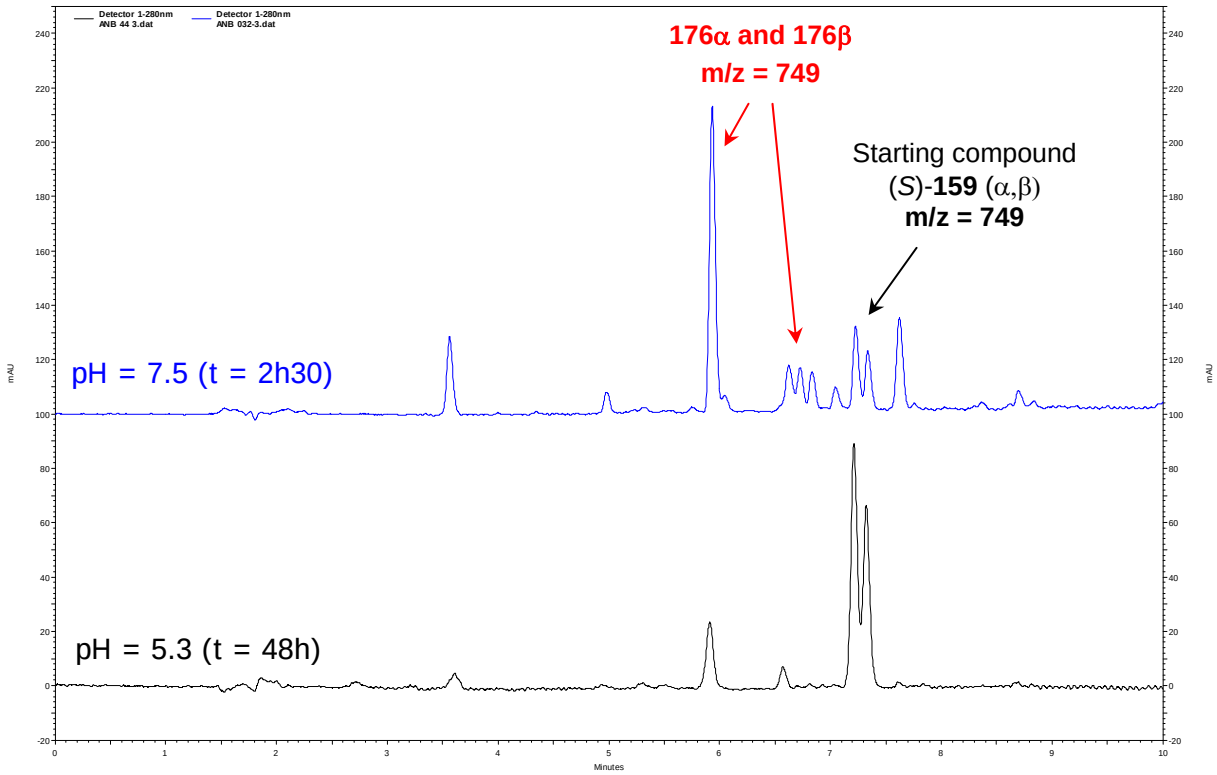
Analysis conditions : Column : Pursuit 3 C18 (150 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 40 to 100% of B in 10 min, Flow : 1mL/min, Detector UV (280nm).

Figure 36. HPLC profile *C*-arylglucosidation at pH = 5.3 after 48h on compound (*S*)-159

The benzyl group in *para* of the HHDP galloyl units allowed to mask the pseudo-catecholic function producing two *meta* phenol function. Then we guest that this structure changing (as respect to the polyhydroxylated compound (*S*)-**158**) conferred major stability to oxidation. On this hypothesis we tried to carry out the reaction in more basic conditions (pH = 7.5) in order to increment the kinetic of the reaction by the augmentation of the enol nucleophilicity. After only 2h in these conditions at 65°C, the starting material was almost completely consumed and four new products were formed, one major and three in little amount (Figure 37).



Scheme 64 : *C*-arylglucosidation in phosphate buffer at pH = 7.5 on compound (*S*)-159



Analysis conditions : Column : Pursuit 3 C18 (150 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 40 to 100% of B in 10 min, Flow : 1mL/min, Detector UV (280nm).

Figure 37. HPLC-UV *C*-arylglucosydation in phosphate buffer at several pH

After 2h30 at 65°C at pH = 7.5 the reaction was almost complete, whereas at pH = 5.3 is just starting after 48h (Figure 37). But we had to observe that the increasing in the pH caused an augmentation of collateral processes leading to a more complex reaction mixture.

The main product and one little (the one in the medium) presented the same molecular mass (m/z = 750) at an LC-MS analysis corresponding to the expected product **176**. The remaining two little product were not ionizing in the analysis conditions. They were not attributed.

3.9.1 *C*-arylglucosidation products of (*S*)-159

Reaction work-up and products purification

(*S*)-**159** was dissolved in methanol/phosphate buffer at pH = 7.5 and the resulting solution was stirred at 65°C for 2h30. Then the reaction mixture was carefully (without warming) concentrated *in vacuum* (in order to remove the methanol) and purified by semipreparative reverse phase HPLC (Microsorb C18, 250 x 41.4 mm).

After lyophilization of the fraction collected the major product of the reaction **176β** was obtained with a 25% of yield. The minor compound was not yet obtained in pure forme because it resulted difficult so separate from the two other by-products.

As in the case of the polyhydroxylated compound the yields obtained on little scale resulted difficult to reproduce it on larger scale

The ethyl acetate extraction was carried out after methanol remotion when the reaction was performed with a buffer volum major than 10 ml.

Prepurification steps were tried as RP C-18 silica gel filtration and or preparative TLC (eluent : CH_2Cl_2:EtOAc = 2:8) but big amount of mass went lost. So it was decided to avoid as much as possible pretreatment of the reaction mixture, to run the reaction on little scale in order to purify directly.

Products 176α and β characterization

The major product was easily characterized. While the characterization of the second compound, obtained in very little amount, resulted more difficult.

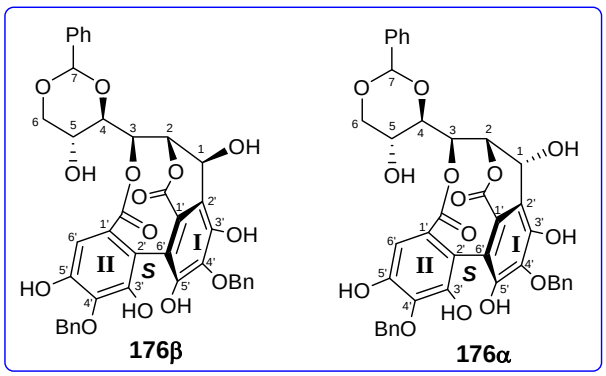


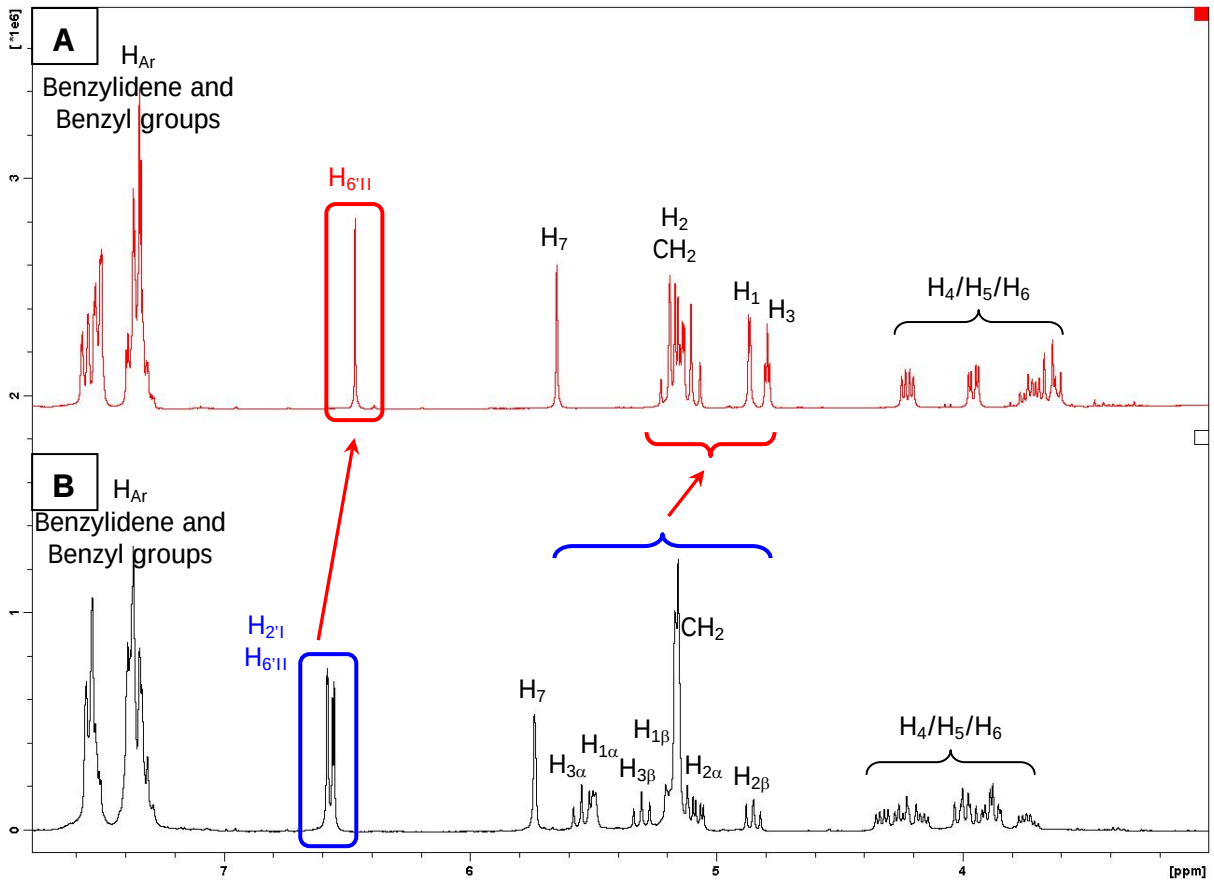
Figure 38. Epimeric products 176α and β from *C*-arylglucosidation on (*S*)-159

The NMR spectra obtained for the main product resulted superimposable to the spectra obtained for the polyhydroxylated **175β**, with the only differences due to the presence of the benzyl group on the HHDP unit.

The formation of the new *C*-arylglucosidic bond was confirmed by full NMR analysis and comparison of the ^{1}H and ^{13}C spectra of the starting material (*S*)-**159** and of the compound **175β** already described. The chemical schift and the coupling patterns of protons and carbons were assigned by mono and bi dimensional NMR experiments as ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C-HMBC.

Diagnostic features in the ^{1}H-NMR spectra (Figure 39) :

- The presence of only one of the two isolated proton singlet at 6.5 attributable to the HHDP moiety ($H_{6'II}$, *red marked*) vs. 4 singlets in the region between 6.56 and 6.58 ppm in the starting material ($H_{2'I}$ et $H_{6'II}$ α/β-anomers *blue marked*)
- The sugar protons H_1 and H_3 were shielded to 4.79 and 5.07 ppm with coupling constants varying between 2.1 and 2.9 Hz.



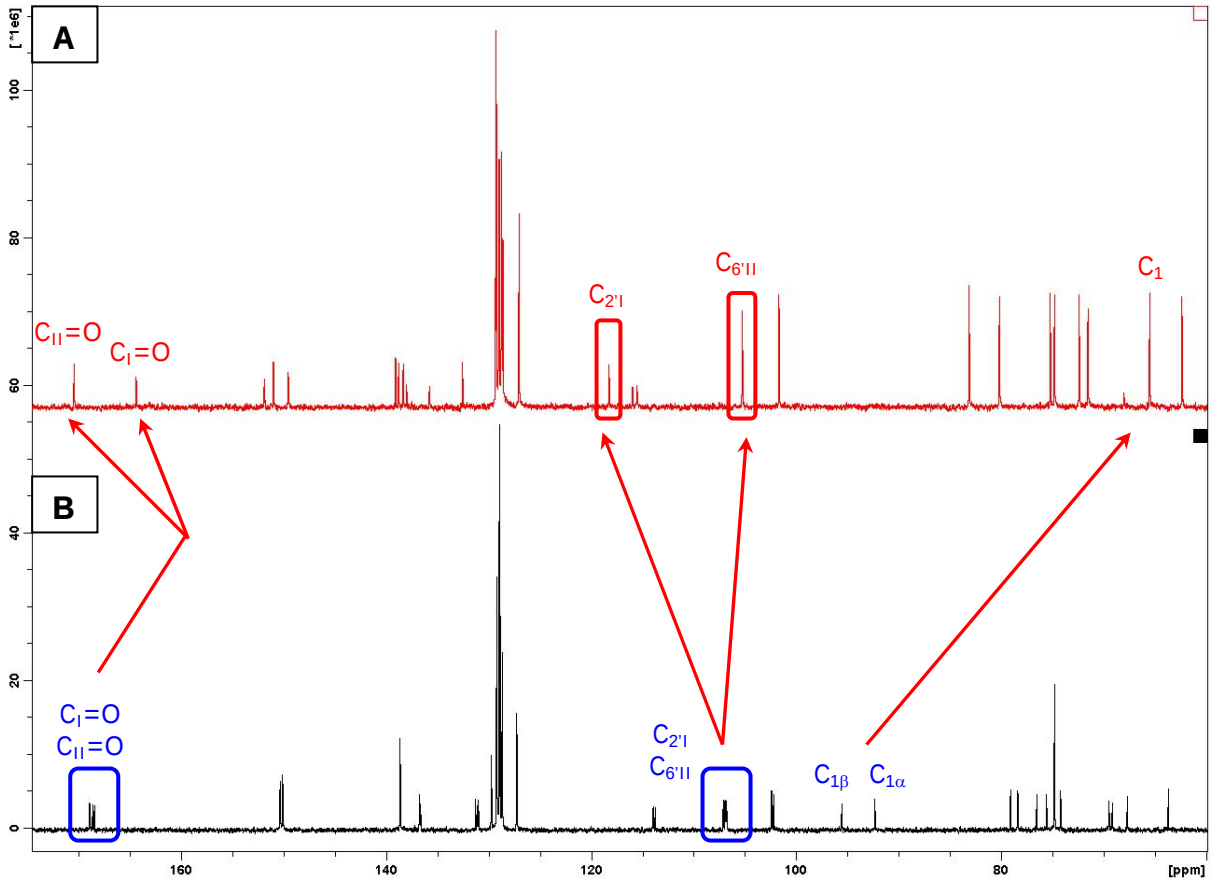
*A : ^{1}H-NMR (acetone-d_6) compound **175** major product of C-arylglucosidation*
*B : ^{1}H-NMR (acetone-d_6) compound (S)-**159** (mixture of anomers α:β = 1:1) starting material of C-arylglucosidation*

Figure 39. ^{1}H-NMR spectra of the major epimer compared with the starting compound

The reaction product showed coupling constants $^{3}J_{H1\text{-}H2}$ of 2.1 Hz identical to **175 β** and close to vescalin **27** ($^{3}J_{H1\text{-}H2}$ = 1.5 Hz). It was so possible to confirm the β configuration of the C_1 carbon.

The ^{13}C-NMR spectra (Figure 40) presented the same features than the compound **175 β** :

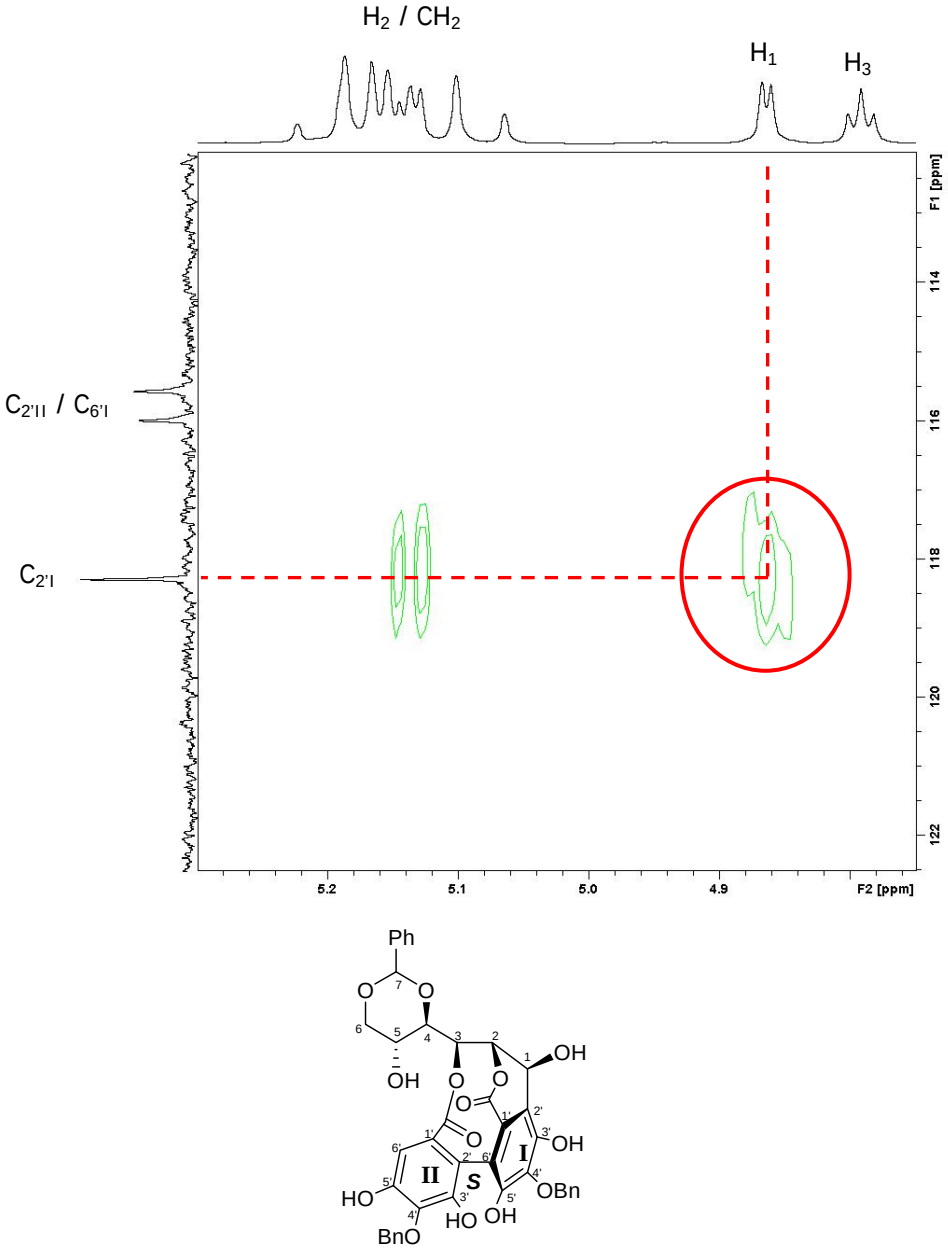
- C_1 upfielded to 65.5 ppm (*vs* 92.4/95.6 ppm for the starting material);
- two HHDP carbons one quaternary $C_{2'I}$ and tertiary the other $C_{6'II}$ at 118.8 and 105.8 ppm, clear sign of the *C*-arylglucosidic bond formation;
- carbonylic carbons C_I=O and C_{II}=O at 164.4 and 170.4 ppm respectively.



*A : ^{1}H-NMR (acetone-d_6) compound **176** major product of C-arylglucosidation*
*B : ^{1}H-NMR (acetone-d_6) compound (S)-**159** (mixture of anomers α:β = 1:1) starting material of C-arylglucosidation*

Figure 40. ^{13}C-NMR spectra of the major epimer compared and the starting compound

A correlation HMBC (Figure 41) among H-1 and H-2 and the quaternary carbon $C_{2'I}$ involved in the new C-C bond gave further confirmation of the structure.



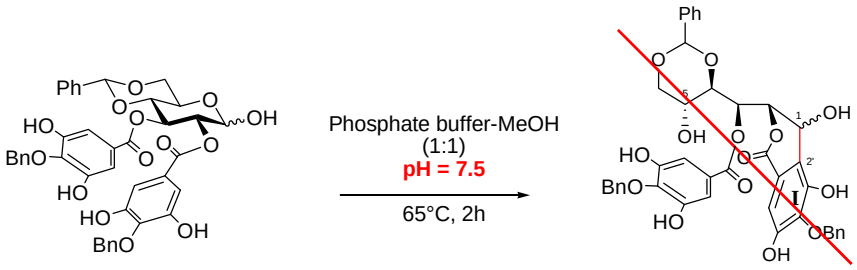
176β *(25%)*

Figure 41. HMBC detail, experiment on compound 176β

The minor compound obtained resulted difficult to purify by HPLC and it was obtained in very little amounts.

3.9.2 *C*-arylglucosidation on the architecture D

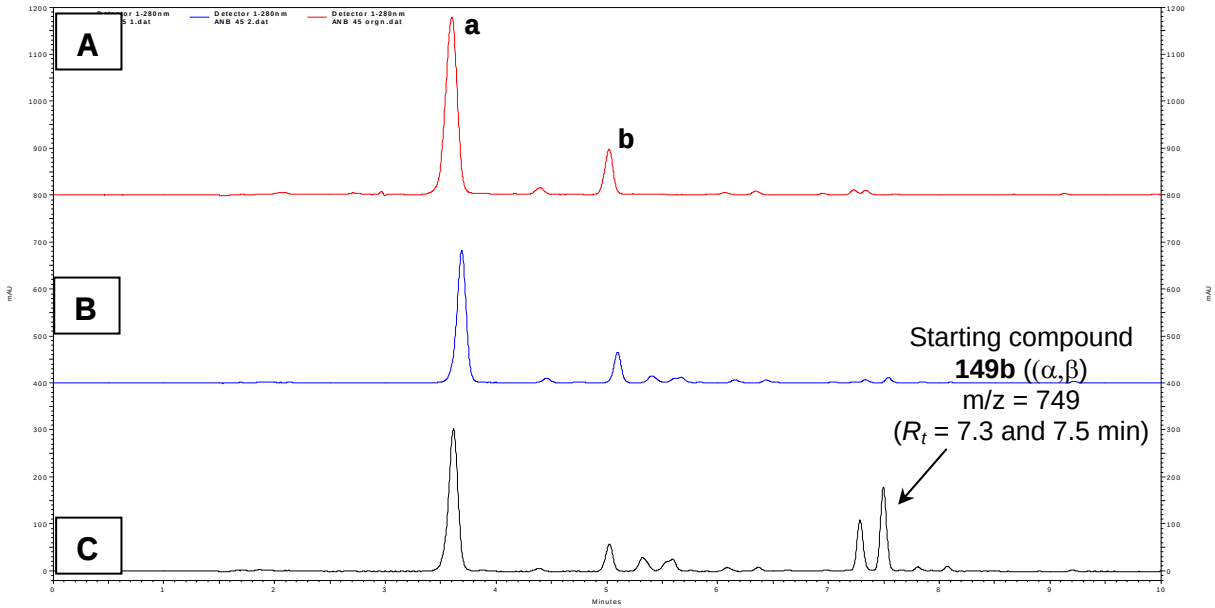
On the basis of the satisfactory results obtained on the compound **B** the same conditions were carried out on the intermediates with two galloyl units not coupled *para*-benzylated compound **149b** (route II retrosynthesis).



149b **178**

Scheme 65. *C*-arylglucosidation in phosphate buffer at pH = 5.3 on compound 149b

After only 2h30 the starting compound was completely consumed to give two major products (**a** and **b** Figure 42) corresponding to the galloyl units **77** (acid) and **132** (methyl ester).



A : HPLC-UV Profile (280 nm) reaction mixture after 1h
B : HPLC-UV Profile (280 nm) reaction mixture after 2h30
C : HPLC-UV Profile (280 nm) of the organic phase after acidification and extraction
Analysis conditions : Column : Pursuit 3 C18 (150 x 4,6 mm), Eluent : A : H_2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Method : gradient from 40 to 100% of B in 10 min, Flow : 1mL/min, Detector UV (280nm).

Figure 42. HPLC profile *C*-arylglucosidation at pH = 5.3 and work-up on compound 149b

Again it was possible to confirm that the presence of the HHDP unit is essential for the C-arylglucosidic bond formation in agreement with the proposed biosynthesic pathway.

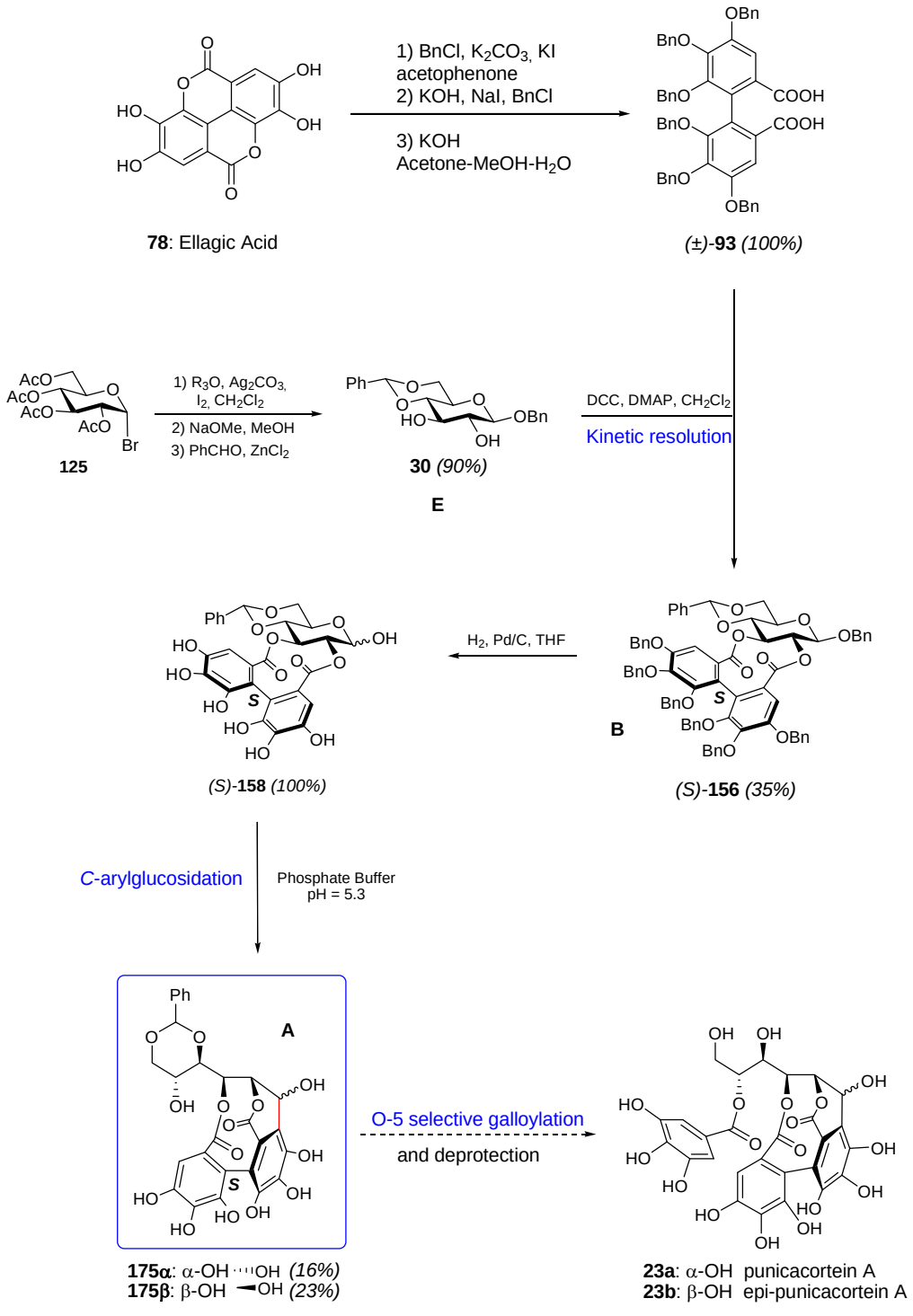
Chapter 4
Conclusion and perspectives

4.1 Conclusion and perspectives

C-arylglucosidic ellagitannins represent a unique sub-class of hydrolyzable tannins. Polyphenols such these have attracted considerable interest in the past fifteen years because of possible benefits in human health care and prevention of diseases such as carcinogenesis and arteriosclerosis.[4,29,31] However, this class of natural product, with such unique structural architectures and potent biological activities, has not yet been fully explored for therapeutic potential. From here our interest in developing a synthetic strategy for generation of these compounds and their analogues with enhanced pharmacological properties.

Our synthetic efforts were so focused on the synthesis of punicacortein A (**23a**) and its C-1 epimer, epi-punicacortein A (**23b**) as simple structures of this class of natural compounds. The key step towards these molecular structures is the *C*-arylglucosidation reaction. In order to get this first objective several precursors sugar bearing HHDP unit (**B**) or two galloyl units (**C**) were synthesized as described in the second chapter of this manuscript.
The compounds so obtained were employed in the following *C*-arylglucosidation step described in the third chapter. The opening of the sugar followed by the intramolecular aldol-type nucleophilic addition to the aldehyde function are the two steps towards the *C*-glucosidic bond formation. After several attempts, the reaction was finally achieved in phosphate buffer.
According to our guest and to the biosynthetic pathway the key *C*-arylglucosidic bond was achieved only in the case of the conformationally-constrained HHDP-bearing intermediate.
Moreover it was showed that the presence of a cyclic protecting group at the O-4 and O-6 positions of the sugar core is of paramount importance for the formation of the *C*-arylglucosidic bond formation. It may induce a structural strain essential to the cyclization.
Selective galloylation at the 5 position of the open-chain glucose on synthons **A** will give the punicacortein A (**23a**).

In the end of this work we managed to obtain a route to access the *C*-arylglucosidic ellagitannins. This general strategy is showed in Scheme 66.

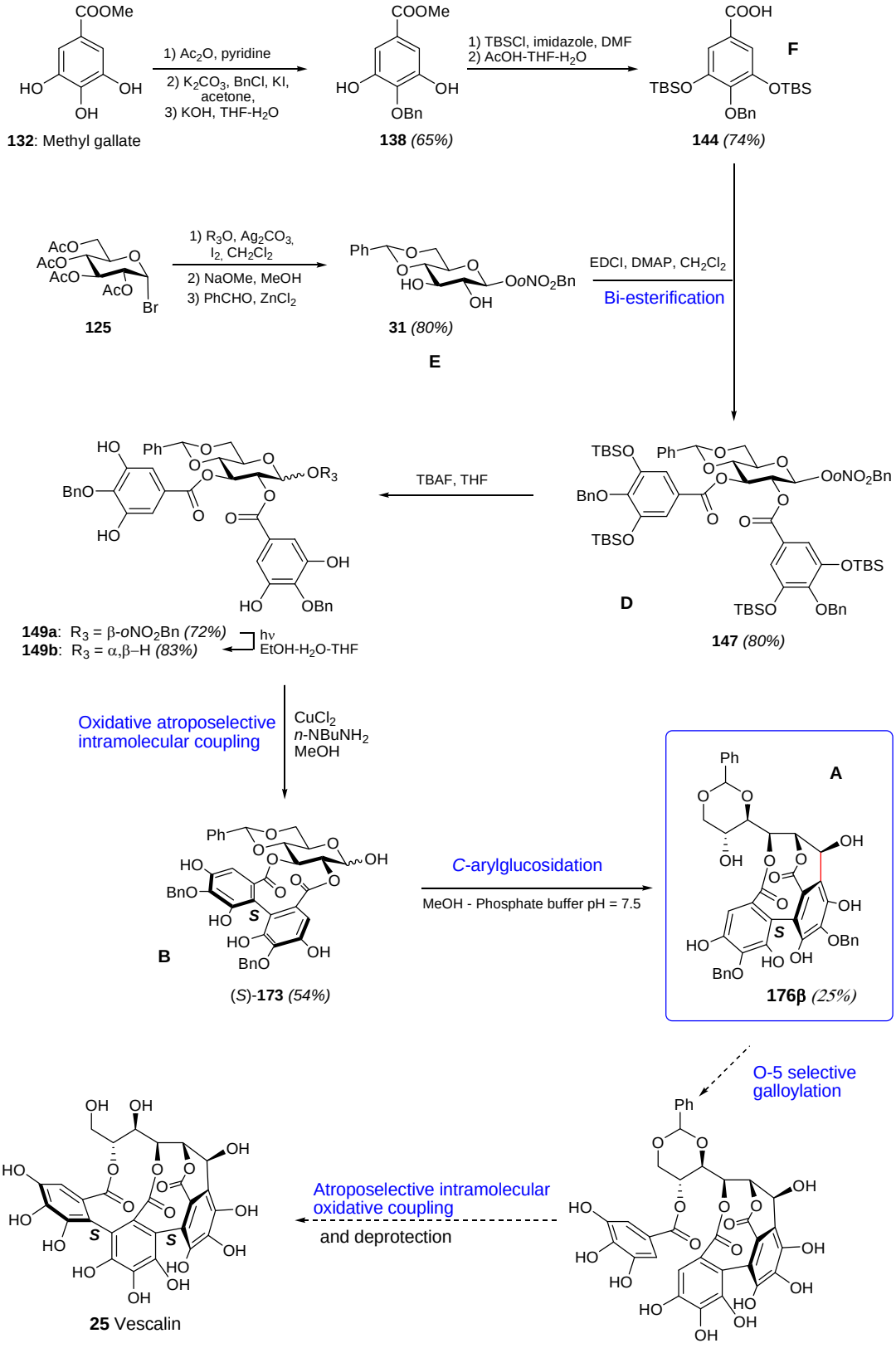


Scheme 66. Synthetic approach to punicacortein A 23

In the meantime an intramolecular atroposelective methodology for the construction of the hexahydroxyterphenolyl unit (HHDP) was developed in the laboratory by G. Malik, another PhD student in the Quideau's research group.
As discussed in the section **2.4**, the developed methodology resulted not reproducible and neither applicable to our substrates. However an alternate route, inspired to the Yamada's total synthesis of corilagin (**55**), was adapted to the synthesis of architectures **B** and we are confident it could be successfully applied to the NHTP construction. This strategy required the preparation of a precursor featuring a *para*-protected galloyl units.

Our methodology for the *C*-arylglucosidic bond formation into biomimetic conditions resulted applicable even on differently protected substrates. So a biomimetic route to *C*-glucosidic ellagitannins have been developed as showed in Scheme 67.

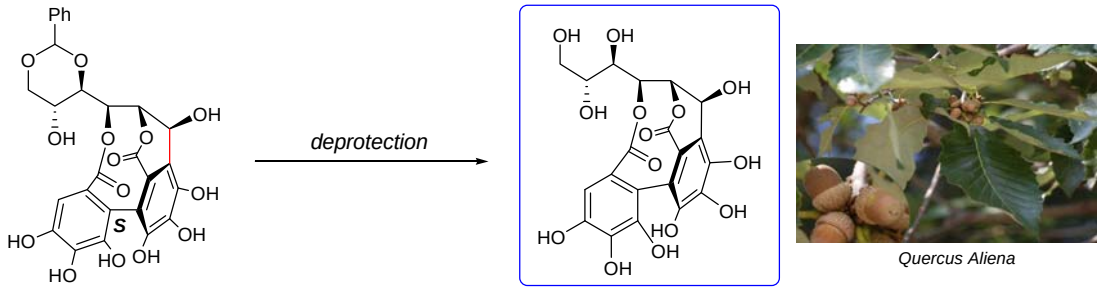
The introduction of a conveniently protected galloyl unit on the intermediates **A** gives access to the a product that could be further submitted to an oxidative coupling in the Yamada's conditions to give, after deprotection, the NHTP-bearing *C*-arylglucosidic ellagitannin vescalin (**25**) (Scheme 67).



Scheme 67. Synthetic approach to vescalin 25

First galloylation attempts on compound **175** resulted unsatisfactory. Studies are still on going to address this point.

At this point of the synthesis it was possible to obtain a first member of the *C*-arylglucosidic ellagitannin family.
The benzylidene cleavage of compound **175** delivered the degalloyl epi-punicacortein A **179** (Scheme 68).



175β

179
degalloyl epi-punicacortein A

Scheme 68. Degalloyl epi-punicacortein A

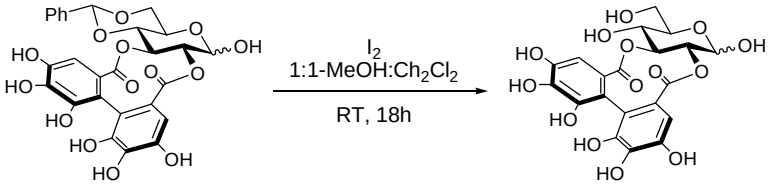
This molecule has not yet isolated form a natural source, but it is reasonable to suppose that its structure corresponds to a natural compound. The hydrolysis of esters is the most frequent modification incurred by ellagitannins [42,44] so *O*-5-degalloyl epipunicacortein A could derive from epipunicacortein A (**23b**)[44] as *O*-5-degalloyl punicacortein A (**24**) derives from hydrolysis of its precursor punicacortein A (**23a**).

4.2 Benzylidene cleavage and synthesis of O-5-degalloyl epipunicacortein A

A benzylidene acetal is a commonly used protective group for 1,2- and 1,3-diols. It presents the advantage that it can be removed under neutral conditions by hydrogenolysis or by acid hydrolysis.[157] The well documented difficulties associated with purification of the perhydroxylated natural products[37] oriented our choice towards cleavage conditions not demanding further purification.

In this vein deprotection conditions as microwaves-promoted hydrolysis in pure water[158] or Lewis acid catalyzed[159-162] were tested on compound **174**, as model compound. These methodologies resulted not applicable owing to the numerous collateral processes, specially hydrolysis of esters functions.

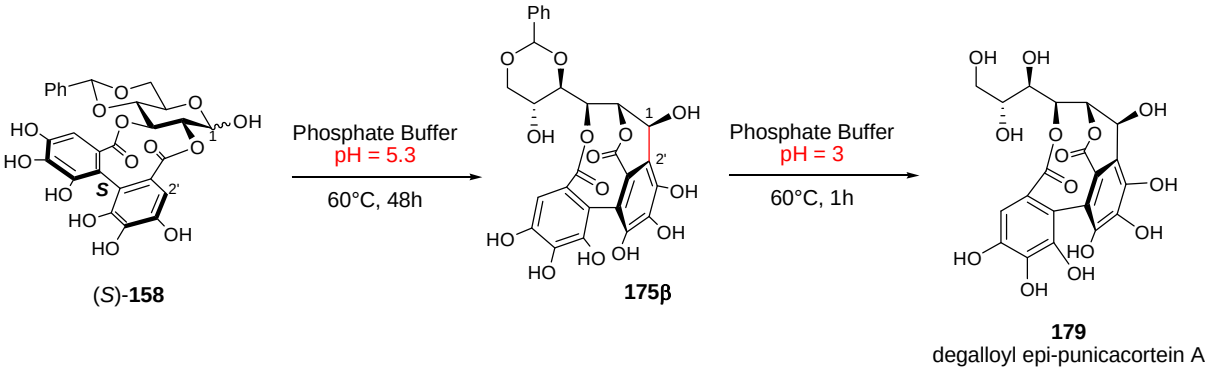
In another series of experiments the same conditions reported by Feldman in his ellagitannins total synthesis were exploited. The I_2-promoted methanolysis (Scheme 69. I_2-promoted benzylidene methanolysis) (employed by Feldman in the total synthesis of pedunculagin)[74] led to the deprotected product **161** in 15% yields after preparative HPLC purification.



(*S*)-**158** (*S*)-**161** *(15%)*

Scheme 69. I_2-promoted benzylidene methanolysis

In order to reduce the purification steps it was tried to carry out the benzylidene cleavage "one-pot" after the *C*-arylglucosidation, through acidification of the reaction mixture (Scheme 70).



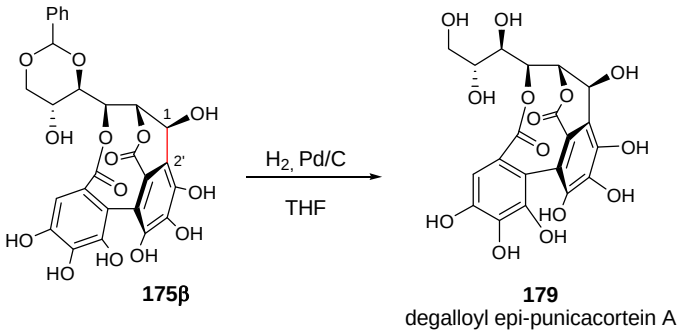
(*S*)-**158** **175β** **179**
degalloyl epi-punicacortein A

Scheme 70. "One-pot" *C*-arylglucosidation and benzylidene cleavage

Also in this conditions the product of deprotection was obtained in poor yields with significant impurities, requiring cumbersome chromatographic purification steps.

In the light of these results the best deprotection method seemed to be the palladium-catalyzed hydrogenolysis that could be carried out in neutral conditions, allowing to avoid hydrolysis collateral processes.

Cleavage by catalytic hydrogenation can be performed with good selectivity under mild conditions using heterogeneous Palladium on Carbon (Pd/C) catalyst in the presence of hydrogen gas or a hydrogen transfer agent, e.g. ammonium formate or isopropanol. Efficient removal depends on selection of the most active and selective catalyst, and an optimized set of reaction conditions (see Annex 2). This method presents the advantage to deliver the product pure after simple filtration of the catalyst.
At first the reaction was carried out in tetrahydrofuran with Pd/C as catalyst (Scheme 71), the same conditions that led to the formation of **161**.

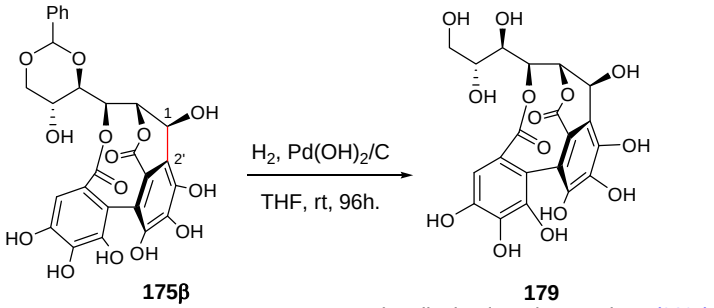


175β **179**
degalloyl epi-punicacortein A

Scheme 71. Pd/C catalyzed hydrogenolysis of 175β

The reaction was followed by HPLC and seven days were needed in order to get a complete consumption of the starting material. The formation of the deprotection product was accompanied by the formation of several products of degradation, and that it resulted impossible in the end to purify the reaction product.

In a final set of experiments compound **175β** was efficiently debenzylated by treatment with $Pd(OH)_2/C$ in tetrahydrofuran under an argon atmosphere (Scheme 72).
The formation of a stable complex between the compound **175** and Pd catalyst implied that at least a stoichiometric amount of catalyst was required.
Pure **179** was completely characterized by NMR (see annex 3).



175β **179**
degalloyl epi-punicacortein A *(93%)*

Scheme 72. Degalloyl epi-punicacortein A synthesis

In conclusion, the first total synthesis of a *C*-arylglucosidic ellagitannin, the 5-O degalloyl epipunicacortein A **179** was accomplished (Scheme 66).

This allows access to diverse *C*-arylglucosidic ellagitannins scaffolds and derivatives.

Attempts at synthesizing NHTP bearing *C*-arylglucosidic ellagitannins were retarded by difficulties encountered with the selective esterification on **A** precursors as the necessary intermediate. The search for alternate approaches was postponed to studies currently under development

Chapter 5

Experimental Section

5.1 General Methods

Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated.

All moisture and oxygen sensitive reactions were carried out in flame-dried glassware under inert atmosphere with dry solvents. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purified immediately before use by filtration through activated alumina columns under nitrogen. Methanol (MeOH) was distilled from Mg under nitrogen prior to use. Benzaldehyde was purified by fractioned distillation with toluene in order to remove its oxidation products. Benzyl chloride was dinstilled under nitroger prior to use. Acetone, ethanol (EtOH), ethyl acetate (EtOAc), petroleum ether (PET), cyclohexane and diethyl ether (Et_2O) were used as received.

The molecular sieves were activated through in oven at 110°C. The zinc chloride ($ZnCl_2$) was flammed under vacuum prior to use. The DMAP-HCl was prepared from DMAP and HCl in THF. *o*-chloranil was purified by christallization in benzene. Evaporations were conducted under reduced pressure at temperatures less than 45 °C.

The phosphate buffers (0.2 M) were prepared prior to use (6 g of KH_2PO_4 in 240 mL of water). The pH (measured by a pHmeter) was adjusted by addition of aqueous solutions of HCl or NaOH.

The photochemical reaction were realized with an UV Fischer Scientific Bioblock at 365 nm (6W) lamp on a maximum amount of starting compound of 300 mg.

Room temperature is at around 20 and 25°C. The reaction at low temperatures were carried out in glaced (0°C) or ethanol/liquid nitrogen (0°C to -78°C) bath. A cryostat Julabo FT 901 was employed for long reaction at temperature lower than 0°C.

Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60 F_{254}), using UV light as the visualizing agent and a potassium permanganate solution and heat as the developing agent. A ferric chloride solution in HCl (0.5M) was used to reveal catechol functions. In the case of polar compounds, reactions were monitored by reverse phase (RP) thin layer chromatography (TLC) carried out on E. Merck aluminium sheets (RP-18 F_{254s}), using UV light as the visualizing agent, or by HPLC on a reverse phase column (Pursuit C18, Varian), using MeCN/H_2O/0.1% HCOOH as the mobile phase (UV detection at 280 nm). Column chromatography was carried out under positive pressure using 40-63 μm silica gel (Merck) and the indicated solvents. Preparatory

HPLC was performed on a Varian semi-preparative LC system using a Varian Microsorb 100-8 C18 (41.4 x 250 mm) column.

Melting points were recorded in open capillary tubes on a Buchi B-540 apparatus and are uncorrected.

Optical rotations were determined on a Krüss P3001 digital polarimeter at 589 nm, and are given as $[\alpha]_t$°CD (concentration in g/100 mL solvent).

IR spectra were recorded on a Bruker IFS55 FT-IR spectrometer.

NMR spectra of samples in the indicated solvent were recorded on Bruker Avance 300 or 400 spectrometer and were calibrated using residual undeuterated solvent as an internal reference.

- chloroform-d_1 : 7.26 ppm for ^{1}H-NMR, 77.0 ppm for ^{13}C-NMR
- acetone-d_6 : 2.05 ppm for ^{1}H-NMR, 29.84 ppm for ^{13}C-NMR
- DMSO-d_6 : 2.50 ppm for ^{1}H-NMR, 39.52 ppm for ^{13}C-NMR
- methanol-d_4 : 3.31 ppm for ^{1}H-NMR, 49.00 ppm for ^{13}C-NMR

The coupling constants (J) are expressed in Hz. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, AB = AB quartet, br = broad singulet, H_{Ar} = aromatic proton, CH_{Ar} = tertiary aromatic carbon, Cq = quaternary carbon. Carbon multiplicities were determined by DEPT135 experiment. Diagnostic correlations were obtained by two-dimensional COSY, HSQC and HMBC experiments.

Mass Spectromety Chemical ionization (CIMS) and electrospray (ESIMS) low and/or high resolution (HRMS) mass spectrometric analyses were obtained from the mass spectrometry laboratory at the Institut Européen de Chimie et Biologie (IECB), France.

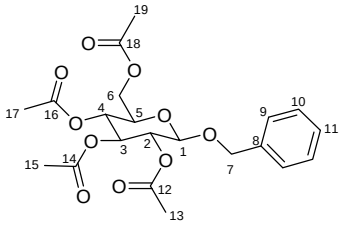
Elemental analyses were carried out at the Service Central d'Analyses du CNRS, Vernaison, France.

5.2 Synthesis and characterization of products

Sugar precursors (E)

126a

Benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside



$C_{21}H_{26}O_{10}$

MW = 438,43 Da

CAS : [10343-13-2]

According to the procedure described in the literature,[131] Ag_2CO_3 (2.01 g, 7.29 mmol, 3 eq) and a crystal of iodine were added to a solution of commercially available benzyl alcohol (1.31 g, 12.15 mmol, 5 eq) in dry CH_2Cl_2 (15 mL) and the mixture was stirred over 4 Å molecular sieves for 15 minutes. A solution of commercially available 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**125**, 1 g, 2.43 mmol, 1 eq) in dry CH_2Cl_2 (5 mL) (also stirred over 4 Å molecular sieves for 15 minutes) was then added dropwise. The reaction flask was shielded from light and stirred at room temperature under nitrogen for 20 hours. The reaction mixture was diluted with EtOAc, filtered through Celite®, and concentrated *in vacuo*. Crude was purified by column chromatography (4:1 cyclohexane:EtOAc) to give **126a** as a white solid (976 mg, 92%).

m.p. 93-94°C [lit.[163] m.p. 93-93.3°C (EtOH)]; $\boldsymbol{R_f}$ = 0.05 (4:1 cyclohexane:EtOAc)

$[\alpha]^{21}_D$ = -52.0° (c = 1, $CHCl_3$) [lit.[163] $[\alpha]^{25}_D$ = -51.0° (c = 1, $CHCl_3$)]

IR (NaCl) ν_{max} 1752, 1369, 1221 cm^{-1}

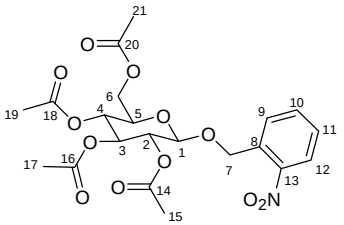
^{1}H NMR (300 MHz, chloroform-d_1) δ 1.98-2.09 (m, 12H, $H_{13}/H_{15}/H_{17}/H_{19}$), 3.63-3.69 (m, 1H, H_5), 4.15 (dd, J = 2.4, 12.2 Hz, 1H, H_6), 4.26 (dd, J = 4.7, 12.3 Hz, 1H, H_6), 4.54 (d, J = 7.8 Hz, 1H, H_1), 4.61 and 4.88 (AB, J_{AB} = 12.3 Hz, 2H, H_7), 5.02-5.19 (m, 3H, $H_2/H_4/H_3$), 7.25-7.36 (m, 5H, $H_9/H_{10}/H_{11}$)

^{13}C NMR (75 MHz, chloroform-d_1) δ 170.4/170.0/169.2/169.0 ($C_{12}/C_{14}/C_{16}/C_{18}$), 136.6 ($C_8$), 128.3/127.8/127.6 ($C_9/C_{10}/C_{11}$), 99.2 ($C_1$), 72.7 ($C_3$), 71.7 ($C_5$), 71.2 ($C_7$), 70.6 ($C_2$), 68.4 ($C_4$), 61.8 ($C_6$), 20.5/20.4/20.4 ($C_{13}/C_{15}/C_{17}/C_{19}$)

CIMS *m/z* (%) 457 $[M+NH_4]^+$ (100), 331 (54)

126b

2-Nitrobenzyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside



$C_{21}H_{25}NO_{12}$

MW = 483,42 Da

CAS : [34546-55-9]

According to the procedure described in the literature,[131] to a solution of commercially available 2-nitrobenzyl alcohol (3.72 g, 24.32 mmol, 5 eq) in dry CH_2Cl_2 (20 mL) were added Ag_2CO_3 (4.02 g, 14.58 mmol, 3 eq), and one crystal of iodine. The reaction was stirred over 4 Å molecular sieves for 15 minutes. A solution of commercially available 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**166**, 2 g, 4.86 mmol, 1 eq) in dry CH_2Cl_2 (10 mL) (also stirred over 4 Å molecular sieves for 15 minutes) was then added dropwise. The reaction flask was shielded from light and stirred at room temperature under nitrogen for 6 hours. The reaction mixture was diluted with EtOAc, filtered through Celite, and concentrated *in vacuo*. Crude material was purified by column chromatography (8:2 cyclohexane:EtOAc) to afford **126b** as white crystals (2.27 g, 100 %).

m.p. 67-68°C

R_f = 0.20 (7:3 cyclohexane:EtOAc)

$[\alpha]^{24}_D$ = -1.96° (c = 0.51, acetone)

IR (NaCl) ν_{max} 2962, 1740, 1530, 1369, 1227, 1042 cm^{-1}

^{1}H NMR (300 MHz, chloroform-d_1) δ 2.02 (s, 3H, CH_3 from Ac groups), 2.03 (s, 3H, CH_3 from Ac groups), 2.06 (s, 3H, CH_3 from Ac groups), 2.08 (s, 3H, CH_3 from Ac groups), 3.73-3.78 (m, 1H, H_5), 4.15 (dd, J = 2.2, 12.3 Hz, 1H, H_6), 4.30 (dd, J = 4.8, 12.4 Hz, 1H, H_6), 4.68 (d, J = 7.9 Hz, 1H, H_1), 5.06 and 5.26 (AB, J_{AB} = 14.5 Hz, 2H, H_7), 5.10-5.25 (m, 3H, $H_2/H_3/H_4$), 7.46 (t, J = 7.6 Hz, 1H, H_{11}), 7.63 (d, J = 7.6 Hz, 1H, H_9), 7.70 (t, J = 7.7 Hz, 1H, H_{10}), 8.08 (d, J = 8.1 Hz, 1H, H_{12})

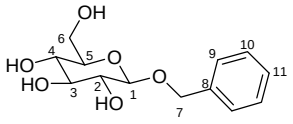
^{13}C NMR (75 MHz, chloroform-d_1) δ 170.6/170.1/169.4 ($C_{14}/C_{16}/C_{18}/C_{20}$), 147.1 ($C_{13}$), 133.8 ($C_9$), 133.4 ($C_8$), 128.9 ($C_{10}$), 128.4 ($C_{11}$), 124.7 ($C_{12}$), 100.5 ($C_1$), 72.0 ($C_5$), 72.7/71.3/68.4 ($C_2/C_3/C_4$), 68.1 ($C_7$), 61.8 ($C_6$), 20.6/20.6/20.5 ($C_{15}/C_{17}/C_{19}/C_{21}$)

CIMS *m/z* (%) 501 $[M+NH_4]^+$ (100), 455 (61), 366 (34), 331 (33), 106 (76)

Anal. calcd for $C_{21}H_{25}NO_{12}$: C, 52.18; H, 5.21; N, 2.90. Found : C, 52.22; H, 5.24; N, 2.80

33

Benzyl-β-D-glucopyranoside



$C_{13}H_{18}O_6$

MW = 270,28 Da

CAS : [4304-12-5]

According to the procedure described in the literature,[163] a catalytic amount of sodium methoxide was added to a solution of **126a** (2.87 g, 6.55 mmol) in dry MeOH (40 mL). TLC analysis indicated after 3 hours complete conversion of starting material. The solution was then neutralized with Dowex® 50X8-400 ion-exchange resin (H^+ form), filtered, and concentrated *in vacuo* to leave **33** in pure form as white crystals (1.77 g, 100%).

m.p. 104°C [lit.[163] m.p. 105-106°C ($CHCl_3$-PET)]

R_f = 0.34 (5% acetone in EtOAc)

$[\alpha]^{21}_D$ = -56.3° (c = 0.9, MeOH) [lit.[163] $[\alpha]^{25}_D$ = -49.9° (c = 1, MeOH)]

IR (KBr) ν_{max} 3502 (st), 3062, 2931, 2883, 1497, 1455, 1370, 1280, 1157, 1083, 1048, 990 cm^{-1}

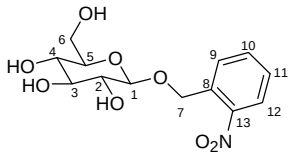
^{1}H NMR (300 MHz, methanol-d_4) δ 3.20-3.33 (m, 4H, $H_2/H_3/H_4/H_5$), 3.66 (dd, J = 5.2, 11.8 Hz, 1H, H_6), 3.86 (d, J = 11.7 Hz, 1H, H_6), 4.32 (d, J = 7.5 Hz, 1H, H_1), 4.63 and 4.89 (AB, J_{AB} = 11.8 Hz, 2H, H_7), 7.20-7.39 (m, 5H, $H_9/H_{10}/H_{11}$)

^{13}C NMR (75 MHz, methanol-d_4) δ 139.0 (C_8), 129.2/129.2/128.6 ($C_9/C_{10}/C_{11}$), 103.2 (C_1), 78.0/77.9/75.1/71.7 ($C_2/C_3/C_4/C_5$), 71.6 (C_7), 62.8 (C_6)

CIMS *m/z* (%) 288 $[M+NH_4]^+$ (100), 270 $[M+H]^+$ (82), 180 (89), 108 (68), 91 (27)

34

2-Nitrobenzyl-β-D-glucopyranoside



$C_{13}H_{17}NO_8$

MW = 315,28 Da

CAS : [34546-53-7]

According to the procedure described in the literature,[163] a catalytic amount of sodium methoxide was added to a stirred solution of **126b** (4.60 g, 3.36 mmol) in dry MeOH (20 mL). TLC analysis indicated after 30 minutes complete conversion of starting material. The solution was then neutralized with Dowex® 50X8-400 ion-exchange resin (H^+ form), filtered, and concentrated *in vacuo*. Crude material was purified by column chromatography (5% acetone in EtOAc) to yield **34** as white crystals (3.10 g, 100%).

m.p. 125°C [lit.[130] m.p. 131°C (H_2O)]

R_f = 0.15 (5% acetone in EtOAc)

$[\alpha]^{21}_D$ = -36.4° (c = 0.55, pyridine) [lit.[130] $[\alpha]^{25}_D$ = -4.39° (c = 0.55, pyridine)]

IR (KBr) ν_{max} 3302 (st), 1522, 1336, 1077, 1037, 737 cm^{-1}

^{1}H NMR (300 MHz, methanol-d_4) δ 3.29-3.40 (m, 4H, $H_2/H_3/H_4/H_5$), 3.66 (dd, J = 4.9, 11.9 Hz, 1H, H_6), 3.85 (d, J = 11.1 Hz, 1H, H_6), 4.41 (d, J = 7.6 Hz, 1H, H_1), 5.05 and 5.25 (AB, J_{AB} = 15.3 Hz, 2H, H_7), 7.47 (t, J = 7.7 Hz, 1H, H_{10}), 7.68 (t, J = 7.2 Hz, 1H, H_{11}), 7.99 (d, J = 7.7 Hz, 1H, H_{12}), 8.03 (d, J = 8.1 Hz, 1H, H_9)

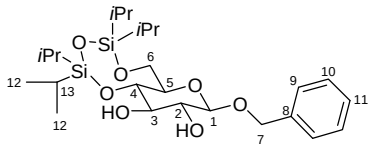
^{13}C NMR (75 MHz, methanol-d_4) δ 148.7 (C_{13}), 135.7 (C_8), 134.7 (C_{11}), 130.3 (C_{12}), 129.2 (C_{10}), 125.5 (C_9), 104.0 (C_1), 78.0/75.1/71.5 ($C_2/C_3/C_4/C_5$), 68.4 (C_7), 62.6 (C_6)

CIMS *m/z* (%) 333 $[M+NH_4]^+$ (100), 180 (49), 122 (47), 120 (73), 88 (41)

Anal. calcd for $C_{13}H_{17}NO_8$: C, 49.53; H, 5.44; N, 4.44. Found : C, 49.32; H, 5.64; N, 4.00

127

Benzyl-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-glucopyranoside



$C_{25}H_{44}O_7Si_2$

MW = 512,78 Da

CAS : [89291-61-2]

According to the procedure described in the literature,[132] dichlorotetraisopropyldisiloxane (2.84 mL, 8.88 mmol, 1.2 eq) was added dropwise to a solution of **33** (2 g, 7.40 mmol, 1 eq) and imidazole (2.51 g, 37.0 mmol, 5 eq) in dry DMF (150 mL). After 5 hours, excess of silylating agent was decomposed by the addition of 10 mL of MeOH, which was followed by the addition of 100 mL of EtOAc. The solution was poured into 150 mL of brine and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Crude was purified by column chromatography (9:1 → 8:2 cyclohexane:EtOAc) to give **127** as a yellow oil (2.33 g, 61%).

***R*$_f$** = 0.48 (7:3 cyclohexane:EtOAc)

[α]$^{21}_D$ = -74.5° (c = 0.9, $CHCl_3$) [lit.[163] $[\alpha]^{25}_D$ = -72.3° (c = 1, $CHCl_3$)]

IR (NaCl) ν_{max} 3429, 1252, 1036 cm^{-1}

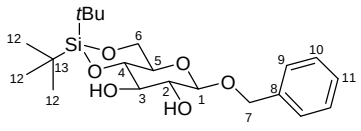
^{1}H NMR (300 MHz, chloroform-d_1) δ 1.02-1.11 (m, 28H, H_{12}/H_{13}), 3.19 (d, J = 9.3 Hz, 1H, H_5), 3.42 (t, J = 8.4 Hz, 1H, H_2), 3.57 (t, J = 9.0 Hz, 1H, H_3), 3.85 (t, J = 9.1 Hz, 1H, H_4), 4.01 and 4.12 (AB, J_{AB} = 12.5 Hz, 2H, H_6), 4.35 (d, J = 7.8 Hz, 1H, H_1), 4.59 and 4.98 (AB, J_{AB} = 11.7 Hz, 2H, H_7), 7.28-7.36 (m, 5H, $H_9/H_{10}/H_{11}$)

^{13}C NMR (75 MHz, chloroform-d_1) δ 137.1 (C_8), 128.4/128.1/127.8 ($C_9/C_{10}/C_{11}$), 101.8 (C_1), 76.7 (C_5), 76.1 (C_3), 73.9 (C_2), 70.8 (C_7), 69.2 (C_4), 60.9 (C_6), 17.3/17.3/17.2/17.2/17.2/17.0 (C_{12}), 13.6/13.2/12.5/12.5 (C_{13})

CIMS *m/z* (%) 531 $[M+NH_4]^+$ (100), 423 (30), 405 (35), 108 (36), 91 (42)

128

Benzyl-4,6-*O*-*t*-butylsilylanediyl-β-D-glucopyranoside



$C_{21}H_{34}O_6Si$

MW = 410,58 Da

No CAS

According to the procedure described in the literature,[133] **33** (1.35 g, 4.99 mmol, 1 eq) was azeotropically dried with benzene (3 x 5 mL) and taken up in DMF (8 mL). The mixture was cooled to –40°C and stirred for 30 minutes. Addition of di-*tert*-butylsilyl ditriflate (1.82 ml, 4.99 mmol, 1 eq) over 5 minutes afforded a clear solution that was further stirred at –40°C for 1 hour. Upon warming to room temperature, the reaction mixture was diluted with 100 mL of diethyl ether and washed with saturated aqueous solution of $NaHCO_3$ (30 mL), H_2O (30 mL) and brine (30 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide a very hygroscopic white solid. Crude was purified by column chromatography (75:25 cyclohexane:EtOAc) to give **128** as a very hygroscopic white foam (1,73 g, 84%).

$\boldsymbol{R_f}$ = 0.44 (7:3 cyclohexane:EtOAc)

$\boldsymbol{[\alpha]_D^{24}}$ = +7.0° (*c* = 0.1, CH_2Cl_2)

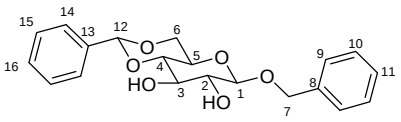
^{1}H NMR (300 MHz, chloroform-d_1) δ 1.00 (s, 9H, H_{12}), 1.06 (s, 9H, H_{12}), 2.46 (brs, 1H, OH), 2.72 (brs, 1H, OH), 3.38-3.61 (m, 3H, H_2/H_3/H_5), 3.74 (t, J= 8.9 Hz, 1H, H_4), 3.95 (t, J= 10.2 Hz, 1H, H_6), 4.20 (dd, J= 5.1 Hz, J = 10.2 Hz, 1H, H_6), 4.47 (d, J= 7.2 Hz, 1H, H_1), 4.62 and 4.91 (AB, J_{AB} = 11.7 Hz, 1H, H_7), 7.31-7.37 (m, 5H, H_9/H_{10}/H_{11})

^{13}C NMR (75 MHz, chloroform-d_1) δ 136.8 (C_8), 128.5/128.1/128.0 (C_9/C_{10}/C_{11}), 102.0 (C_1), 76.7 (C_4), 76.3 (C_3), 73.6 (C_2), 71.3 (C_7), 70.5 (C_5), 66.1 (C_6), 27.4/27.0 (C_{12}), 22.6/19.9 (C_{13})

CIMS *m/z* (%) 411 $[M+H]^+$ (100)

30

Benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside



$C_{20}H_{22}O_6$

MW = 358,39 Da

CAS : [113973-86-7]

According to the procedure described in the literature,[73] zinc chloride (13.8 g, 0.10 mol, 5.3 eq) was added under nitrogen to a suspension of **33** (5.13 g, 19 mmol, 1 eq) in 50 mL of benzaldehyde and the mixture was allowed to stir at room temperature for 16 hours. The reaction solution was then diluted with ice, and the crude product was extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The liquid residue (containing an excess of benzaldehyde) was purified by column chromatography (10:0 → 9:1 CH_2Cl_2:acetone) to give **30** as a white solid (6.1 g, 90%).

m.p. 158.5°C

R_f = 0.10 (3:2 cyclohexane:EtOAc)

$[\alpha]_D^{24}$ = -61.0° (*c* = 1.2, $CHCl_3$)

IR (neat) ν_{max} 3434, 3063, 3031, 2917, 2874, 1455, 1380, 1094, 1027, 1002 cm^{-1}

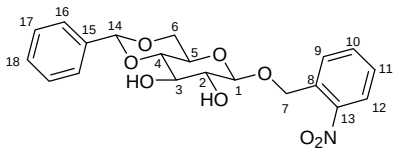
^{1}H NMR (300 MHz, chloroform-d_1) δ 2.65 (brs, OH), 3.46 (dt, J = 4.8 Hz, J = 9.5 Hz, 1H, H_2), 3.53-3.60 (m, 2H, H_4/H_5), 3.78-3.85 (m, 2H, H_3/H_6), 4.37 (dd, J = 4.8 Hz, J = 10.5 Hz, 1H, H_6), 4.50 (d, J = 7.8 Hz, 1H, H_1), 4.64 and 4.94 (AB, J_{AB} = 11.5 Hz, 2H, H_7), 5.54 (s, 1H, H_{12}), 7.32-7.51 (m, 10H, H_{Ar})

^{13}C NMR (75 MHz, DMSO-d_6) δ 128.8 (C_{11} or C_{16}), 128.2/128.0/127.6/126.4 (C_9/C_{10}/C_{14}/C_{15}), 127.5 (C_{11} or C_{16}), 103.0 (C_1), 100.7 (C_{12}), 80.6 (C_4), 74.4 (C_2), 72.9 (C_3), 70.2 (C_7), 68.0 (C_6), 65.9 (C_5)

ESIMS *m/z* (%) 739 $[2M+Na]^+$ (100)

31

2-Nitrobenzyl-4,6-*O*-benzylidene-β-D-glucopyranoside



$C_{20}H_{21}NO_8$

MW = 403,38 Da

CAS : [173204-63-2]

According to the procedure described in the literature,[73] zinc chloride (22.9 g, 168.1 mmol, 5.3 eq) was added under nitrogen to a suspension of **34** (10 g, 31.7 mmol, 1.0 eq) in 100 mL of benzaldehyde and the mixture was stirred at room temperature for 24 hours. The reaction solution was then poured into ice, and the crude product was extracted with EtOAc (3 x 75 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Further concentration under high vacuum using Kugelrohr to remove excess of benzaldehyde furnished an orange solid which was purified by column chromatography (8:2 → 4:6 cyclohexane:EtOAc) to yield **31** as a slight yellow solid (10.20 g, 80%).

m.p. 165°C

R_f = 0.10 (3:2 cyclohexane:EtOAc)

$[\alpha]^{24}_D$ = -82.8° (c = 0.99, acetone)

IR (neat) ν_{max} 3430, 3050, 3025, 2921, 2871, 1749, 1443, 1379, 1087, 998 cm^{-1}

^{1}H NMR (300 MHz, chloroform-d_1) δ 3.41-3.64 (m, 3H, H_2/H_4/H_5), 3.72-3.85 (m, 2H, H_3/H_6), 4.35 (dd, J = 4.8, 10.5 Hz, 1H, H_6), 4.55 (d, J = 7.6 Hz, 1H, H_1), 5.10 and 5.26 (AB, J_{AB} = 14.7 Hz, 2H, H_7), 5.52 (s, 1H, H_{14}), 7.35-7.50 (m, 6H, H_{16}/H_{17}/H_{18}/H_{10}), 7.65 (t, J = 7.6 Hz, 1H, H_{11}), 7.84 (d, J = 7.7 Hz, 1H, H_{12}), 8.07 (d, J = 8.1 Hz, 1H, H_9)

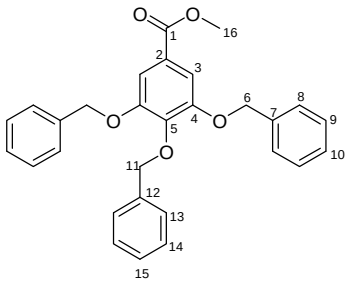
^{13}C NMR (75 MHz, DMSO-d_6) δ 147.3 (C_{13}), 136.9 (C_{15}), 133.7 (C_{11}), 133.6 (C_8), 129.3 (C_{18}), 129.1 (C_{12}), 128.3/128.3 (C_{16}/C_{17}), 126.3 (C_{10}), 124.7 (C_9), 102.8 (C_1), 101.9 (C_{14}), 80.4 (C_4), 74.6 (C_2), 73.3 (C_3), 68.5 (C_6), 68.1 (C_7), 66.4 (C_5)

CIMS *m/z* (%) 404 $[M+H]^+$ (48), 122 (94), 108 (100)

Galloyl units (F)

66

Methyl 3,4,5-tribenzyloxybenzoate



$C_{29}H_{26}O_5$

MW = 454,51 Da

CAS : [70424-94-1]

According to the procedure described in the literature,[137] a mixture of methyl gallate (**132**, 2 g, 10.86 mmol, 1.0 eq), KI (0.8 g, 4.78 mmol, 0.5 eq) and anhydrous powdered K_2CO_3 (8.8 g, 63.64 mmol, 5.9 eq) in 120 mL of acetone was stirred at room temperature for 20 minutes. Benzyl chloride (4 mL, 34.75 mmol, 3.2 eq) was dissolved in 20 mL of acetone and added to the reaction mixture. The suspension was refluxed for 20 hours at which time TLC showed full conversion of the starting material. The mixture was filtered through Celite® and the filtrate was evaporated *in vacuo* to give **66** as a pale yellow solid (4.94 g, 100%).

m.p. 97°C [lit.[91] m.p. 99-100°C (hexane)]

R_f = 0.45 (4:1 cyclohexane:EtOAc)

IR (NaCl) ν_{max} 3064, 3033, 2950, 2892, 1715, 1126 cm^{-1}

^{1}H NMR (300 MHz, chloroform-d_1) δ 3.89 (s, 3H, H_{16}), 5.12 (s, 2H, H_{11}), 5.14 (s, 4H, H_6), 7.25-7.45 (m, 17H, H_{Ar})

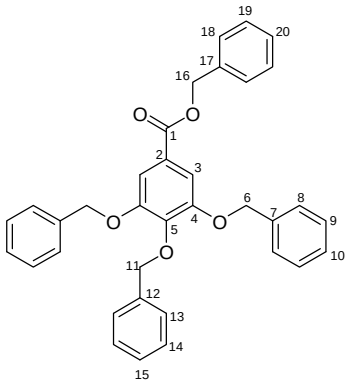
^{13}C NMR (75 MHz, chloroform-d_1) δ 166.5 (C_1), 152.5 (C_4), 142.4 (C_5), 137.4 (C_{12}), 136.6 (C_7), 128.4/128.4/128.1/127.9/127.8/127.5 (C_8/C_9/C_{10}/C_{13}/C_{14}/C_{15}), 125.2 (C_2), 109.0 (C_3), 75.0 (C_{11}), 71.1 (C_6), 52.1 (C_{16})

ESIMS *m/z* (%) 931 $[2M+Na]^+$ (55), 477 $[M+Na]^+$ (100), 445 $[M+H]^+$ (67)

HRMS calcd for $C_{29}H_{27}O_5$ $[M+H]^+$ 455.1858, found 455.1855

133

Benzyl 3,4,5-tribenzyloxybenzoate



$C_{35}H_{30}O_5$

MW = 530,61 Da

CAS : [475161-97-8]

According to the procedure described in the literature,[138] gallic acid (**77**, 1 g, 5.88 mmol, 1 eq) was dissolved in acetone (60 mL). K_2CO_3 (3.6 g, 25.87 mmol, 4.4 eq) and benzyl bromide (3.1 mL, 25.87 mmol, 4.4 eq) were added to the solution and the mixture was stirred under reflux for 18 hours. After adding H_2O (200 mL), the mixture was extracted with EtOAc (3 x 100 mL). The solvent was removed *in vacuo*, and the residual oil was crystallized from ethanol to yield **133** (1.18 g, 38%) as white crystals.

m.p. 92-93°C (EtOH) [lit.[138] m.p. 93.5-94.5°C (EtOH)]

R_f = 0.70 (4:1 PET:EtOAc)

IR (NaCl) ν_{max} 1714, 1428, 1335, 1205 cm^{-1}

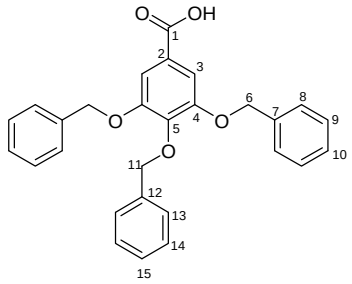
^{1}H NMR (300 MHz, DMSO-d_6) δ 5.06 (s, 2H, H_{11}), 5.19 (s, 4H, H_6), 5.33 (s, 2H, H_{16}), 7.27-7.46 (m, 22H, H_{Ar})

^{13}C NMR (75 MHz, DMSO-d_6) δ 165.1 (C_1), 152.1 (C_4), 141.5 (C_5), 137.3 (C_{12}), 136.7 (C_{17}), 136.2 (C_7), 128.5/128.2/128.1/128.0/127.9/127.8/127.6 (CH_{Ar}), 124.7 (C_2), 108.2 (C_3), 74.2 (C_{11}), 70.3 (C_6), 66.1 (C_{16})

CIMS *m/z* (%) 549 $[M+NH_4]^+$ (84), 532 $[M+H]^+$ (45), 108 (100), 91 (92)

32

3,4,5-tribenzyloxybenzoic acid



$C_{28}H_{24}O_5$

MW = 440,49 Da

CAS : [1486-48-2]

*Via hydrolysis of methyl ester **66** :*[137]

To a suspension of crude **66** (5.91 g) in 100 mL of ethanol was added NaOH (708 mg, 17.70 mmol, 1.6 eq). The mixture was heated to reflux for 2 hours. The hot solution was poured into 100 mL of 1M aqueous solution of HCl and the resulting mixture was stirred for 10 minutes before the solid was filtered off. The product was washed successively with a 1:1 mixture of ethanol and water (20 mL), pure water (20 mL), ethanol (20 mL), methanol (20 mL) and Et_2O (20 mL). The solid was then crystallized from ethanol to afford **32** as a white solid (3.93 g, 82%).

*Via hydrolysis of benzyl ester **133** :*[138]

A suspension of **133** (945 mg) in 50 mL of a methanolic solution of KOH (3N) was heated to reflux for 9 hours. The hot solution was then acidified at room temperature with a solution of HCl (3N) until pH = 1. The resulting precipitate was filtered off and the product was dissolved in EtOAc (100 mL). The organic layer was washed with water (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The solid was then crystallized from ethanol to afford **32** as a white solid (340 mg, 43%).

m.p. 194-195°C (EtOH) [lit.[164] m.p. 196-196.5°C (benzene-PET)]

R_f = 0.40 (1:1 cyclohexane:EtOAc)

IR (KBr) ν_{max} 1688, 1428, 1124 cm^{-1}

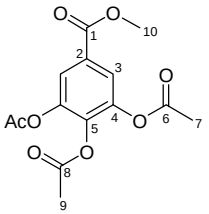
^{1}H NMR (300 MHz, DMSO-d_6) δ 5.04 (s, 2H, H_{11}), 5.18 (s, 4H, H_6), 7.27-7.48 (m, 17H, H_{Ar}), 12.95 (s large, 1H, H_{16})

^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9 (C_1), 152.0 (C_4), 141.0 (C_5), 137.4 (C_{12}), 136.9 (C_7), 128.4/128.2/128.1/127.9/127.6 (C_8/C_9/C_{10}/C_{13}/C_{14}/C_{15}), 126.1 (C_2), 108.2 (C_3), 74.2 (C_{11}), 70.2 (C_6)

CIMS *m/z* (%) 459 $[M+NH_4]^+$ (100), 368 (49), 108 (51), 91 (39)

136

Methyl 3,4,5-triacetoxybenzoate



$C_{14}H_{14}O_8$

MW = 310,26 Da

CAS : [20189-90-6]

According to the procedure described in the literature,[140] a mixture of commercially available methyl gallate (**132**, 5 g, 0.027 mol) and acetic anhydride (10 mL, 0.106 mol, 4 eq) in pyridine (25 mL) was stirred 16 hours at room temperature. The reaction mixture was then poured into 10% solution of HCl in brine (100 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with 10% aqueous solution of $NaHCO_3$ until pH 8 and brine (75 mL), dried over $MgSO_4$ and evaporated *in vacuo*. After recrystallisation in EtOH, **136** was obtained as white crystals (6.26 g, 75%).

m.p. 127°C (EtOH) [lit.[140] m.p. 126.5-128°C (EtOH)]

R_f = 0.28 (3:2 cyclohexane:EtOAc)

IR (neat) ν_{max} 1783, 1720, 1430, 1370, 1325, 1166 cm^{-1}

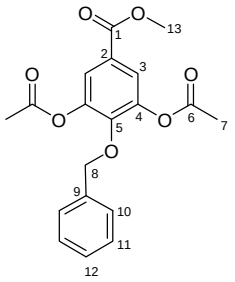
^{1}H NMR (300 MHz, chloroform-d_1) δ 2.27 (s, 6H, H_7), 2.28 (s, 3H, H_9), 3.88 (s, 3H, H_{10}), 7.78 (s, 2H, H_3)

^{13}C NMR (75 MHz, chloroform-d_1) δ 167.5 (C_6), 166.4/164.8 (C_1/C_8), 143.3 (C_4), 138.5 (C_5), 128.1 (C_2), 122.1 (C_3), 52.5 (C_{10}), 20.4 (C_7), 20.0 (C_9)

ESIMS *m/z* (%) 638 $[2M+NH_4]^+$ (58), 328 $[M+NH_4]^+$ (100)

137

Methyl-3,5-diacetoxy-4-(benzyloxy)benzoate



$C_{19}H_{18}O_7$

MW = 358,34 Da

CAS : [102019-30-7]

According to the procedure described in the literature,[140] a mixture of **136** (66.85 g, 0.215 mol, 1 eq), K_2CO_3 (89.15 g, 0.645 mol, 3 eq), KI (5.37 g, 0.032 mol, 0.15 eq) and benzyl chloride (50 mL, 54.43 g, 0.430 mol, 2 eq) was heated in acetone (500 mL) under reflux for 18 hours. The reaction mixture was then cooled, poured into water (500 mL) and extracted with Et_2O (3 x 300 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over $MgSO_4$ and evaporated *in vacuo*. After recrystallization in EtOH, **137** was obtained as white crystals (66.2 g, 86%).

m.p. 94°C (EtOH) [lit.[140] m.p. 94-96°C (EtOH)]

R_f = 0.61 (3:2 PET:EtOAc)

IR (neat) ν_{max} 1776, 1722, 1499, 1435, 1374, 1325, 1183, 1041 cm^{-1}

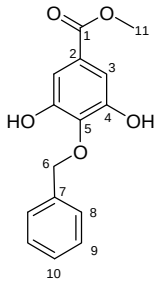
^{1}H NMR (300 MHz, chloroform-d_1) δ 2.18 (s, 6H, H_7), 3.87 (s, 3H, H_{13}), 5.05 (s, 2H, H_8), 7.32-7.37 (m, 5H, H_{10}/H_{11}/H_{12}), 7.70 (s, 2H, H_3)

^{13}C NMR (75 MHz, chloroform-d_1) δ 168.3 (C_6), 165.0 (C_1), 147.3 (C_9), 144.0 (C_4), 136.5 (C_5), 128.2 (C_{12}), 128.4/127.5 (C_{10}/C_{11}), 125.4 (C_2), 122.5 (C_3), 75.5 (C_8), 52.2 (C_{13}), 20.4 (C_7)

ESIMS *m/z* (%) 359 $[M+H]^+$ (100)

138

Methyl-4-(benzyloxy)-3,5-dihydroxybenzoate



$C_{15}H_{14}O_5$

MW = 274,27 Da

CAS : [91925-82-5]

According to the procedure described in the literature,[140] a solution of K_2CO_3 (45.82 g, 331.53 mmol, 6.6 eq) in water (200 mL) was added to a solution of **137** (18 g, 50.23 mmol, 1 eq) in MeOH (400 mL). After being stirred at room temperature for 3 hours, the reaction mixture was acidified with an excess of 3M HCl until pH 1. The acidified aqueous solution was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (2 x 300 mL) and water (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. After recrystallization in 1:4 $CHCl_3$:pentane, **138** was obtained as orange crystals (12.54 g, 91%).

m.p. 134°C (1:4 $CHCl_3$:pentane) [lit.[140] m.p. 133-134°C ($CHCl_3$-pentane)]

R_f = 0.23 (7:3 cyclohexane:EtOAc)

IR (neat) ν_{max} 3540, 1720, 1603, 1456, 1440, 1366, 1005 cm^{-1}

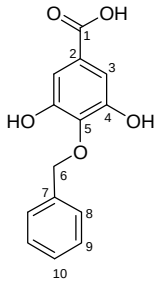
^{1}H NMR (300 MHz, acetone-d_6) δ 3.81 (s, 3H, H_{11}), 5.19 (s, 2H, H_6), 7.12 (s, 2H, H_3), 7.29-7.53 (m, 5H, H_8/H_9/H_{10}), 8.38 (brs, 2H, OH)

^{13}C NMR (75 MHz, acetone-d_6) δ 166.9 (C_1), 151.3 (C_4), 138.9/138.5 (C_5/C_7), 129.2/129.0 (C_8/C_9), 128.8 (C_{10}), 126.4 (C_2), 109.9 (C_3), 74.5 (C_6), 52.2 (C_{11})

CIMS *m/z* (%) 292 $[M+NH_4]^+$ (82), 275 $[M+H]^+$ (100)

139

4-(benzyloxy)-3,5-dihydroxybenzoic acid



$C_{14}H_{12}O_5$

MW = 260,24 Da

CAS : [100622-15-9]

*Via hydrolysis of **137** :*

To a stirred solution of **137** (563 mg, 1.57 mmol, 1 eq) in a 1:1 mixture of THF:H_2O (40 mL) was added KOH (1.76 g, 31.40 mmol, 20 eq) and the resulting mixture was heated to 50°C for 16 hours. After cooling to room temperature, the reaction mixture was diluted with 40 mL of water. The mixture was then washed with EtOAc to remove excess of THF. 1M aqueous solution HCl was then added to the aqueous layer until pH 1. After extraction with EtOAc (3 x 50 mL), the organic layer was washed with brine (50 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give **139** as an orange powder (408 mg, 100%).

*Via hydrolysis of **138** :*

A 5M aqueous solution of NaOH (28 mL, 0.14 mol, 3.3 eq) was added to a solution of **138** (11.48 g, 0.042 mol, 1 eq) in MeOH (33 mL) and the mixture was stirred under reflux for 2 hours and 30 minutes. After cooling to room temperature, excess of MeOH was evaporated and 5M aqueous solution of HCl (30 mL) was added to acidified the reaction mixture. The mixture was extracted with EtOAc (3 x 50 mL) and the organic layer was washed with brine (50 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give **139** as an orange powder (10.78 g, 99%).

m.p. 170°C [lit.[165] m.p. 169.5-170.5°C (Et_2O-PET) lit.[166] m.p. 170°C (aqueous MeOH)]

R_f = 0.05 (3:2 PET:EtOAc)

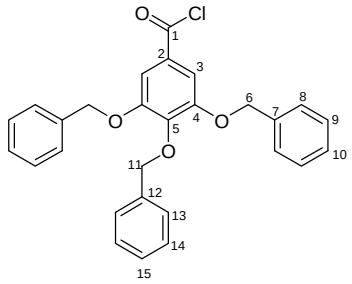
IR (neat) ν_{max} 3305, 1691, 1599, 1456, 1344, 1265, 1181, 1055 cm^{-1}

^{1}H NMR (300 MHz, acetone-d_6) δ 5.19 (s, 2H, H_6), 7.13 (s, 2H, H_3), 7.28-7.54 (m, 5H, H_8/H_9/H_{10}), 8.35 (brs, 1H, OH)

^{13}C NMR (75 MHz, acetone-d_6) δ 168.0 (C_1), 151.2 (C_4), 138.9/138.4 (C_5/C_7), 129.2/128.9 (C_8/C_9), 128.7 (C_{10}), 126.4 (C_2), 110.2 (C_3), 74.5 (C_6)

32b

3,4,5-tribenzyloxybenzoyl chloride



$C_{28}H_{23}ClO_4$

MW = 458,93 Da

CAS : [1486-47-1]

According to the procedure described in the literature,[137] a suspension of **32** (1 g, 2.27 mmol, 1 eq) in 25 mL of dry toluene and 0.1 mL of dry DMF was stirred at room temperature. A solution of oxalyl chloride (292 µL, 3.41 mmol, 1.5 eq) in 3 mL of dry toluene was then added slowly *via* a dropping funnel. After being stirred at room temperature for an additional 15 minutes, the mixture was heated to 50°C. The ceasing of gas evolution indicated the end of the reaction after 45 min. The solvent was evaporated *in vacuo* to give **32b** as white crystals (1.05 g, 100%, basisd on TLC analysis and ^{1}H NMR analysis on crude).

m.p. 114°C [lit.[137] m.p. 116-117°C (toluene-cyclohexane)]

R_f = 0.91 (1:1 cyclohexane:EtOAc)

^{1}H NMR (300 MHz, DMSO-d_6) δ 5.04 (s, 2H, H_{11}), 5.18 (s, 4H, H_6), 7.27-7.48 (m, 17H, H_3/H_{Ar})

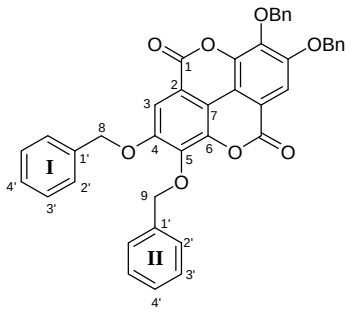
^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8 (C_1), 152.0 (C_4), 141.0 (C_5), 137.4 (C_{12}), 136.9 (C_7), 128.4/128.2/128.1/128.1/127.9/127.6 (C_8/C_9/C_{10}/C_{13}/C_{14}/C_{15}), 126.0 (C_2), 108.3 (C_3), 74.3 (C_{11}), 70.2 (C_6)

ESIMS *m/z* (%) 481 $[M+Na]^+$ (100)

HHDP units (G)

220

Tetrabenzylellagic acid



$C_{42}H_{30}O_8$

MW = 662,68 Da

CAS : [103442-14-4]

Adapted from the method of Kashiwada *et al*.[147] To a mixture of commercially available ellagic acid (20.0 g, 66 mmol, 1.0 eq), NaI (4.0 g, 27 mmol, 0.4 eq) and anhydrous powdered K_2CO_3 (76.8 g, 556 mmol, 8.4 eq) in 260 mL of acetophenone was added freshly distilled benzyl chloride (41 mL, 351 mmol, 5.3 eq). After 18 hours stirring at 140 °C, inorganic salts and unreacted ellagic acid were removed by filtration. Tetrabenzyl ellagic acid was crystallized from the filtrate by addition of cyclohexane. A large amount of cyclohexane was added until complete precipitation occurred. Compound **220** was obtained as a white solid (22.0 g, 50%).

m.p. 265-266°C [lit.[118] m.p. 267°C (1,4-dioxane)]

$\boldsymbol{R_f}$ = 0.60 (4:1 cyclohexane:EtOAc)

IR (KBr) ν_{max} 2939, 2854, 1746, 1606, 1495, 1457, 1410, 1360, 1317, 1258, 1179, 1094 cm^{-1}

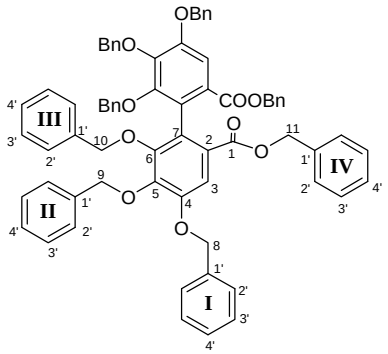
^{1}H NMR (300 MHz, DMSO-d_6) δ 5.37 (s, 8H, H_8/H_9), 7.34-7.66 (m, 22H, H_{Ar}), 11.08 (s, 2H, COOH formed by equilibrium between ester groups and their hydrolysed form)

^{13}C NMR (75 MHz, DMSO-d_6) δ The compound is not enough soluble in DMSO-d_6 to obtain a good spectrum

ESIMS *m/z* (%) The compound is insoluble in all the solvents generally used for MS spectroscopy

221

Dibenzyl 2,2',3,3',4,4'-Hexakis(benzyloxy)-1,1'-diphenyl-6,6'-dicarboxylate



$C_{70}H_{58}O_{10}$

MW = 1059,20 Da

CAS : [154675-20-4]

Adapted from the method of Schmidt *et al*.[119] In a dry round-bottomed flask, a mixture of **220** (5.3 g, 8 mmol, 1 eq), KOH (11.5 g, 205 mmol, 25 eq), NaI (0.6 g, 4 mmol, 0.5 eq) and benzyl chloride (40 mL) was heated at 145°C for 4 hours under argon atmosphere. The reaction mixture was then quenched with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting mixture was distilled at 120°C under high vacuum using Kugelrohr to remove excess of benzyl alcohol. Crude material was purified by column chromatography (9:1 → 8:2 PET/EtOAc) to give **221** as a colorless syrup (7.4 g, 87%).

***R*$_f$** = 0.46 (9:1 cyclohexane:EtOAc)

IR (neat) ν_{max} 3032, 1712, 1458, 1371, 1326, 1096, 1019, 977 cm^{-1}

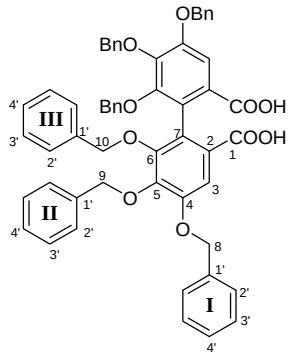
^{1}H NMR (300 MHz, chloroform-d_1) δ 4.65 and 4.75 (AB, J_{AB} = 11.1 Hz, 4H, H_{10}), 4.89 (d, J = 3.2 Hz, 4H, H_9), 5.01 (d, J = 4.5 Hz, 4H, H_{11}), 5.16 (brs, 4H, H_8), 6.83-7.54 (m, 42H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-d_1) δ 166.2 (C_1), 151.5 (C_4), 150.7 (C_6), 145.5 (C_5), 137.6/137.2/ 136.6/135.5 ($C_{1'I}$/$C_{1'II}$/$C_{1'III}$/$C_{1'IV}$), 128.5/128.5/128.4/128.4/128.3/128.3/128.2/128.1/128.0/127.9/ 127.8/127.7/127.6/127.5/127.4/127.3/127.2 (CH_{Ar}/C_7), 125.3 (C_2), 111.1 (C_3), 75.1 (C_{10}), 74.3 (C_9), 70.8 (C_8), 66.6 (C_{11})

ESIMS *m/z* (%) 1060 $[M+H]^+$ (57), 1059 (100), 952 (36), 951 (66)

(±)-93

2,2',3,3',4,4'-Hexakis(benzyloxy)-1,1'-diphenyl-6,6'-dicarboxylic acid



$C_{56}H_{46}O_{10}$
MW = 878,96 Da
CAS : [97152-40-4]

Adapted from the method of Schmidt *et al*.[119] To a solution of **221** (12.3 g, 12 mmol, 1 eq) in a 5:5:0.3 mixture of acetone/MeOH/H_2O (187 mL) was added KOH (14.6 g, 260 mmol, 22 eq). The suspension was stirred at 75°C for 4 hours before the volume of solvents was reduced of 1/3 *in vacuo*. The reaction mixture was then diluted with H_2O (250 ml), acidified to pH 1 with concentrated HCl (3 mL) and extracted with EtOAc (4 x 200 mL). The organic layer was washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oily residue was dissolved in a small amount of EtOAc and **(±)-93** was crystallized as a white solid (1.94 g) by adding cyclohexane. The liquid phase obtained was then concentrated *in vacuo* and purified by column chromatography (1:1 cyclohexane/EtOAc to remove apolar impurities then 10:10:0.1 → 0:10:0.1 EtOAc/acetone/AcOH) to afford **(±)-93** as a white solid (4.70 g) (63%).

m.p. 185-186°C (cyclohexane) [lit.[118] m.p. 187°C ($CHCl_3$)]

***R*$_f$** = 0.53 (98:2 EtOAc:acetone)

IR (neat) ν_{max} 3032, 1685, 1584, 1454, 1410, 1363, 1322, 1097 cm^{-1}

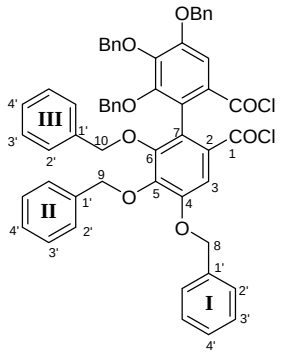
^{1}H NMR (300 MHz, chloroform-d_1) δ 4.74 (d, J = 11.1 Hz, 2H, $H_8/H_9/H_{10}$), 4.94-5.02 (m, 6H, $H_8/H_9/H_{10}$), 5.14-5.30 (m, 4H, $H_8/H_9/H_{10}$), 6.82 (d, J = 6.1 Hz, 4H, H_{Ar}), 7.03-7.51 (m, 26H, H_{Ar}), 7.63 (s, 2H, H_3), 12.58 (brs, 1H, COO<u>H</u>)

^{13}C NMR (75 MHz, chloroform-d_1) δ 172.1 (C_1), 151.6 (C_4), 151.0 (C_6), 146.3 (C_5), 137.7/137.2/136.6 ($C_{1'I}/C_{1'II}/C_{1'III}$), 128.9/128.6/128.6/128.2/128.1/127.9/127.8/127.3 (CH_{Ar}), 123.6 (C_2), 112.0 (C_3), 76.6 (C_{10}), 74.5 (C_8), 71.0 (C_9)

ESIMS *m/z* (%) 901 $[M+Na]^+$ (100)

(±)-<u>152</u>

2,2',3,3',4,4'-Hexakis(benzyloxy)biphenyl-6,6'-dicarboxylic acid chloride



$C_{56}H_{44}Cl_2O_8$

MW = 915,85 Da

CAS : [193535-28-3]

According to the procedure described in the literature,[95] a suspension of (±)-**93** (1.5 g, 1.71 mmol, 1 eq) in 20 mL of benzene and 2 drops of DMF was stirred at room temperature. Oxalyl chloride (1 mL, 11.70 mmol, 6.8 eq) was then added dropwise to the solution and the mixture was gradually heated to boiling. After refluxing for 12 hours, solvents were removed *in vacuo*. Product was tritured in PET, filtered and cristallized from a benzene-PET mixture to give (±)-**152** as a slight rose solid (1.43 g, 91%).

m.p. 142-143°C [lit.[118] m.p. 143.5°C (Benzene-PET)]

R_f = 0.37 (8:2 cyclohexane:EtOAc)

^{1}H NMR (300 MHz, chloroform-d_1) δ 4.75 (s, 4H, $H_8/H_9/H_{10}$), 5.02 and 5.06 (AB, J_{AB} = 11.0 Hz, 4H, $H_8/H_9/H_{10}$), 5.20 (s, 4H, $H_8/H_9/H_{10}$), 6.84 (d, J = 6.6 Hz, 4H, $H_8/H_9/H_{10}$), 7.10-7.50 (m, 26H, H_{Ar}), 7.70 (s, 2H, H_3)

^{13}C NMR (75 MHz, chloroform-d_1) δ 172.1 (C_1), 151.6 (C_4), 151.0 (C_6), 146.4 (C_5), 137.8/137.2/136.6 ($C_{1'I}/C_{1'II}/C_{1'III}$), 129.0/128.6/128.6/128.2/128.1/127.9/127.8/127.3 (CH_{Ar}), 123.7 (C_2), 112.2 (C_3), 75.3 (C_{10}), 74.5 (C_8), 71.1 (C_9)

ESIMS *m/z* (%) 915 $[M]^{+\cdot}$ (100)

Sugar derivatives (D)

General procedure a_1 (Steglich esterification) :

To a solution of the appropriate glucose derivative **E** (1 eq) and acid **F** (2.2 eq) in dry CH_2Cl_2 (0.025M in glucose derivative, volume V) were added at 0°C DMAP (2.2 eq) and DCC (4.4 eq). The mixture was stirred under nitrogen at room temperature for 16-48h and then, the white precipitate (dicyclohexylurea DCU) was filtered through Celite®. The filter cake was washed with CH_2Cl_2 (2 x V) and the solvent was evaporated *in vacuo*.[108] The residue was purified by column chromatography with the indicated eluent to furnish the desired esters **D**.

General procedure a_2 (modified Steglich esterification) :

To a solution of the appropriate glucose derivative **E** (1 eq) and acid **F** (2.2 eq) in dry CH_2Cl_2 (0.025M in glucose derivative, volume V) were added DMAP (0.5 eq), DMAP·HCl (0.5 eq) and DCC (2.2 eq). The solution was purged with nitrogen and stirred under reflux for 15-24h. The solution was then returned to room temperature and the white precipitate (dicyclohexylurea DCU) was filtered through Celite®. The filter cake was washed with CH_2Cl_2 (2 x V) and the filtrate was worked-up as indicated (i, ii or iii). The residue was purified by column chromatography with the indicated eluent to furnish the desired esters.[107]

Work-up procedures :

(i) the filtrate is concentrated *in vacuo*.

(ii) the filtrate is washed with H_2O (3 x V), brine (V), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

(iii) the filtrate is poured into ice-cold 1M aqueous solution of H_3PO_4 (V) and the organic layer is separated, washed with brine (V), dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

General procedure a_3 :

To a solution of the appropriate glucose derivative **E** (1 eq) and acid **F** (2.5 eq) in dry CH_2Cl_2 (0.025M in glucose derivative) were added at 0°C DMAP (7 eq) and EDCI (5 eq). The solution was purged with nitrogen and stirred at room temperature for 8-18h. A 1M aqueous solution of H_3PO_4 was then added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3 x V). The organic layer was then washed with brine (2 x V), dried over $MgSO_4$,

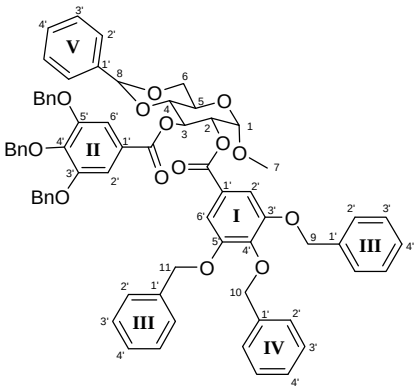
filtered and concentrated *in vacuo*.[92] The resulting residue was purified by column chromatography with the indicated eluent to furnish the desired esters **D**.

General procedure b_1 (« two steps » acylation) :

To a solution of the appropriate glucose derivative **E** (1 eq) and DMAP (3 eq) in dry CH_2Cl_2 (0.025M in glucose derivative) was added slowly at 0°C the appropriate acyl chloride (2.4 eq). The solution was purged with nitrogen and stirred at room temperature for 16-22h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (V) and the aqueous layer was extracted with CH_2Cl_2 (3 x V). The combined organic layers were washed with brine (2 x V), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography with the indicated eluent to furnish the desired esters **D**.

134a

Methyl-4,6-*O*-benzylidene-2,3-bis(3,4,5-tribenzyloxy)benzoyl-α-D-glucopyranoside



$C_{70}H_{62}O_{14}$

MW = 1127,23 Da

CAS : [183270-10-2]

By use of general procedure ***a₂***, commercially available Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**129**, 1 g, 3.54 mmol, 1 eq) was coupled with acid **32** (3.43 g, 7.79 mmol, 2.2 eq). After the work-up procedure (i) and purification by column chromatography (7:3 8:2 CH_2Cl_2:PET), **134a** was obtained as a white solid (3.89 g, 97%).

By use of general procedure ***b₁***, compound **129** (1 g, 3.54 mmol, 1 eq) was coupled with crude acyl chloride **32b** (3.9 g, 8.50 mmol, 2.4 eq) to afford **134a** as a white solid (3.19 g, 80%) following column chromatography (4:1 → 1:0 CH_2Cl_2:PET).

m.p. 177°C (lit.[167] m.p. 180-180.5°C)

R_f = 0.39 (4:1 CH_2Cl_2:PET)

$[\alpha]^{22}_{D}$ = +61.5° (c = 1.04, $CHCl_3$)

IR (neat) ν_{max} 1723, 1588, 1431, 1339, 1201, 1102, 755, 741, 697 cm^{-1}

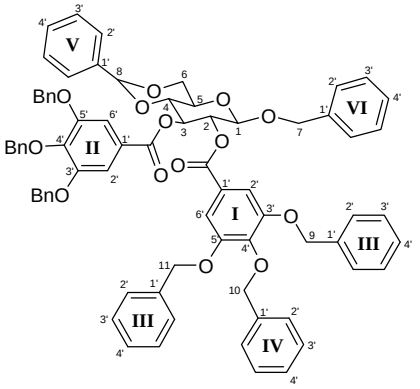
^{1}H NMR (300 MHz, chloroform-*d*$_1$) δ 3.45 (s, 3H, H_7), 3.88 (dt, J = 4.4, 9.6 Hz, 2H, H_4/H_6), 4.08 (dt, J = 4.9, 10.0 Hz, 1H, H_5), 4.38 (dd, J = 4.7 Hz, 10.2 Hz, 1H, H_6), 4.87-5.12 (m, 13H, H_2/H_9/H_{10}/H_{11}), 5.25 (d, J = 3.6 Hz, 1H, H_1), 5.57 (s, 1H, H_8), 6.03 (t, J = 9.8 Hz, 1H, H_3), 7.19-7.43 (m, 39H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-*d*$_1$) δ 165.6/165.4 (C_I=O/C_{II}=O), 152.5 ($C_{3'I}$/$C_{3'II}$/$C_{5'I}$/$C_{5'II}$), 142.9/142.8 ($C_{4'I}$/$C_{4'II}$), 137.4/137.4/136.9/136.5/136.5 ($C_{1'III}$/$C_{1'IV}$/$C_{1'V}$), 129.0 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 126.2 ($C_{2'V}$/$C_{3'V}$), 124.7/124.0 ($C_{1'I}$/$C_{1'II}$), 109.4/109.3 ($C_{2'I}$/$C_{2'II}$/$C_{6'I}$/$C_{6'II}$), 101.6 (C_8), 97.8 (C_1), 79.2 (C_4), 75.1/75.0 (C_9/C_{10}/C_{11}), 73.1 (C_2), 71.2/71.1 (C_9/C_{10}/C_{11}), 69.9 (C_3), 68.9 (C_6), 62.6 (C_5), 55.5 (C_7)

ESIMS *m/z* (%) 1126 $[M+H]^+$ (100)

134b

Benzyl 4,6-*O*-benzylidene-2,3-bis(3,4,5-tribenzyloxy)benzoyl-β-D-glucopyranoside



$C_{76}H_{66}O_{14}$

MW = 1203,33 Da

CAS : [154774-22-8]

By use of general procedure ***a₂***, compound **30** (500 mg, 1.40 mmol, 1 eq) was coupled with acid **32** (1.36 g, 3.08 mmol, 2.2 eq). After the work-up procedure (i) and purification by column chromatography (9:1 → 1:0 CH_2Cl_2:PET), **134b** was obtained as a slight yellow solid (940 mg, 56%).

m.p. 174.5-175.5°C

R_f = 0.55 (4:1 CH_2Cl_2:PET)

$[\alpha]^{22}_{D}$ = +37.4° (c = 0.97, $CHCl_3$)

IR (neat) ν_{max} 1723, 1588, 1427, 1332, 1201, 1099, 1000, 752, 734, 697 cm^{-1}

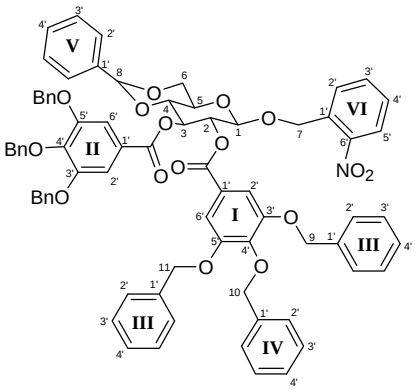
^{1}H NMR (300 MHz, chloroform-d_1) δ 3.76 (dt, J = 4.8, 9.5 Hz, 1H, H_5), 3.95-4.05 (m, 2H, H_4/H_6), 4.54 (dd, J = 4.6, 10.3 Hz, 1H, H_6), 4.74 and 5.00 (AB, J_{AB} = 12.4 Hz, 2H, H_7), 4.90 (d, J = 7.7 Hz, 1H, H_1), 5.06-5.17 (m, 12H, H_9/H_{10}/H_{11}), 5.63 (s, 1H, H_8), 5.63 (t, J = 8.6 Hz, 1H, H_2), 5.80 (t, J = 9.5 Hz, 1H, H_3), 7.23-7.52 (m, 44H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-d_1) δ 165.3/164.8 (C_I=O/C_{II}=O), 152.4/152.4 ($C_{3'I}$/$C_{3'II}$/$C_{5'I}$/$C_{5'II}$), 142.7 ($C_{4'I}$/$C_{4'II}$), 137.4/137.3/136.7/136.5/136.5 ($C_{1'III}$/$C_{1'IV}$/$C_{1'V}$/$C_{1'VI}$), 129.0 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (CH_{Ar}), 127.5 (CH_{Ar}), 126.1 ($C_{2'V}$/$C_{3'V}$), 124.4/124.2 ($C_{1'I}$/$C_{1'II}$), 109.3 ($C_{2'I}$/$C_{2'II}$/$C_{6'I}$/$C_{6'II}$), 101.4 (C_8), 100.0 (C_1), 78.7 (C_4), 75.0 (C_9/C_{10}/C_{11}), 72.6 (C_2), 72.4 (C_3), 71.1 (C_9/C_{10}/C_{11}), 70.8 (C_7), 68.6 (C_6), 66.6 (C_5)

ESIMS *m/z* (%) 1203 $[M+H]^+$ (100)

134c

2-Nitrobenzyl 4,6-O-benzylidene-2,3-bis(3,4,5-tribenzyloxy)benzoyl-β-D-glucopyranoside



$C_{76}H_{65}NO_{16}$

MW = 1248,33 Da

CAS : [341035-12-9]

By use of general procedure a_2, compound **31** (1 g, 2.48 mmol, 1 eq) was coupled with acid **32** (2.40 g, 5.45 mmol, 2.2 eq). After the work-up procedure (i) and purification by column chromatography (3:2 → 4:1 CH_2Cl_2:PET), **134c** was obtained as a white solid (3.10 g, 100%).

m.p. 165.5°C

R_f = 0.60 (4:1 CH_2Cl_2:PET)

$[\alpha]^{22}_D$ = +42.4° (c = 0.99, $CHCl_3$)

IR (neat) ν_{max} 1723, 1588, 1526, 1500, 1431, 1336, 1201, 1102, 1026, 1004, 752, 737, 697 cm^{-1}

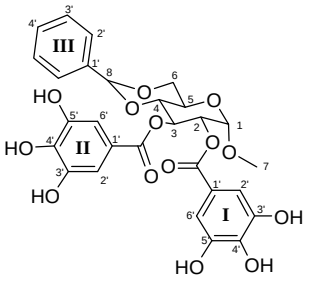
^{1}H NMR (300 MHz, chloroform-d_1) δ 3.67 (dt, J = 4.7, 9.4 Hz, 1H, H_5), 3.78-3.92 (m, 2H, H_4/H_6), 4.40 (dd, J = 4.6, 10.3 Hz, 1H, H_6), 4.86 (d, J = 7.7 Hz, 1H, H_1), 4.93-5.27 (m, 14H, H_7/H_9/H_{10}/H_{11}), 5.48 (s, 1H, H_8), 5.51 (t, J = 8.2 Hz, 1H, H_2), 5.71 (t, J = 9.5 Hz, 1H, H_3), 7.14-7.37 (m, 41H, H_{Ar}), 7.57 (d, J = 6.8 Hz, 1H, $H_{2'V}$), 7.96 (d, J = 7.2 Hz, 1H, $H_{5'V}$)

^{13}C NMR (75 MHz, chloroform-d_1) δ 165.3/165.0 (C_I=O/C_{II}=O), 152.5/152.5 ($C_{3'I}$/$C_{3'II}$/$C_{5'I}$/$C_{5'II}$), 146.7 ($C_{6'VI}$), 142.8/142.8 ($C_{4'I}$/$C_{4'II}$), 137.4/137.3/136.7/136.5/136.5 ($C_{1'III}$/$C_{1'IV}$/$C_{1'V}$), 133.8/133.7 ($C_{1'VI}$/$C_{4'VI}$), 129.1 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (Cq), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.5 (CH_{Ar}), 126.1 ($C_{2'V}$/$C_{3'V}$), 124.6 ($C_{5'VI}$), 124.3/124.1 ($C_{1'I}$/$C_{1'II}$), 109.3/109.3 ($C_{2'I}$/$C_{2'II}$/$C_{6'I}$/$C_{6'II}$), 101.5 (C_8), 101.3 (C_1), 78.7 (C_4), 75.1 (C_9/C_{10}/C_{11}), 72.7 (C_2), 72.3 (C_3), 71.2/71.2 (C_9/C_{10}/C_{11}), 68.5 (C_6), 68.1 (C_7), 66.8 (C_5)

ESIMS *m/z* (%) 1270 $[M+Na]^+$ (100)

135a

Methyl-4,6-*O*-benzylidene-2,3-bis(3,4,5-trihydroxy)benzoyl-α-D-glucopyranoside



$C_{28}H_{26}O_{14}$

MW = 586,50 Da

CAS : [732310-87-1]

A solution of **134a** (2.75 g, 2.44 mmol) and 10% Pd/C (500 mg) in 120 mL of anhydrous THF was purged 3 times with H_2. The mixture was stirred at room temperature under H_2 for 24 hours, filtered through Celite®. The filter cake was then washed with acetone (60 mL). Concentration *in vacuo* give **135a** as a black solid (1.43 g, 100%).

m.p. 195-197°C

R_f = 0.39 (1:4 cyclohexane:EtOAc)

$[\alpha]^{22}_D$ = +18.0° (c = 1.06, acetone)

IR (neat) ν_{max} 3397 (st), 1704, 1617, 1540, 1452, 1336, 1226, 1094, 1040, 767 cm^{-1}

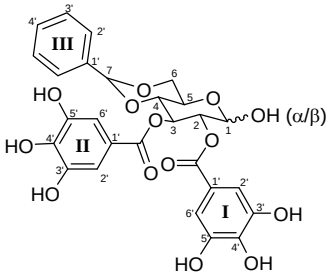
^{1}H NMR (300 MHz, acetone-d_6) δ 3.46 (s, 3H, H_7), 3.87-4.07 (m, 3H, H_4/H_5/H_6), 4.33 (dd, J = 2.9, 8.8 Hz, 1H, H_6), 5.11-5.20 (m, 2H, H_1/H_2), 5.67 (s, 1H, H_8), 5.86 (t, J = 9.4 Hz, 1H, H_3), 7.06-7.07 (m, 4H, $H_{2'I}$/$H_{6'I}$/$H_{2'II}$/$H_{6'II}$), 7.30-7.43 (m, 5H, $H_{2'III}$/$H_{3'III}$/$H_{4'III}$)

^{13}C NMR (75 MHz, acetone-d_6) δ 166.2/166.2 (C_I=O/C_{II}=O), 146.0/145.9 ($C_{4'I}$/$C_{4'II}$), 139.0 ($C_{1'III}$), 138.5 ($C_{3'I}$/$C_{3'II}$/$C_{5'I}$/$C_{5'II}$), 129.6 ($C_{4'III}$), 128.8 ($C_{2'III}$), 127.0 ($C_{3'III}$), 121.1/120.4 ($C_{1'I}$/$C_{1'II}$), 110.1/110.0 ($C_{2'I}$/$C_{2'II}$/$C_{6'I}$/$C_{6'II}$), 102.2 (C_8), 98.7 (C_1), 79.9 (C_4), 72.7 (C_2), 69.9 (C_3), 69.2 (C_6), 63.6 (C_5), 55.6 (C_7)

ESIMS *m/z* (%) 609 $[M+Na]^+$ (100)

135d

4,6-*O*-benzylidene-2,3-bis(3,4,5-trihydroxy)benzoyl-D-glucopyranose



$C_{27}H_{24}O_{14}$

MW = 572,47 Da

No CAS

A solution of **134b** (761 mg, 0.63 mmol) and 10% Pd/C (300 mg) in 40 mL of anhydrous THF was purged 3 times with H_2. The mixture was stirred at room temperature under H_2 for 24 hours, filtered through Celite®. The filter cake was then washed with THF (100 mL) and concentration *in vacuo* of the filtrate gave a pale green oil. The resultant crude product was purified by RP column chromatography Reverse Phase (C_{18}) column chromatography (100:0:0.1 → 30:70:0.1 H_2O:MeOH:HCOOH) to give **135d** as a pale yellow solid (144 mg, 40%) and mono-benzylated product **135c** (65 mg, 15%).

Compound **135c** was obtained as a 1:0.8 mixture of α and β anomers.

m.p. 120-122°C

***R*$_f$** = 0.67 (C_{18}-TLC; 30:70:0.1 H_2O:MeOH:HCOOH)

IR (neat) ν_{max} 3175 (st), 1701, 1609, 1452, 1343, 1211, 1095, 1040, 766 cm^{-1}

ESIMS *m/z* (%) 1143 $[2M-H]^-$ (53), 684 (100), 571 $[M-H]^-$ (99)

A pure sample of **α-135d** or **β-135d** could not be separated, and only assignable peaks from the mixture are listed.

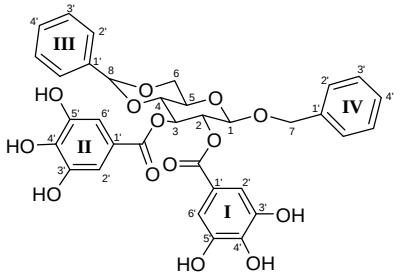
^{1}H NMR (300 MHz, acetone-d_6) δ 3.77 (dt, J = 4.7 Hz, J = 9.6 Hz, 1H, H_5), 3.85-4.04 (m, 4H, $H_{4\alpha}/H_{4\beta}/H_{6\alpha}/H_{6\beta}$), 4.19-4.28 (m, 2H, $H_{5\alpha}/H_{6\alpha}$), 4.33 (dd, J = 4.6, 10.1 Hz, 1H, $H_{6\beta}$), 5.13 (dd, J = 3.7, 9.7 Hz, 1H, $H_{2\alpha}$), 5.15 (d, J = 7.4 Hz, 1H, $H_{1\beta}$), 5.25 (t, J = 8.7 Hz, 1H, $H_{2\beta}$), 5.55 (d, J = 3.4 Hz, 1H, $H_{1\alpha}$), 5.62-5.69 (m, 1H, $H_{3\beta}$), 5.68 (s, 1H, $H_{7\beta}$), 5.69 (s, 1H, $H_{7\alpha}$), 5.94 (t, J = 9.8 Hz, 1H, $H_{3\alpha}$), 7.03 (s, 2H, $H_{2'I\beta}/H_{6'I\beta}$ or $H_{2'II\beta}/H_{6'II\beta}$), 7.05 (s, 2H, $H_{2'I\beta}/H_{6'I\beta}$ or $H_{2'II\beta}/H_{6'II\beta}$), 7.06 (s, 2H, $H_{2'I\alpha}/H_{6'I\alpha}$ or $H_{2'II\alpha}/H_{6'II\alpha}$), 7.07 (s, 2H, $H_{2'I\alpha}/H_{6'I\alpha}$ or $H_{2'II\alpha}/H_{6'II\alpha}$), 7.30-7.43 (m, 10H, $H_{2'III}/H_{3'III}/H_{4'III}$)

^{13}C NMR (75 MHz, acetone-d_6) δ 166.5 ($C_{II\alpha}$=O), 166.3 ($C_{I\alpha}$=O), 166.1 ($C_{II\beta}$=O), 166.0 ($C_{I\beta}$=O), 146.2/146.2 ($C_{3'I}/C_{3'II}/C_{5'I}/C_{5'II}$), 140.2/139.8 ($C_{4'I}/C_{4'II}$), 138.6 ($C_{1'III\alpha}$), 138.5 ($C_{1'III\beta}$), 129.7 ($CH_{Ar}$), 129.5 ($CH_{Ar}$), 128.9 ($CH_{Ar}$), 128.7 ($CH_{Ar}$), 127.1 ($C_{2'III\alpha}/C_{3'III\alpha}$), 127.0 ($C_{2'III\beta}/C_{3'III\beta}$),

120.6 ($C_{1'II\alpha}$), 120.4 ($C_{1'II\beta}$), 120.3 ($C_{1'I\beta}$), 119.9 ($C_{1'I\alpha}$), 110.0/109.9 ($C_{2'I\alpha}$/$C_{2'II\alpha}$/$C_{6'I\alpha}$/$C_{6'II\alpha}$), 109.7 ($C_{2'I\beta}$/$C_{2'II\beta}$/$C_{6'I\beta}$/$C_{6'II\beta}$), 102.1 ($C_{7\alpha}$), 101.9 ($C_{7\beta}$), 96.7 ($C_{1\beta}$), 91.7 ($C_{1\alpha}$), 80.3 ($C_{4\alpha}$), 79.8 ($C_{4\beta}$), 74.5 ($C_{2\beta}$), 73.3 ($C_{2\alpha}$), 72.6 ($C_{3\beta}$), 69.7 ($C_{3\alpha}$), 69.4 ($C_{6\alpha}$), 69.1 ($C_{6\beta}$), 67.2 ($C_{5\beta}$), 63.3 ($C_{5\alpha}$)

135c

Benzyl 4,6-*O*-benzylidene-2,3-bis(3,4,5-trihydroxy)benzoyl-D-glucopyranoside



$C_{34}H_{30}O_{14}$

MW = 662,59 Da

No CAS

Pale yellow solid

***R*$_f$** = 0.27 (C_{18}-TLC; 30:70:0.1 H_2O:MeOH:HCOOH)

^{1}H NMR (300 MHz, acetone-d_6) δ 3.81 (dt, J = 4.7 Hz, J = 9.6 Hz, 1H, H_5), 3.94 (t, J = 10.1 Hz, 1H, H_6), 4.04 (t, J = 9.5 Hz, 1H, H_4), 4.40 (dd, J = 4.7, 10.0 Hz, 1H, H_6), 4.72 and 4.89 (AB, J_{AB} = 12.7 Hz, 2H, H_7), 5.05 (d, J = 7.7 Hz, 1H, H_1), 5.38 (t, J = 8.8 Hz, 1H, H_2), 5.67 (t, J = 9.0 Hz, 1H, H_3), 5.70 (s, 1H, H_8), 7.04 (s, 2H, $H_{2'I}$/$H_{6'I}$ or $H_{2'II}$/$H_{6'II}$), 7.06 (s, 2H, $H_{2'I}$/$H_{6'I}$ or $H_{2'II}$/$H_{6'II}$), 7.21-7.42 (m, 5H, $H_{2'III}$/$H_{3'III}$/$H_{4'III}$/$H_{2'IV}$/$H_{3'IV}$/$H_{4'IV}$)

^{13}C NMR (75 MHz, acetone-d_6) δ 165.9/165.6 (C_I=O/C_{II}=O), 146.0/145.9 ($C_{3'I}$/$C_{3'II}$/$C_{5'I}$/$C_{5'II}$), 139.1/139.0/138.6/138.4 ($C_{4'I}$/$C_{4'II}$/$C_{1'III}$/$C_{1'IV}$), 129.6 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.4 (CH_{Ar}), 128.2 (CH_{Ar}), 127.1 (CH_{Ar}), 121.1/121.1 ($C_{1'I}$/$C_{1'II}$), 110.2/110.1 ($C_{2'I}$/$C_{2'II}$/$C_{6'I}$/$C_{6'II}$), 102.0 (C_8), 101.6 (C_1), 79.7 (C_4), 73.1 (C_2), 72.7 (C_3), 71.4 (C_7), 69.1 (C_6), 67.3 (C_5)

ESIMS *m/z* (%) 661 $[M-H]^-$ (100)

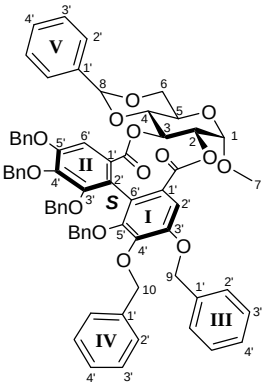
Sugar derivatives HHDP bearing (B)

Bis-esterification of glucose derivative 129 with HHDP unit

A solution of commercially available Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**129**, 849 mg, 3.01 mmol, 1 eq) and DMAP (1.1 g, 9.00 mmol, 3 eq) in dry CH_2Cl_2 (60 mL) was added slowly at 0°C a solution of racemic bis-acyl chloride (±)-**93** (2.75 g, 3.00 mmol, 1 eq) in 20 mL of dry CH_2Cl_2. The solution was purged with nitrogen and stirred at room temperature for 24 hours. The reaction was quenched by addition of ice. After extraction with CH_2Cl_2 (2 x 60 mL), the combined organic layers were dried over $MgSO_4$, filtered off, and concentrated *in vacuo*. The residue was purified by column chromatography (7:3 CH_2Cl_2:$CHCl_3$) to give 1.6 g of a mixture of (*S*)-**153**, (*R*)-**153** and dimer **154**. The mixture was purified an other time to obtain pure fractions of (*S*)-**153** (823 mg, 24%), (*R*)-**153** (143 mg, 4%) and **154** (632 mg, 17%).

(*S*)-<u>153</u>

α-D-Glucopyranoside, Methyl 4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,5,5´,6,6´-hexakis(benzyloxy)-1,1´-(*S*)-biphenyl]-2,2´-dicarboxylate



$C_{70}H_{60}O_{14}$

MW = 1125,22 Da

No CAS

Yellow crystals

m.p. 118-120°C

***R*$_f$** = 0.32 (7:3 CH_2Cl_2:$CHCl_3$)

[α]$^{22}_D$ = -34.0° (c = 0.5, $CHCl_3$)

IR (neat) ν_{max} 1755, 1591, 1452, 1364, 1332, 1178, 1095, 1058, 741, 697 cm^{-1}

^{1}H NMR (300 MHz, chloroform-d_1) δ 3.51 (s, 3H, H_7), 3.83-3.94 (m, 2H, H_4/H_6), 4.00 (dd, J = 4.4, 9.7 Hz, 1H, H_5), 4.36 (dd, J = 4.4, 10.1 Hz, 1H, H_6), 4.58-5.27 (m, 14H, H_1/H_2/H_9/H_{10}), 5.61 (s, 1H, H_8), 5.67 (t, J = 9.5 Hz, 1H, H_3), 6.94-7.55 (m, 37H, H_{Ar})

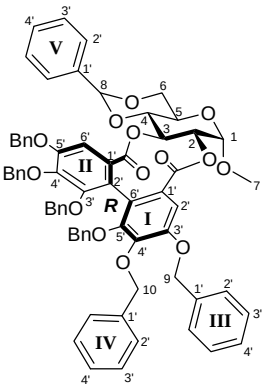
^{13}C NMR (75 MHz, chloroform-d_1) δ 168.0/168.0 (C_I=O/C_{II}=O), 152.8/152.7/152.7/152.5 ($C_{3'I}$/$C_{3'II}$/$C_{5'II}$/$C_{5'II}$), 144.6/144.3 ($C_{4'I}$/$C_{4'II}$), 137.7/137.6/137.5/136.9/136.5/136.5 ($C_{1'III}$/$C_{1'IV}$/$C_{1'V}$), 129.3 (CH_{Ar}), 129.2 (Cq), 128.7 (Cq), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.7 (CH_{Ar}), 127.4 (CH_{Ar}), 126.4 (CH_{Ar}), 122.2/121.9 ($C_{1'I}$/$C_{1'II}$), 107.2/107.1 ($C_{2'I}$/$C_{6'II}$), 101.8 (C_8), 98.3 (C_1), 78.3 (C_4), 75.5/75.4/75.3 (C_9/C_{10}), 74.3 (C_2), 73.6 (C_3), 71.3/71.4 (C_9/C_{10}), 68.9 (C_6), 62.9 (C_5), 55.3 (C_7)

ESIMS *m/z* (%) 1147 $[M+Na]^+$ (100)

Anal. calcd for $C_{70}H_{60}O_{14}$: C, 74.72; H, 5.37 ; found : C, 74.91; H, 5.56

(*R*)-<u>221</u>

α-D-Glucopyranoside, Methyl 4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,5,5´,6,6´-hexakis(benzyloxy)-1,1´-(*R*)-biphenyl]-2,2´-dicarboxylate



$C_{70}H_{60}O_{14}$

MW = 1125,22 Da

No CAS

White crystals

m.p. 76-78°C

***R*$_f$** = 0.21 (7:3 CH_2Cl_2:$CHCl_3$)

[α]$^{22}_D$ = +152.8° (c = 0.53, $CHCl_3$)

IR (neat) ν_{max} 1754, 1590, 1449, 1360, 1335, 1178, 1094, 1052, 739, 697 cm^{-1}

^{1}H NMR (300 MHz, chloroform-d_1) δ 3.32 (s, 3H, H_7), 3.80-3.83 (m, 3H, H_4/H_5/H_6), 4.30-4.33 (m, 1H, H_6), 4.51-5.25 (m, 15H, H_1/H_2/H_3/H_9/H_{10}), 5.59 (s, 1H, H_8), 6.81-7.53 (m, 37H, H_{Ar})

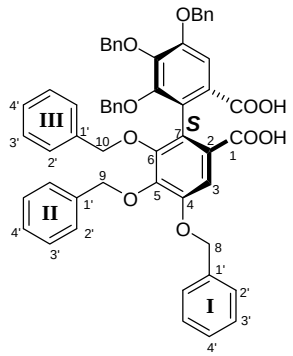
^{13}C NMR (75 MHz, chloroform-d_1) δ 168.6/166.2 (C_I=O/C_{II}=O), 153.1/152.6/152.1/151.8 ($C_{3'I}$/$C_{3'II}$/$C_{5'II}$/$C_{5'II}$), 137.5/137.5/137.4/137.3/137.1/136.5/136.2 ($C_{4'I}$/$C_{4'II}$/$C_{1'III}$/$C_{1'IV}$/$C_{1'V}$), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 127.5 (CH_{Ar}), 127.2 (CH_{Ar}), 126.2 (CH_{Ar}), 125.4 ($C_{1'I}$/$C_{1'II}$), 101.6 (C_8), 98.1 (C_1), 78.3 (C_4), 75.5/75.3/75.1 (C_9/C_{10}), 71.1/71.1 (C_2/C_3), 68.7 (C_6), 62.7 (C_5), 55.5 (C_7)

ESIMS *m/z* (%) 1147 $[M+Na]^+$ (100)

Anal. calcd for $C_{70}H_{60}O_{14}$: C, 74.72; H, 5.37 ; found : C, 74.91; H, 5.42

(*S*)-93

2,2',3,3',4,4'-Hexakis(benzyloxy)-(*S*)-biphenyl-6,6'-dicarboxylic acid



$C_{56}H_{46}O_{10}$

MW = 878,96 Da

CAS : [188855-50-7]

According to the procedure described in the literature,[95] to a solution of potassium *tert*-butoxide (301 mg, 2.64 mmol, 6 eq) and H_2O (48 µL, 2.64 mmol, 6 eq) in THF (20 mL), stirred at room temperature for 5 minutes, was added (*S*)-**153** (500 mg, 0.44 mmol, 1 eq) and the mixture was stirred for 12 hours at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and a 2M aqueous solution of HCl (20 mL) was added. This mixture was stirred for 30 minutes before the resulting aqueous portion was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried on $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was recrystallized from Et_2O:hexane (1:1) to give (*S*)-**93** as a white solid (387 mg, 100%).

m.p. 185-186°C (lit.[118] m.p. 187°C)

R_f = 0.24 (15:1 CH_2Cl_2:MeOH)

$[\alpha]_D^{24}$ = -9.8° (*c* = 1.5, CH_2Cl_2)

IR (neat) ν_{max} 3032, 1685, 1584, 1454, 1410, 1363, 1322, 1097 cm^{-1}

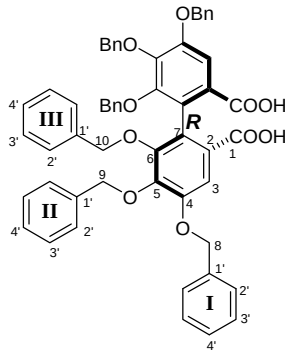
^{1}H NMR (300 MHz, chloroform-d_1) δ 4.72-5.02 (m, 8H, $H_8/H_9/H_{10}$), 5.16 and 5.24 (AB, J_{AB} = 11.4 Hz, 4H, $H_8/H_9/H_{10}$), 6.81 (d, J = 7.7 Hz, 4H, H_{Ar}), 7.02-7.11 (m, 5H, H_{Ar}), 7.22-7.51 (m, 21H, H_{Ar}), 7.63 (s, 2H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-d_1) δ 172.2 (C_1), 151.5 (C_4), 151.0 (C_6), 146.3 (C_5), 137.7/137.2/136.5 ($C_{1'I}/C_{1'II}/C_{1'III}$), 129.0 ($CH_{Ar}$), 128.6 ($CH_{Ar}$), 128.5 ($CH_{Ar}$), 128.2 ($CH_{Ar}$), 128.1 ($CH_{Ar}$), 127.9 ($CH_{Ar}$), 127.8 ($CH_{Ar}$), 127.3 ($CH_{Ar}$), 123.6 ($C_2$), 112.1 ($C_3$), 75.2 ($C_{10}$), 74.5 ($C_8$), 71.0 ($C_9$)

ESIMS *m/z* (%) 901 $[M+Na]^+$ (100)

(*R*)-93

2,2',3,3',4,4'-Hexakis(benzyloxy)-(*R*)-biphenyl-6,6'-dicarboxylic acid



$C_{56}H_{46}O_{10}$

MW = 878,96 Da

CAS : [219670-14-1]

According to the procedure described in the literature,[95] to a solution of potassium *tert*-butoxide (152 mg, 1.33 mmol, 6 eq) and H_2O (24 µL, 1.33 mmol, 6 eq) in THF (10 mL), stirred at room temperature for 5 minutes, was added (*R*)-**153** (250 mg, 0.22 mmol, 1 eq) and the mixture was stirred for 12 hours at room temperature. The reaction mixture was then diluted with CH_2Cl_2 and a 2M aqueous solution of HCl (10 mL) was added. This mixture was stirred for 30 minutes before the resulting aqueous portion was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried on $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was recrystallized from Et_2O:hexane (1:1) to give (*R*)-**93** as a white solid (195 mg, 100%).

m.p. 185-186°C (lit.[118] m.p. 187°C)

R_f = 0.24 (15:1 CH_2Cl_2:MeOH)

$[\alpha]_D^{24}$ = +9.4° (*c* = 1.5, CH_2Cl_2)

IR (neat) ν_{max} 3032, 1685, 1584, 1454, 1410, 1363, 1322, 1097 cm^{-1}

^{1}H NMR (300 MHz, chloroform-d_1) δ 4.72-5.02 (m, 8H, $H_8/H_9/H_{10}$), 5.16 and 5.24 (AB, J_{AB} = 11.3 Hz, 4H, $H_8/H_9/H_{10}$), 6.82 (d, J = 6.0 Hz, 4H, H_{Ar}), 7.03-7.09 (m, 5H, H_{Ar}), 7.22-7.51 (m, 21H, H_{Ar}), 7.63 (s, 2H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-d_1) δ 172.2 (C_1), 151.6 (C_4), 151.0 (C_6), 146.3 (C_5), 137.7/137.2/136.5 ($C_{1'I}/C_{1'II}/C_{1'III}$), 129.0 ($CH_{Ar}$), 128.6 ($CH_{Ar}$), 128.6 ($CH_{Ar}$), 128.2 ($CH_{Ar}$), 128.1 ($CH_{Ar}$), 127.9 ($CH_{Ar}$), 127.8 ($CH_{Ar}$), 127.3 ($CH_{Ar}$), 123.6 ($C_2$), 112.1 ($C_3$), 75.2 ($C_{10}$), 74.5 ($C_8$), 71.0 ($C_9$)

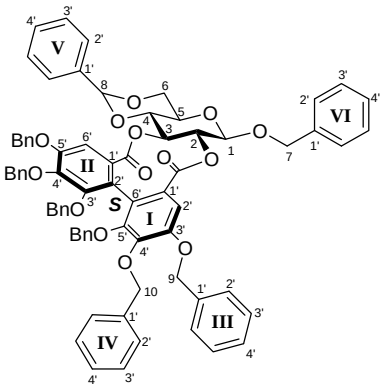
ESIMS *m/z* (%) 901 $[M+Na]^+$ (100)

Bis-esterification of glucose derivative 30 with HHBP unit

To a solution of **30** (410 mg, 1.15 mmol, 1 eq), racemic bis-acid (±)-**93** (1.11 g, 1.26 mmol, 1.1 eq) and DMAP (309 mg, 2.53 mmol, 2.2 eq) in dry CH_2Cl_2 (10 mL) at 0°C was added DCC (1.04 g, 5.05 mmol, 4.4 eq). The solution was purged with nitrogen and stirred at room temperature for 18 hours. The mixture was then filtered through Celite®. The filter cake was washed with CH_2Cl_2 and the combined filtrates were concentrated *in vacuo*. After addition of EtOAc, the excess of DCU was removed by filtration (this manipulation was repeated 5 times). The resultant crude product was purified by column chromatography (90:10:0 → 100:0:0 → 95:0:5 CH_2Cl_2:PET:Et_2O) to obtain in pure form (*S*)-**156** (485 mg, 35%) and (*R*)-**156** (535 mg, 39%).

(*S*)-<u>156</u>

Benzyl 4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,5,5´,6,6´-hexakis(benzyloxy)-1,1´-(*S*)-biphenyl-2,2´-dicarboxylate]-β-D-Glucopyranoside



$C_{76}H_{64}O_{14}$

MW = 1201,31 Da

No CAS

Pale yellow foam

m.p. 91-92°C

***R*$_f$** = 0.75 (4:1 CH_2Cl_2:PET)

[α]$^{21}_D$ = -73.1° (c = 0.52, $CHCl_3$)

IR (neat) ν_{max} 3430 (st), 1752, 1590, 1452, 1368, 1332, 1186, 1094, 1007, 748, 697 cm^{-1}

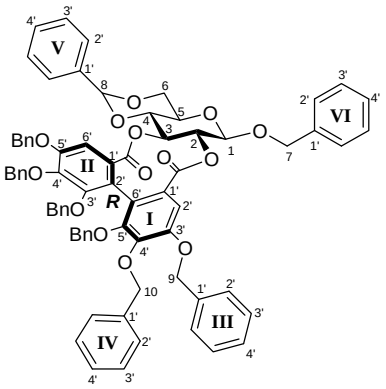
^{1}H NMR (300 MHz, chloroform-d_1) δ 3.56-3.64 (m, 1H, H_5), 3.90-3.99 (m, 2H, H_4/H_6), 4.46 (dd, J = 4.6, 10.5 Hz, 1H, H_6), 4.63-5.22 (m, 16H, H_1/H_2/H_9/H_{10}), 5.42 (t, J = 9.6 Hz, 1H, H_3), 5.62 (s, 1H, H_8), 6.83 (s, 1H, $H_{2'I}$ or $H_{6'II}$), 6.98-7.54 (m, 41H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-d_1) δ 168.3/167.4 (C_I=O/C_{II}=O), 152.7/152.6/152.6/152.5 ($C_{3'I}$/$C_{3'II}$/$C_{5'II}$/$C_{5'II}$), 144.5 ($C_{4'I}$/$C_{4'II}$), 137.6/137.5/137.5/136.8/136.8/136.4/136.4 ($C_{1'III}$/$C_{1'IV}$/$C_{1'V}$), 129.4 (CH_{Ar}), 128.9 (Cq), 128.8 (Cq), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.8 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (CH_{Ar}), 126.4 (CH_{Ar}), 122.3/122.2 ($C_{1'I}$/$C_{1'II}$), 107.2/106.9 ($C_{2'I}$/$C_{6'II}$), 101.7 (C_8), 99.1 (C_1), 77.2 (C_4), 75.9/75.8 (C_2/C_3), 75.5/75.5/75.3/75.3/71.3/70.8 (C_9/C_{10}), 68.6 (C_6), 62.2 (C_5)

ESIMS *m/z* (%) 1223 $[M+Na]^+$ (20), 477 (100)

(*R*)-156

Benzyl 4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,5,5´,6,6´-hexakis(benzyloxy)-1,1´-(*R*)-biphenyl-2,2´-dicarboxylate]- β-D-Glucopyranoside



$C_{76}H_{64}O_{14}$

MW = 1201,31 Da

No CAS

Yellow foam

m.p. 94-95°C

R_f = 0.45 (4:1 CH_2Cl_2:PET)

$[\alpha]^{21}_D$ = +4.9° (c = 1.03, $CHCl_3$)

IR (neat) ν_{max} 3436 (st), 1719, 1591, 1456, 1364, 1332, 1197, 1094, 1025, 741, 697 cm^{-1}

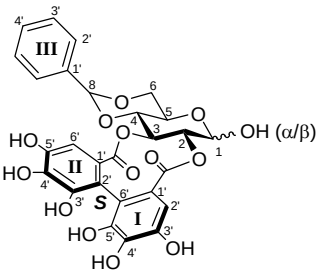
^{1}H NMR (300 MHz, chloroform-d_1) δ 3.44-3.53 (m, 1H, H_5), 3.61-3.67 (m, 1H, H_4), 3.86 (t, J = 10.1 Hz, 1H, H_6), 4.38-4.45 (m, 1H, H_6), 4.60-5.15 (m, 17H, H_1/H_2/H_3/H_9/H_{10}), 5.52 (s, 1H, H_8), 6.81-7.53 (m, 42H, H_{Ar})

^{13}C NMR (75 MHz, chloroform-d_1) δ 167.5/167.0 (C_I=O/C_{II}=O), 152.6/152.6/152.1/152.0 ($C_{3'I}$/$C_{3'II}$/$C_{5'II}$/$C_{5'II}$), 145.5/144.8 ($C_{4'I}$/$C_{4'II}$), 137.4/137.2/136.7/136.6/136.2/136.1 ($C_{1'III}$/$C_{1'IV}$/$C_{1'V}$), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 127.3 (CH_{Ar}), 127.2 (CH_{Ar}), 126.4 (CH_{Ar}), 126.2 (CH_{Ar}), 124.7/124.9 ($C_{1'I}$/$C_{1'II}$), 101.4 (C_8), 99.6 (C_1), 77.6 (C_4), 77.2/75.3/75.2/75.2/75.1/71.4/ 70.9/70.8 (C_2/C_3/C_9/C_{10}), 68.3 (C_6), 66.7 (C_5)

ESIMS *m/z* (%) 1223 $[M+Na]^+$ (6), 477 (100)

(*S*)-158

4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,5,5´,6,6´-hexakis(hydroxy)-1,1´-(*S*)-biphenyl-2,2´-dicarboxylate]-β-D-Glucopyranose



$C_{27}H_{22}O_{14}$

MW = 570,46 Da

No CAS

A solution of (*S*)-**156** (1.99 g, 1.66 mmol) and 10% Pd/C (800 mg) in anhydrous THF (100 mL) was purged 3 times with H_2. The mixture was stirred at room temperature under H_2 for 48 hours, filtered through Celite®. The filter cake was then washed with THF (100 mL). Concentration *in vacuo* give (*S*)-**158** (1:1 mixture of α and β anomers) as a beige foam (947 mg, 100%).

m.p. 210.5°C (decomposition)

R_f = 0.38 (RP-C_{18}; 30:70:0.1 H_2O:MeOH:HCOOH)

IR (neat) 3751, 3496, 3281, 2930, 1743, 1620, 1452, 1361, 1324, 1190 cm^{-1}

A pure sample of **α-**(*S*)-**158** or **β-**(*S*)-**158** could not be separated, and only assignable peaks from the mixture are listed.

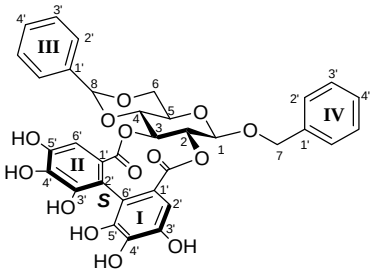
^{1}H NMR (300 MHz, acetone-d_6) δ 3.71-4.34 (m, 8H, $H_{4\alpha}/H_{4\beta}/H_{5\alpha}/H_{5\beta}/H_{6\alpha}/H_{6Q}$), 4.84 (t, J = 8.7 Hz, 1H, $H_{2\beta}$), 5.06 (dd, J = 3.6, 9.3 Hz, 1H, $H_{2\alpha}$), 5.15 (d, J = 8.1 Hz, 1H, $H_{1\beta}$), 5.28 (t, J = 9.6 Hz, 1H, $H_{3\beta}$), 5.47 (d, J = 3.6 Hz, 1H, $H_{1\alpha}$), 5.53 (t, J = 9.6 Hz, 1H, $H_{3\alpha}$), 5.73 (s, 2H, $H_{8\alpha}/H_{8\beta}$), 6.55/6.56/6.58/6.59 (4 s, 4H, $H_{2'I\alpha}/H_{2'I\beta}/H_{6'II\alpha}/H_{6'II\beta}$), 7.37-7.52 (m, 10H, H_{Ar})

^{13}C NMR (75 MHz, acetone-d_6) δ 169.3/169.2/169.0/168.8 (C_I=O/C_{II}=O), 145.2/145.1/144.4/144.4/144.4/144.3/138.7/138.6/136.4/136.3/136.3/136.2 ($C_{3'I}/C_{3'II}/C_{4'II}/C_{4'II}/C_{5'I}$/ $C_{5'II}/C_{1'III}$), 129.7 (CH_{Ar}), 128.9 (CH_{Ar}), 127.3 (CH_{Ar}), 127.2 (CH_{Ar}), 127.0 (Cq), 126.8 (Cq), 126.8 (Cq), 126.7 (Cq), 126.0 (CH_{Ar}), 114.6/114.5/114.4 ($C_{2'II\alpha}/C_{2'II\beta}/C_{6'I\alpha}/C_{6'I\beta}$), 107.7/107.4/107.4/107.3 ($C_{2'I\alpha}/C_{2'I\beta}/C_{6'II\alpha}/C_{6'II\beta}$), 102.4/102.2 ($C_{8\alpha}/C_{8\beta}$), 95.6 ($C_{1\beta}$), 92.4 ($C_{1\alpha}$), 79.1 ($C_{4\alpha}$), 78.5/78.4 ($C_{2\beta}/C_{4\beta}$), 76.6 ($C_{3\beta}$), 75.7 ($C_{2\alpha}$), 74.3 ($C_{3\alpha}$), 69.5/69.2 ($C_{6\alpha}/C_{6\beta}$), 67.7 ($C_{5\beta}$), 63.7 ($C_{5\alpha}$)

ESIMS *m/z* (%) 1139 $[2M-H]^-$ (16), 569 $[M-H]^-$ (100)

(*S*)-<u>160</u>

Benzyl 4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,5,5´,6,6´-hexakis(hydroxy)-1,1´-(*S*)-biphenyl-2,2´-dicarboxylate]-β-D-Glucopyranoside



$C_{34}H_{28}O_{14}$

MW = 660,58 Da

CAS : [176330-22-6]

Brown oil

Partially deprotected product obtained during hydrogenation of (*S*)-**156**

R_f = 0.11 (RP-C_{18}; 30:70:0.1 H_2O:MeOH:HCOOH)

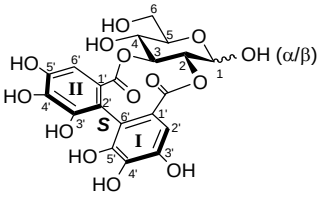
^{1}H NMR (300 MHz, acetone-d_6) δ 3.76 (dt, J = 4.8, 9.5 Hz, 1H, H_5), 3.94 (t, J = 10.3 Hz, 1H, H_6), 4.01 (t, J = 9.6 Hz, 1H, H_4), 4.39 (dd, J = 4.7, 10.2 Hz, 1H, H_6), 4.79 and 4.94 (AB, J_{AB} = 12.4 Hz, 2H, H_7), 4.95 (t, J = 9.1 Hz, 1H, H_2), 5.07 (d, J = 8.1 Hz, 1H, H_1), 5.30 (t, J = 9.5 Hz, 1H, H_3), 5.75 (s, 1H, H_8), 6.56 (s, 1H, $H_{2'I}$ or $H_{6'II}$), 6.58 (s, 1H, $H_{2'I}$ or $H_{6'II}$), 7.33-7.51 (m, 10H, H_{Ar})

^{13}C NMR (75 MHz, acetone-d_6) δ 169.4/168.8 (C_I=O/C_{II}=O), 145.3/145.2/144.6/138.6/138.5/136.5/ 136.4 ($C_{3'I}$/$C_{3'II}$/$C_{4'II}$/$C_{4'II}$/$C_{5'I}$/$C_{5'II}$/$C_{1'III}$/$C_{1'IV}$), 129.8 (CH_{Ar}), 129.3 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.3 (CH_{Ar}), 126.7/126.6 ($C_{1'I}$/$C_{1'II}$), 114.8/114.6 ($C_{2'II}$/$C_{6'I}$), 107.4/107.4 ($C_{2'I}$/$C_{6'II}$), 102.3 (C_8), 100.3 (C_1), 78.3 (C_4), 77.0 (C_2), 76.6 (C_3), 71.5 (C_7), 69.1 (C_6), 67.8 (C_5)

ESIMS *m/z* (%) 1319 $[2M-H]^-$ (12), 659 $[M-H]^-$ (100)

(*S*)-<u>161</u>

2,3-[4,4´,5,5´,6,6´-hexakis(hydroxy)-1,1´-(*S*)-biphenyl-2,2´-dicarboxylate]-β-D-glucopyranose



$C_{20}H_{18}O_{14}$

MW = 482,35 Da

CAS : [7243-72-3]

(α : [83541-37-1]; β : [83541-38-2]; open form : [121153-24-0; 81571-73-5; 36378-47-9])

Pale yellow foam

***R*$_f$** = 0.73 (RP-C_{18}; 30:70:0.1 H_2O:MeOH:HCOOH)

IR (neat) ν_{max} 3387, 2963, 2927, 2857, 1744, 1620, 1445, 1365, 1314, 1230, 1182, 1084, 1037 cm^{-1};

^{1}H-NMR (300 MHz, acetone-d_6/D_2O 8:1) δ 6.68-6.58 (2 s, 4H, H2'Iα/H2'Iβ/H6'IIα/H6'IIβ), 5.42-5.35 (m, 2H, H1α and H3α), 5.05-4.96 (m, 2H, H1β and H3β), 4.91 (dd, J = 3.6, 9.6 Hz, 1H, H2α), 4.70 (dd, J = 8.1, 9.4 Hz, 1H, H2β), 4.03-3.47 (m, 8H, H4α/H4β/H5α/H5β/H6α/H6β) 3.47-3.98 (m, 8Hα,β);

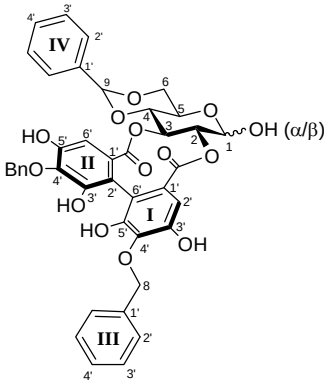
^{13}C-NMR (75 MHz, acetone-d_6/D_2O 8:1) δ 169.6/169.5/169.1/168.9 (C_I=O/C_{II}=O), 145.1/145.0/145.0/144.9/144.3/144.2/144.1/136.1/136.0/130.3/129.5/129.3/129.2/ 128.7/127.6/127.4/127.1/125.4/114.5/114.5/114.4/107.3 ($C_{2'II\alpha}$/$C_{2'II\beta}$/$C_{3'I\alpha}$/$C_{3'I\beta}$/$C_{3'II\alpha}$/$C_{3'II\beta}$/$C_{4'I\alpha}$/$C_{4'I\beta}$/$C_{4'II\alpha}$/$C_{4'II\beta}$/$C_{5'I\alpha}$/$C_{5'I\beta}$/$C_{5'II\alpha}$/$C_{5'II\beta}$/$C_{6'I\alpha}$/$C_{6'I\beta}$), 107.7/107.6 (CH_{ar}), 94.8 ($C_{1\beta}$), 91.5 ($C_{1\alpha}$), 80.7 ($C_{3\beta}$), 78.3 ($C_{3\alpha}$), 77.8 ($C_{2\beta}$), 77.7 ($C_{2\alpha}$), 73.0/69.0/68.7/68.4 ($C_{4\alpha}$/$C_{4\beta}$/$C_{5\alpha}$/$C_{5\beta}$), 62.3/62.2 ($C_{6\alpha}$/$C_{6\beta}$);

ESIMS *m/z* (%): 481 (100) $[M-H]^-$;

HRMS (ESI-TOF) calcd for $C_{20}H_{17}O_{14}$ $[M-H]^-$ 481.0618, found 481.0630.

(*S*)-<u>173</u>

4,6-[(*R*)-phenylmethylene]cyclic 2,3-[4,4´,6,6´-tetrakis(hydroxy)-5,5´-dibenzyloxy-1,1´-(*S*)-biphenyl-2,2´-dicarboxylate]-β-D-Glucopyranose



$C_{41}H_{34}O_{14}$

MW = 750,70 Da

No CAS

To a stirred solution of $CuCl_2$ (179 mg, 1.33 mmol, 5 eq) in dry MeOH (3 mL), *n*-butylamine (525 µL, 5.30 mmol, 20 eq) was added at room temperature, and the mixture was stirred for 30 minutes. To this blue solution, a solution of **159b** (200 mg, 0.265 mmol, 1 eq) in dry MeOH (3 mL) was added and the mixture was stirred for 45 minutes. Addition of 0.5M aqueous solution of HCl (5 mL) quenched the reaction. The mixture was extracted with EtOAc (2 x 20 mL). The organic layer was successively washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (1:1 PET:EtOAc) to give (*S*)-**173** (1:1 mixture of α and β anomers) as a brown powder (107 mg, 54%).

m.p. 165-166°C

***R*$_f$** = 0.38 (2:3 PET:EtOAc) only one product is seen by TLC

IR (neat) ν_{max} 3480, 2954, 2863, 1750, 1455, 1369, 1184, 1096 cm^{-1}

ESIMS *m/z* (%) 1499 $[2M-H]^-$ (46), 749 $[M-H]^-$ (100)

HRMS calcd for $C_{41}H_{33}O_{14}$ $[M-H]^-$ 749.1870, found 749.1873

A pure sample of **α-**(*S*)-**256** or **β-**(*S*)-**256** could not be separated, and only assignable peaks from the mixture are listed.

^{1}H NMR (300 MHz, acetone-d_6) δ 3.73 (dt, J = 4.7, 9.5 Hz, 1H, $H_{5\beta}$), 3.88 (t, J = 9.6 Hz, 1H, $H_{6\beta}$ or $H_{6\alpha}$), 3.89 (t, J = 10.1 Hz, 1H, $H_{6\beta}$ or $H_{6\alpha}$), 3.98 (t, J = 9.4 Hz, 1H, $H_{4\beta}$), 4.00 (t, J = 9.4 Hz, 1H, $H_{4\alpha}$), 4.16 (dd, J = 4.7, 9.6 Hz, 1H, $H_{5\alpha}$), 4.22-4.27 (m, 1H, $H_{6\alpha}$), 4.33 (dd, J = 4.8, 10.1 Hz, 1H, $H_{6\beta}$), 4.85 (dd, J = 8.2, 9.2 Hz, 1H, $H_{2\beta}$), 5.07 (dd, J = 3.6, 9.3 Hz, 1H, $H_{2\alpha}$), 5.12-5.21 (m, 1H, $H_{1\beta}$), 5.15 (s, 4H, $H_{8\alpha}/H_{8\beta}$), 5.17 (s, 4H, $H_{8\alpha}/H_{8\beta}$), 5.30 (t, J = 9.6 Hz, 1H, $H_{3\beta}$), 5.50 (d, J = 3.2 Hz, 1H, $H_{1\alpha}$), 5.55 (t, J = 9.6 Hz, 1H, $H_{3\alpha}$), 5.74 (s, 2H, $H_{9\alpha}/H_{9\beta}$), 6.55 (s,

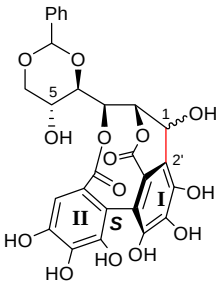
1H, $H_{2'I\beta}$ or $H_{6'II\beta}$), 6.56 (s, 1H, $H_{2'I\beta}$ or $H_{6'II\beta}$), 6.58 (s, 1H, $H_{2'I\alpha}$ or $H_{6'II\alpha}$), 6.58 (s, 1H, $H_{2'I\alpha}$ or $H_{6'II\alpha}$), 7.29-7.56 (m, 30H, $H_{2'III}/H_{3'III}/H_{4'III}/H_{2'IV}/H_{3'IV}/H_{4'IV}$)

^{13}C NMR (75 MHz, acetone-d_6) δ 169.0/168.9 ($C_{I\beta}$=O/$C_{II\beta}$=O), 168.7/168.5 ($C_{I\alpha}$=O/$C_{II\alpha}$=O), 150.4/150.3/150.2/150.1/150.1 ($C_{3'I}/C_{3'II}/C_{5'I}/C_{5'II}$), 138.7 ($C_{4'I}/C_{4'II}$), 131.3/131.1/131.1/131.0 ($C_{1'III}$), 138.6 ($C_{1'IV}$), 129.8 (CH_{Ar}), 129.2 (CH_{Ar}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.7 (CH_{Ar}), 127.3/127.3 ($C_{2'IV}/C_{3'IV}$), 136.8/136.8/136.7 ($C_{1'I}/C_{1'II}$), 114.0/114.0/113.9/113.8 ($C_{2'II}/C_{6'I}$), 107.1/107.1/106.9/106.8 ($C_{2'I}/C_{6'II}$), 102.4 ($C_{9\beta}$), 102.2 ($C_{9\alpha}$), 95.6 ($C_{1\beta}$), 92.4 ($C_{1\alpha}$), 79.1 ($C_{4\alpha}$), 78.4 ($C_{4\beta}$), 78.4 ($C_{2\beta}$), 76.6 ($C_{3\beta}$), 75.6 ($C_{2\alpha}$), 74.8 ($C_{8\alpha}/C_{8\beta}$), 74.2 ($C_{3\alpha}$), 69.5 ($C_{6\alpha}$), 69.2 ($C_{6\beta}$), 67.7 ($C_{5\beta}$), 63.7 ($C_{5\alpha}$)

Synthons A

175

7-methanodibenzo[f, h][1,4]dioxecin-5,10-dione, 7, 8- *O*-benzylidene, 2, 3, 12, 13, 14, 15-heptahydroxy-8-(1, 2, 3-trihydroxypropyl)-stereoisomer



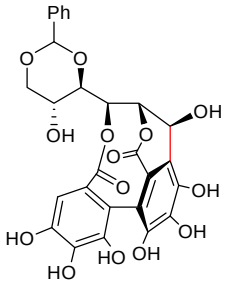
$C_{41}H_{34}O_{14}$

MW = 570,46 Da

No CAS

Compound (S)-**158** (60 mg, 0.10 mmol) was dissolved in 9 mL of phosphate buffer solution (0.2 M, pH 5.3) and stirred at 65°C for 4 days. The reaction mixture was then lyophylized and purified by preparative HPLC (microsorb C-18; solvent A: H2O + 0.1% HCOOH, solvent B: MeCN + 0.1% HCOOH; method: gradient 0-100% B in 25 min; flow: 20 mL/min) to give **161** as a pale yellow solid (9 mg, 16%) and β-**157** (11 mg, 23%). Epimer α-**157** was only obtained as an impure fraction (4 mg, brown solid)

β–175



$C_{27}H_{22}O_{14}$

MW = 750,70 Da

No CAS

m.p. 179.3-180.5°C;

***R*$_f$** = 0.37 (RP-TLC, 30:20:0.1 H_2O/MeCN/HCOOH);

***R*$_t$** = 6.8 min (Pursuit 3 C-18, 150 x 4.6 mm, solvent A: H_2O + 0.1% HCOOH, solvent B: MeCN + 0.1% HCOOH; method: gradient 0-100% of B in 10 min; flow: 1 mL/min);

$[\alpha]^{21}_D$ = -56.5° (c = 0.23, MeOH);

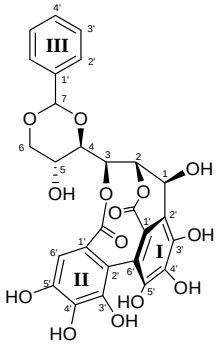
IR (neat) ν_{max} 3385, 1721, 1599, 1463, 1374, 1320, 1190, 1072 cm^{-1};

^{1}H NMR (300 MHz, acetone-*d*$_6$) δ 7.31-7.52 (m, 5H, $H_{2'III}$/$H_{3'III}$/$H_{4'III}$), 6.43 (s, 1H, $H_{6'II}$), 5.65 (s, 1H, H_7), 5.10 (t, *J* = 2.5 Hz, 1H, H_2), 4.87 (d, *J* = 2.1 Hz, 1H, H_1), 4.76 (t, 1H, *J* = 2.8 Hz, H_3), 4.12 (dd, 1H, *J* = 4.4, 9.6 Hz, H_6), 3.95 (dd, *J* = 3.0, 8.9 Hz, 1H, H_4), 3.59-3.75 (m, 2H, H_5/H_6);

^{13}C NMR (75 MHz, acetone-*d*$_6$) δ 171.0 (C_{II}=O), 164.6 (C_I=O), 146.5 ($C_{5'I}$), 145.9 ($C_{5'II}$), 143.9 ($C_{3'I}$), 144.4 ($C_{3'II}$), 139.2 ($C_{1'III}$), 137.3 ($C_{4'I}$/$C_{4'II}$), 134.9 ($C_{4'I}$/$C_{4'II}$), 129.3 ($C_{4'III}$), 128.7 ($C_{3'III}$), 128.3 ($C_{1'II}$), 127.1 ($C_{2'III}$), 124.0 ($C_{1'I}$), 118.8 ($C_{2'I}$), 116.2/115.4 ($C_{2'II}$/$C_{6'I}$), 105.5 ($C_{6'II}$), 101.7 (C_8), 83.3 (C_4), 80.0 (C_2), 72.6 (C_3), 71.5 (C_6), 65.7 (C_1), 62.5 (C_5);

ESIMS *m/z* (%)1139 (10) $[2M-H]^-$, 569 (100) $[M-H]^-$;

HRMS (ESI-TOF) calcd for $C_{27}H_{21}O_{14}$ $[M-H]^-$ 569.0931, found 569.0947

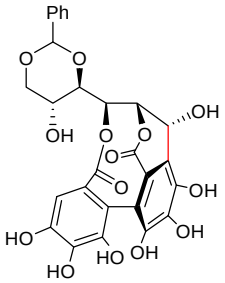


β-175

position	δ_H (mult., *J* in Hz)	δ_C (mult.)	HMQC[a]	HMBC[b]
		glucose		
1	4.86 (d, *1.7*)	65.6	C_1	H_2, H_3, C_2, $C_{1'I}$, $C_{2'I}$, $C_{3'I}$
2	5.10 (br)	80.0	C_2	H_1, C_1, C_4, $C_{2'I}$, C_I=O
3	4.78 (t, *2.6*)	72.5	C_3	H_4, C_1, C_{II}=O
4	3.94 (dd, *2.6*, *8.7*)	83.3	C_4	H_2, H_6, H_7, C_3, C_7
5	3.59-3.73 (m)	62.4	C_5	H_4, H_6, H_7
6	3.59-3.73 (m) 4.21 (dd, *4.0*, *9.4*)	71.5	C_6	H_7, C_4, C_5
		aromatics I and II		
$1'_I$		124.0		H_1
$1'_{II}$		128.7		
$2'_I$		118.8		H_1, H_2
$2'_{II}$		115.4 or 116.2		$H_{6'II}$
$3'_I$		144.3		H_1
$3'_{II}$		143.8		$H_{6'II}$
$4'_I$		139.1		
$4'_{II}$		139.1		
$5'_I$		146.5		
$5'_{II}$		145.7		$H_{6'II}$
$6'_I$		115.4 or 116.2		
$6'_{II}$	6.41 (s)	105.4	$C_{6'II}$	$C_{2'II}$, $C_{3'II}$, $C_{5'II}$
		benzylidene group		
7	5.64 (s)	101.7	C_7	$H_{2'III}$, $H_{3'III}$, $H_{4'III}$, H_4, C_4, C_5, C_6, $C_{1'III}$, $C_{2'III}$, C_{II}=O
$1'_{III}$		134.8		H_7
$2'_{III}$	7.32-7.52 (m)	128.2	$C_{2'III}$	H_7
$3'_{III}$	7.32-7.52 (m)	129.3	$C_{3'III}$	$H_{2'III}$, $H_{3'III}$, $H_{4'III}$
$4'_{III}$	7.32-7.52 (m)	129.4	$C_{4'III}$	$H_{2'III}$, $H_{3'III}$, $H_{4'III}$
		carbonyls		
C_I=O		164.6		H_2
C_{II}=O		171.0		H_3, H_7

[a] Carbons correlate with the protons resonating at the ppm value indicated in the δ_H column.
[b] Indicated carbons and protons correlated with the protons or carbons at the position indicated in the left column.

α–<u>175</u>



$C_{27}H_{22}O_{14}$

MW = 750,70 Da

No CAS

R_f = 0.52 (RP-C18; 3:2 H_2O:ACN 0.1% HCOOH double elution);

R_t = 13.15 min (Pursuit 3 C-18, 150 x 4.6 mm, solvent A: H_2O + 0.1% HCOOH, solvent B: MeCN + 0.1% HCOOH; method: gradient 0-100% of B in 10 min; flow: 1 mL/min);

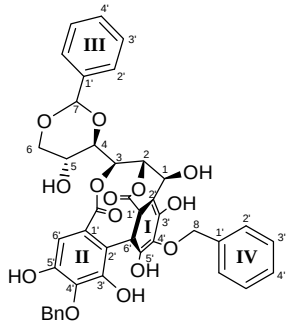
IR (neat) ν_{max} 3385, 1721, 1599, 1463, 1374, 1190, 1072 cm^{-1};

^{1}H NMR (300 MHz, acetone-d_6) δ 5.63 (s, 1H, H_7), 5.60 (d, *J* = 4.6, 1H, H_1), 5.35 (t, 1H, *J* = 2.6 Hz, H_3), 4.97 (dd, *J* = 2.81, 4.53, Hz, 1H, H_2), 4.21 (dd, 1H, *J* = 4.8, 10.2 Hz, H_6), 3.78-3.60 (m, 3H, H_4/H_5/H_6);

^{13}C NMR (75 MHz, acetone-d_6) δ 138.8 ($C_{1'III}$), 129.3 ($C_{4'III}$), 128.6 ($C_{3'III}$/ $C_{5'III}$), 126.9 ($C_{2'III}$ / $C_{6'III}$), 104.9 ($C_{6'II}$), 101.6 (C_7), 84.4 (C_4), 76.1 (C_2), 71.2 (C_6), 70.0 (C_3), 68.0 (C_1), 61.7 (C_5)

ESIMS *m/z* (%) 569 (100) $[M-H]^-$;

176β



$C_{41}H_{34}O_{14}$

MW = 570,46 Da

No CAS

A solution of (S)-**159** (12 mg, 0.016 mmol) in phosphate buffer 0.2 M at pH = 7.5 (800 µL) and MeOH (800 µL) was stirred at 50°C for 2 hours and 30 minutes. The reaction was followed by analytic HPLC (reverse phase, H_2O:MeCN). The mixture was then acidified to pH = 3 with aqueous solution of HCl (2M) and the excess of MeOH was evaporated. The reaction mixture was then purified by preparative HPLC (microsorb C18 250 x 41.4 mm; solvent A: H_2O+0.1% HCOOH, solvent B: MeCN+0.1%HCOOH; method: 40-100% of B in 20 min, 20 mL/min) to give **176** as a white solid (3 mg, 25%).

m.p. 203°C (decomposition)

Rt = 5.9 min [HPLC, Column : Pursuit 3 C18 (150 x 4,6 mm), Solvents : A : H2O + 0.1% HCOOH, B : MeCN + 0.1% HCOOH, Méthod : gradient 40 to 100% B in 10 min, Flow : 1mL/min, UV : 280nm]

$[\alpha]^{21}_{D}$ = +16.7° (c = 0.54, acetone)

IR (neat) ν_{max} 1719, 1628, 1456, 1376, 1215, 1179, 1161, 1110, 1073, 750, 701 cm^{-1}

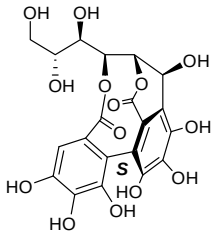
^{1}H NMR (300 MHz, acetone- d_6) δ 3.60-3.69 (m, 1H, H_6), 3.73 (dt, J = 4.8, 9.4 Hz, 1H, H_5), 3.95 (dd, J = 3.0, 8.9 Hz, 1H, H_4), 4.22 (dd, J = 4.7, 10.0 Hz, 1H, H_6), 4.79 (t, J = 2.9 Hz, 1H, H_3), 4.87 (d, J = 2.1 Hz, 1H, H_1), 5.07-5.23 (m, 5H, H_2/H_8), 5.65 (s, 1H, H_7), 6.47 (s, 1H, $H_{6'II}$), 7.31-7.58 (m, 15H, $H_{2'III}$/$H_{3'III}$/$H_{4'III}$/$H_{2'IV}$/$H_{3'IV}$/$H_{4'IV}$)

13C NMR (75 MHz, acetone- d_6) δ 170.4 ($C_{II=O}$), 164.4 ($C_{I=O}$), 151.9 ($C_{5'I}$), 151.0 ($C_{5'II}$), 149.6/149.5 ($C_{3'I}$/$C_{3'II}$), 139.1/138.8/138.4 ($C_{1'III}$/$C_{1'IV}$), 138.0 ($C_{4'I}$), 135.8 ($C_{4'II}$), 132.6 ($C_{1'I}$/$C_{1'II}$), 129.4/129.3/129.1/129.0/128.8/128.8/128.6 ($C_{4'III}$/$C_{2'IV}$/$C_{3'IV}$/$C_{4'IV}$), 127.1 ($C_{2'III}$/$C_{3'III}$), 118.3 ($C_{2'I}$), 116.0/115.6 ($C_{2'II}$/$C_{6'I}$), 105.3 ($C_{6'II}$), 101.7 (C_7), 83.2 (C_4), 80.2 (C_2), 75.2(C_8), 74.8 (C_8), 72.4 (C_3), 71.6 (C_6), 65.5 (C_1), 62.4 (C_5)

ESIMS m/z (%) 1499 [2M-H]- (5), 749 [M-H]- (100)

179

5-*O*-Desgalloyl epipunicacortein A



$C_{20}H_{18}O_{14}$

MW = 482,35 Da

No CAS

In a dry 10 mL schlenk, compound β-**175** (17,7 mg, 0.031 mmol) was dissolved in dry THF (3.5 ml) under argon atmosphere and $Pd(OH)_2/C$ (12 mg) was added. The reaction mixture was repeatedly saturated with H_2 and the reaction was followed by C18-TLC (3:2 H_2O/MeCN, 0.1% HCOOH). Additional amount of $Pd(OH)_2/C$ was added during the reaction in order to consume all the starting material until a total amount of 51.5 mg. After 96 hours, the starting material was completely consumed and the reaction mixture was filtered through a filter (Acrodisc 13 mm syringe filter, with 0.2 µm nylon membrane) and the palladium was washed with THF (3 x 3 mL) then with acetone (3 x 3 mL). The solvent was removed under vacuum to give 13,8 mg (93%) of a yellow amorphous solid. The crude was purified for analysis on Sephadex LH-20 (H_2O) to give 1.1 mg of pure compound **179**

Rf = 0.90 (RP-TLC, 30:20:0.1 H_2O/MeCN/HCOOH)

Rt = 3.2 min (Pursuit 3 C-18, 150 x 4.6 mm, solvent A: H_2O + 0.1% HCOOH, solvent B: MeCN + 0.1% HCOOH; method: isocratic 0% of B in 5 min then gradient 0-100% of B in 13 min; flow: 1 mL/min)

$[\alpha]^{21}_D$ = +16.7° (c = 0.54, acetone)

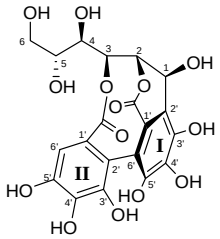
IR (neat) ν_{max} 1719, 1628, 1456, 1376, 1215, 1179, 1161, 1110, 1073, 750, 701 cm^{-1}

^{1}H NMR (400 MHz, acetone-d_6/D_2O 8:1) δ 3.47-3.76 (m, 4H), 4.66 (t, *J* = 2.8 Hz, 1H), 4.82 (d, *J* = 1.8 Hz, 1H), 4.91 (t, *J* = 2.3 Hz, 1H), 6.40 (s, 1H)

^{13}C NMR (100 MHz, acetone-d_6/D_2O 8:1) δ 170.8, 166.5, 146.6, 145.5, 143.9, 143.5, 138.2, 134.8, 127.7, 122.4, 118.4, 116.2, 105.2, 81.3, 74.0, 73.7, 64.9, 63.6, 61.9

ESIMS *m/z* (%): 481 (100) $[M-H]^-$

HRMS (ESI-TOF) calcd for $C_{20}H_{19}O_{14}$ $[M+H]^+$ 483.0775, found 483.0786.



position	δ_H (mult., *J* in Hz)	δ_C (mult.)	HMQC[a]	HMBC[b]
		glucose		
1	4.86 (d, *1.8*)	64.9	C_1	$C_{1'I}$, $C_{2'I}$, $C_{3'I}$
2	4.91 (t, *2.3*)	81.3	C_2	C_3, $C_{2'I}$, C_I=O
3	4.66 (t, *2.8*)	74.0	C_3	H_2
4	3.47-3.76 (m)	73.7	C_4	
5	3.47-3.76 (m)	71.9	C_5	H_6
6	3.47-3.76 (m)	63.6	C_6	C_5
		aromatics I and II		
$1'_I$		122.4		H_1
$1'_{II}$		127.7		
$2'_I$		118.4		H_1, H_2
$2'_{II}$		116.2		$H_{6'II}$
$3'_I$		143.5 / 143.9		H_1
$3'_{II}$				
$4'_I$		138.2		
$4'_{II}$		134.5		$H_{6'II}$
$5'_I$		146.6		
$5'_{II}$		145.5		$H_{6'II}$
$6'_I$		116.2		
$6'_{II}$	6.40 (s)	105.2	$C_{6'II}$	$C_{2'II}$, $C_{4'II}$, $C_{5'II}$, C_{II}=O
		carbonyls		
C_I=O		166.5		H_2
C_{II}=O		170.8		$H_{6'II}$

[a] Carbons correlate with the protons resonating at the ppm value indicated in the δ_H column.
[b] Indicated carbons and protons correlated with the protons or carbons at the position indicated in the left column.

Annex 1

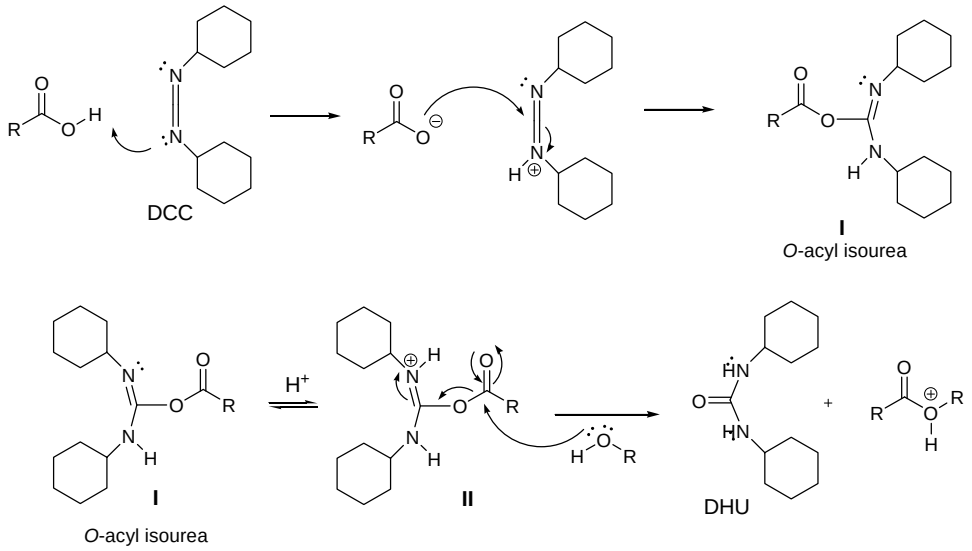
Steglich Esterification

The Steglich Esterification is a mild reaction, which allows the esters and amide formation by reaction with carboxylic acids from sterically demanding and acid labile substrates. It consists in the introduction of dicycloehylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as catalyst.[168]

Mechanism of the Steglich Esterification

The first step is the activation of the carboxylic acid.

DCC (dicyclohexylcarbodiimide) and the carboxylic acid are able to form an *O*-acylisourea (**I**) intermediate, which offers reactivity similar to the corresponding carboxylic acid anhydride. The alcohol may then add to the activated carboxylic acid to form the stable dicyclohexylurea (DHU) and the ester:

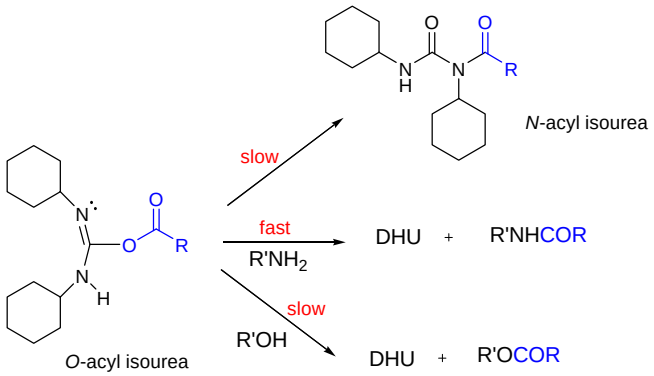


Scheme 73. DCC catalyzed esterification

In practice, the reaction with carboxylic acids, DCC and amines leads to amides without problems, while the addition of approximately 5 mol-% 4-dimethylaminopyridine (DMAP) is crucial for the efficient formation of esters.

N-Acylureas (Scheme 74), which may be quantitatively isolated in the absence of any nucleophile, are the side products of an acyl migration that takes place slowly. Strong

nucleophiles such as amines react readily with the *O*-acylisourea and therefore need no additives:



Scheme 74.

A common explanation of the DMAP (Figure 43) acceleration suggests that DMAP, as a stronger nucleophile than the alcohol, reacts with the protoned *O*-acylisourea (**II**) leading to a reactive amide ("active ester").

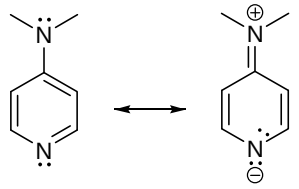
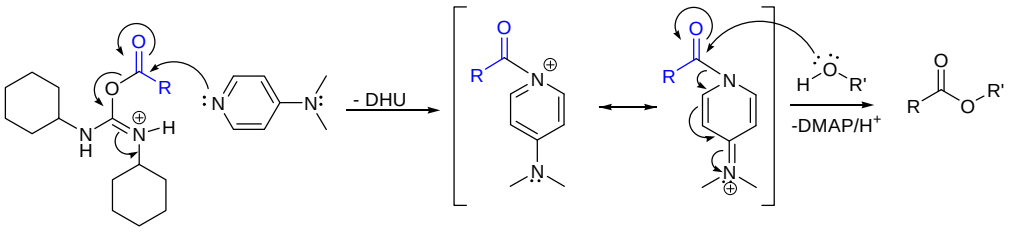


Figure 43. The dimethylamino group acts as an electron-donor substituent, increasing both the nucleophilicity and the basicity of the pyridine nitrogen.

This intermediate cannot form intramolecular side products but reacts rapidly with alcohols. DMAP acts as an acyl transfer reagent in this way, and subsequent reaction with the alcohol gives the ester.



Scheme 75. DCC-DMAP catalyzed esterification

In any case the proton transfer step (from **I** to **II**, Scheme 73) is essential to the success of the reaction. It has been observed that the failure might conceivably arise from low effective concentrations of alcohol and acid (both proton sources). Therefore this approach to esterification was reexamined in the presence of additives (specifically various amine hydrochlorides) to mediate such proton-transfer steps. Best results were obtained in media where such salts were totally soluble, and the use of DMAP-HCl as the amine hydrochloride proved most efficient and convenient.[107]

Annex 2

Palladium catalyzed hydrogenolysis

In the manufacture of pharmaceuticals and fine chemicals there is often a requirement for a protection strategy to minimize possible side reactions during a synthesis.

Small, easily removed protection, available for a range of functional groups, is highly desired. One such easily removed protection is derived from the facile catalytic hydrogenolysis of benzylic groups. An analysis of the published medicinal chemical routes shows that over 1000 drug syntheses currently use this type of protection.

The classic functional groups requiring protection are alcohols, acids and amines.

Simple cleavage of these protecting groups is critical.

Cleavage by catalytic hydrogenation can be performed with good selectivity under mild conditions using a heterogeneous Palladium on Carbon (Pd/C) catalyst in the presence of hydrogen gas or a hydrogen transfer agent, e.g. ammonium formate or isopropanol. Efficient removal depends on selection of the most active and selective catalyst, and an optimized set of reaction conditions as:

- nature and amount of catalyst
- solvent

Nature of catalyst - Pd/C and $Pd(OH)_2/C$

Pd/C is formed from the $PdCl_2$ precursor in acidic media through two consecutive processes:

a) absorption of palladium chloride to form surface complexes

b) redox interaction between $PdCl_2$ and carbon with the formation of palladium media particles.

Effect of such stages of catalyst synthesis as drying, calcination, and reduction of the supported precursors to metal has important effects on the activity of the catalysts.

It is for these reasons that commercial Pd/C catalysts exhibit remarkable supplier-dependent disparity in the property and quality. Even different lots of the same brand can often show different catalytic activity. [169,170]

Since the unexpected reactivity would cause serious damage to a synthetic process, especially in multi-step synthesis of complex natural products, therefore, when a Pd/C catalyst is used in an article, the name of the supplier and the product number of the catalyst must be clarified.

Moreover acid sensitive substrates are often degraded by the residual acids.

$Pd(OH)_2$ doesn't presents these disadvantages. It is often preferred to Pd/C.

In certain cases a combination of Pd/C and $Pd(OH)_2$/C serves as better catalysts than either catalysts alone.[171]

Amount of catalyst

The amount of catalyst can be increased in order to increase the reaction rate.

As during the reaction the catalyst is deactivated (impurities on the surface of the catalyst) the best is to remove the old catalyst before make a new addition. Frequently in the literature it is reported for difficult reactions "repeated hydrogenation" (filter off the old catalyst and add a new one).[172]

Solvent

Solvent choice is critical for any debenzylation reaction.

The most used solvent for hydrogenolysis Pd/C catalyzed is methanol. According to the Hughes and Ingold theory of solvent effect, reactions involving dipolar activated complexes are accelerated by polar solvents.

Obviously the solvent is chosen on the basis of the solubility of the starting compound and of the product.

It is for this that sometimes mixtures of solvents are used.[173]

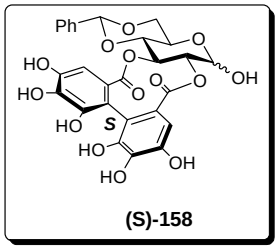
The reaction can be forced by using AcOH as solvent.[172]

Interestingly the reaction can be performed in water.[174]

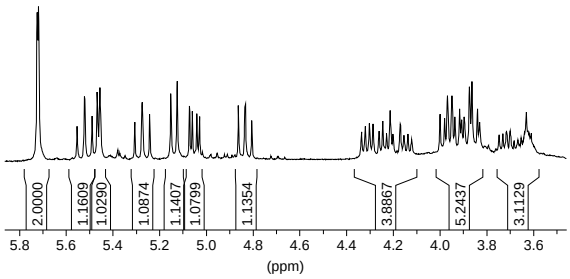
Annex 3

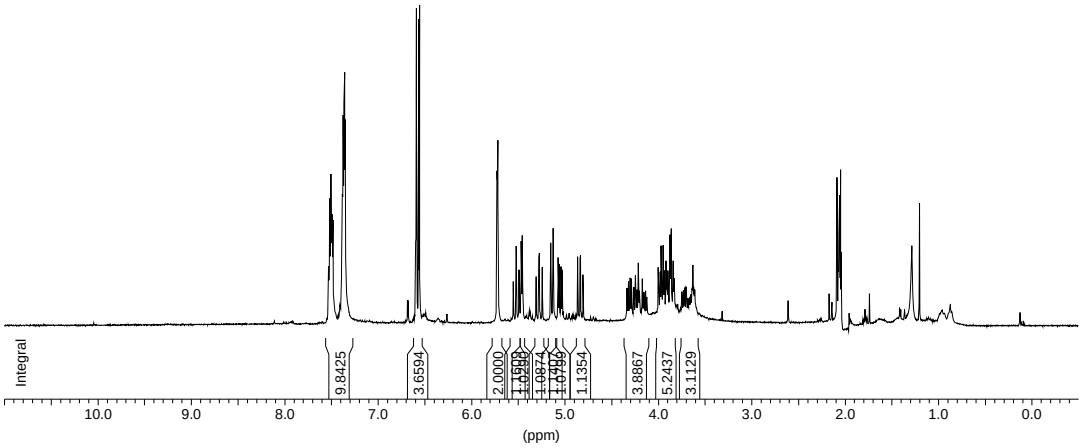
NMR spectra of most significant intermediates of the synthesis

ANB128-3 / acetone / 300 MHz

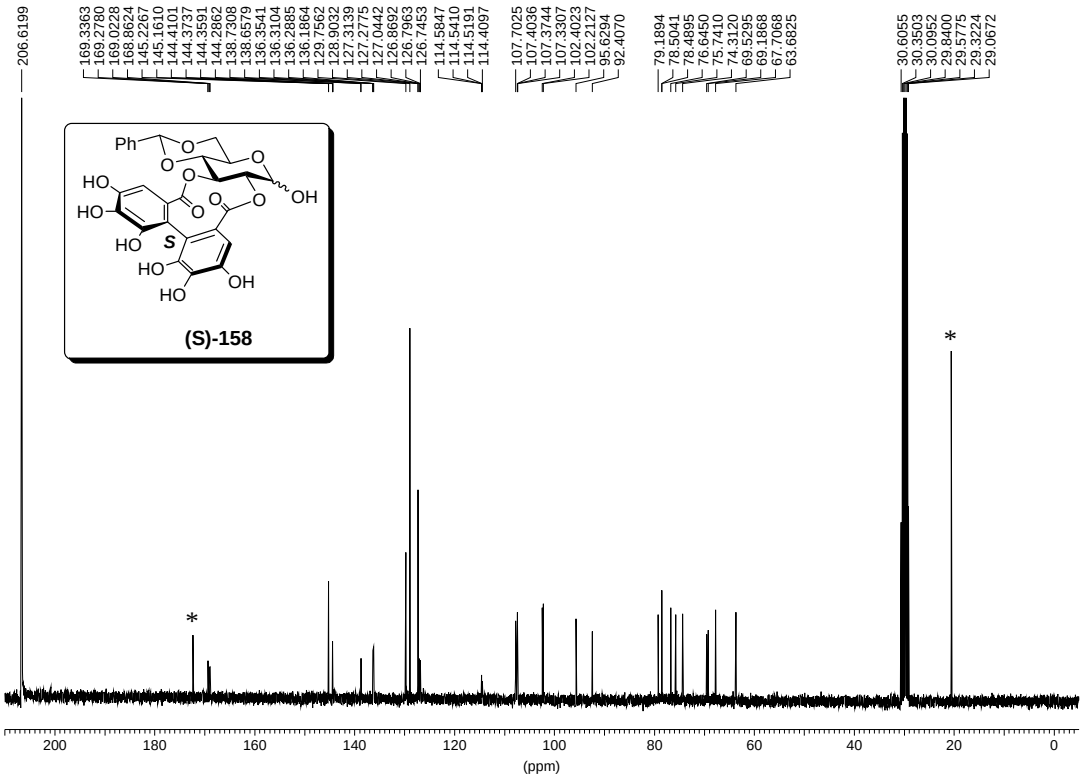


(S)-158



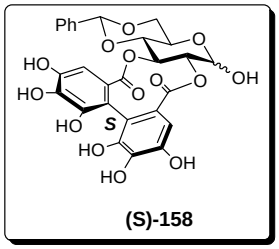


ANB128-3 / acetone / 300 MHz



(S)-158

* Traces of acetic acid in acetone-d_6



(S)-158

Peak Nr.	Data Point	Frequency	PPM	Intensity	%Int.
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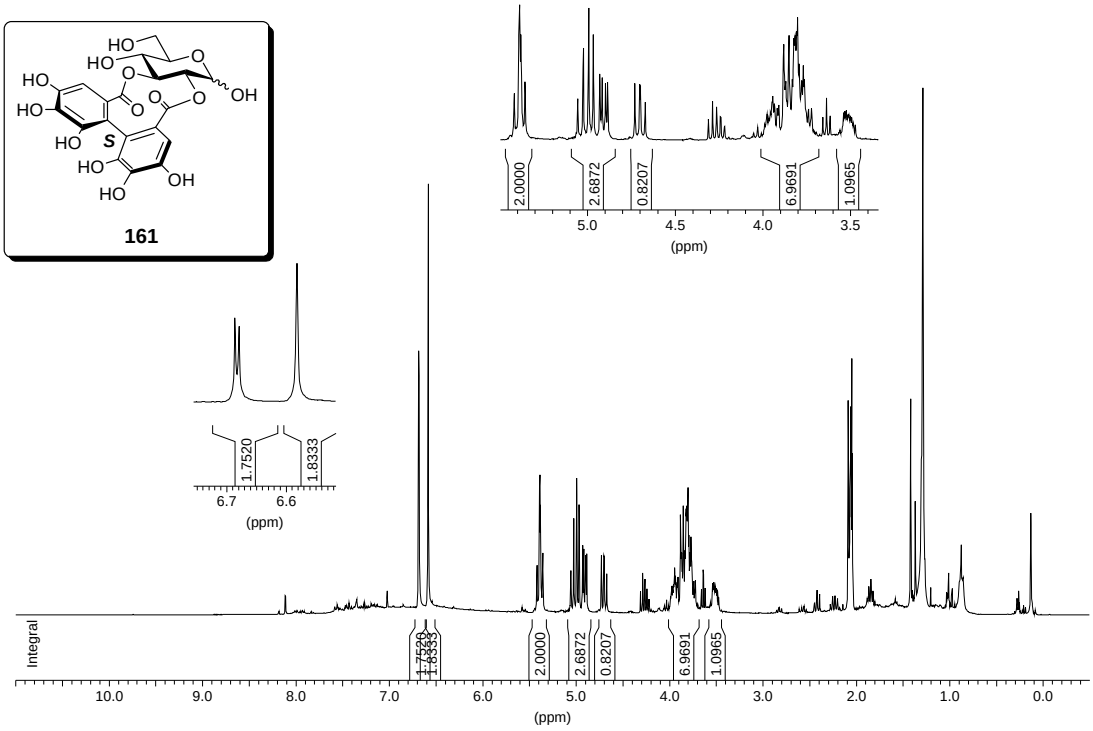
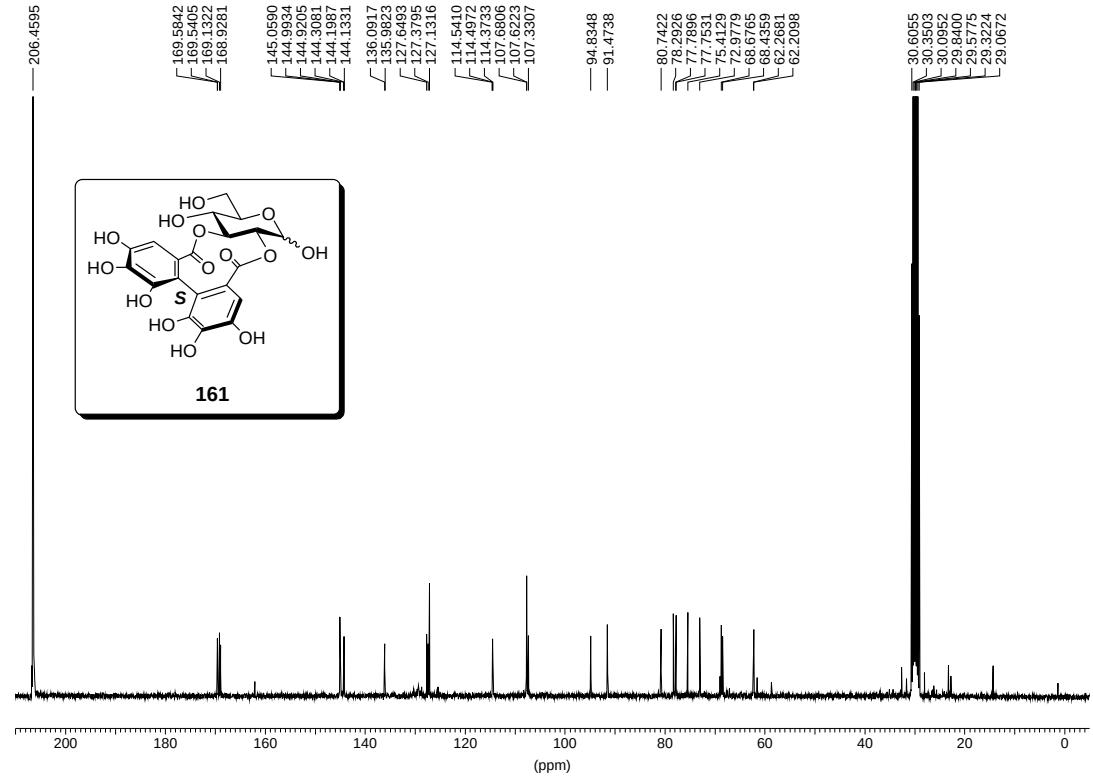
2	7549	2255.78	7.5160	174586320	40.3
3	7568	2252.19	7.5040	206544160	47.7
4	7577	2250.49	7.4984	169035968	39
5	7590	2248.03	7.4902	149004816	34.4
6	7601	2245.96	7.4833	140621104	32.4
7	7745	2218.76	7.3927	64975944	15
8	7754	2217.06	7.3870	92581696	21.4
9	7765	2214.98	7.3801	187511984	43.3
10	7774	2213.28	7.3744	286476928	66.1
11	7791	2210.07	7.3637	301896864	69.6
12	7798	2208.75	7.3593	337196800	77.8
13	7801	2208.19	7.3574	339064768	78.2
14	7809	2206.68	7.3524	274379840	63.3
15	7820	2204.60	7.3455	85839488	19.8
16	9013	1979.30	6.5948	391964832	90.4
17	9024	1977.23	6.5879	429482784	99.1
18	9063	1969.86	6.5634	414873344	95.7
19	9075	1967.60	6.5558	433454944	100
20	10398	1717.75	5.7234	238724000	55.1
21	10407	1716.05	5.7177	251462272	58
22	10669	1666.57	5.5528	58110480	13.4
23	10720	1656.94	5.5208	106006800	24.5
24	10771	1647.31	5.4887	74111752	17.1
25	10806	1640.70	5.4666	112370280	25.9
26	10825	1637.11	5.4547	121519016	28
27	11062	1592.36	5.3056	64956432	15
28	11111	1583.10	5.2747	95896608	22.1
29	11114	1582.54	5.2728	95387600	22
30	11163	1573.28	5.2420	77726944	17.9
31	11307	1546.09	5.1514	110389072	25.5
32	11350	1537.97	5.1243	131730632	30.4
33	11434	1522.11	5.0715	90394880	20.9
34	11453	1518.52	5.0595	82931408	19.1
35	11483	1512.85	5.0407	78949968	18.2
36	11502	1509.27	5.0287	75197984	17.3
37	11766	1459.41	4.8626	91120160	21
38	11809	1451.29	4.8355	87556800	20.2
39	11815	1450.16	4.8318	96364184	22.2
40	11858	1442.04	4.8047	68997144	15.9
41	12603	1301.35	4.3359	47022532	10.8
42	12629	1296.44	4.3196	57374968	13.2
43	12657	1291.15	4.3020	61819312	14.3

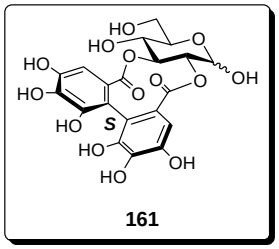
44	12683	1286.24	4.2856	62158920	14.3
45	12723	1278.68	4.2604	49697956	11.5
46	12748	1273.96	4.2447	65708400	15.2
47	12774	1269.05	4.2283	46595772	10.7
48	12799	1264.33	4.2126	82899472	19.1
49	12819	1260.55	4.2000	46670560	10.8
50	12868	1251.30	4.1692	62023180	14.3
51	12893	1246.58	4.1535	44708632	10.3
52	12919	1241.67	4.1371	46337532	10.7
53	12945	1236.76	4.1207	38405772	8.9
54	13138	1200.31	3.9993	75575752	17.4
55	13169	1194.46	3.9798	68966728	15.9
56	13189	1190.68	3.9672	105766432	24.4
57	13218	1185.20	3.9490	106096160	24.5
58	13239	1181.24	3.9358	74312200	17.1
59	13270	1175.38	3.9163	85552160	19.7
60	13284	1172.74	3.9074	69478928	16
61	13303	1169.15	3.8955	74052568	17.1
62	13338	1162.54	3.8735	121343976	28
63	13355	1159.33	3.8628	133959624	30.9
64	13392	1152.35	3.8395	89071200	20.5
65	13406	1149.70	3.8307	69360600	16
66	13539	1124.59	3.7470	45988976	10.6
67	13565	1119.68	3.7306	48270704	11.1
68	13592	1114.58	3.7136	52431392	12.1
69	13614	1110.42	3.6998	53117776	12.3
70	13641	1105.32	3.6828	38039640	8.8
71	13667	1100.41	3.6665	39170560	9
72	13689	1096.26	3.6526	42276380	9.8
73	13693	1095.50	3.6501	37213844	8.6
74	13702	1093.80	3.6444	36595984	8.4
75	13724	1089.65	3.6306	84005200	19.4
76	13736	1087.38	3.6230	54743232	12.6
77	13746	1085.49	3.6167	51439084	11.9
78	13759	1083.04	3.6086	52940884	12.2
79	16198	622.44	2.0739	73114152	16.9
80	16213	619.61	2.0645	119483664	27.6
81	16225	617.34	2.0569	178613616	41.2
82	16236	615.27	2.0500	217127584	50.1
83	16248	613.00	2.0424	140082720	32.3
84	16260	610.73	2.0349	64653696	14.9

ANB091 / acetone + D2O / 300 MHz



ANB091 / acetone+D2O / 300 MHz



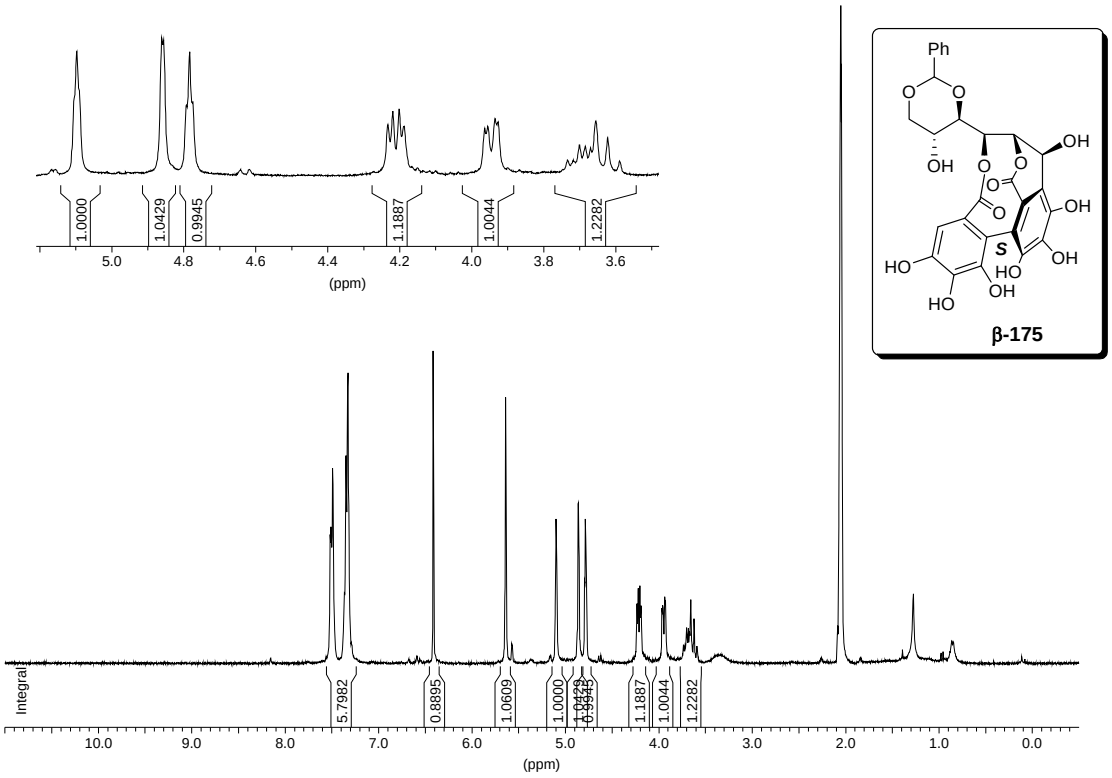


161

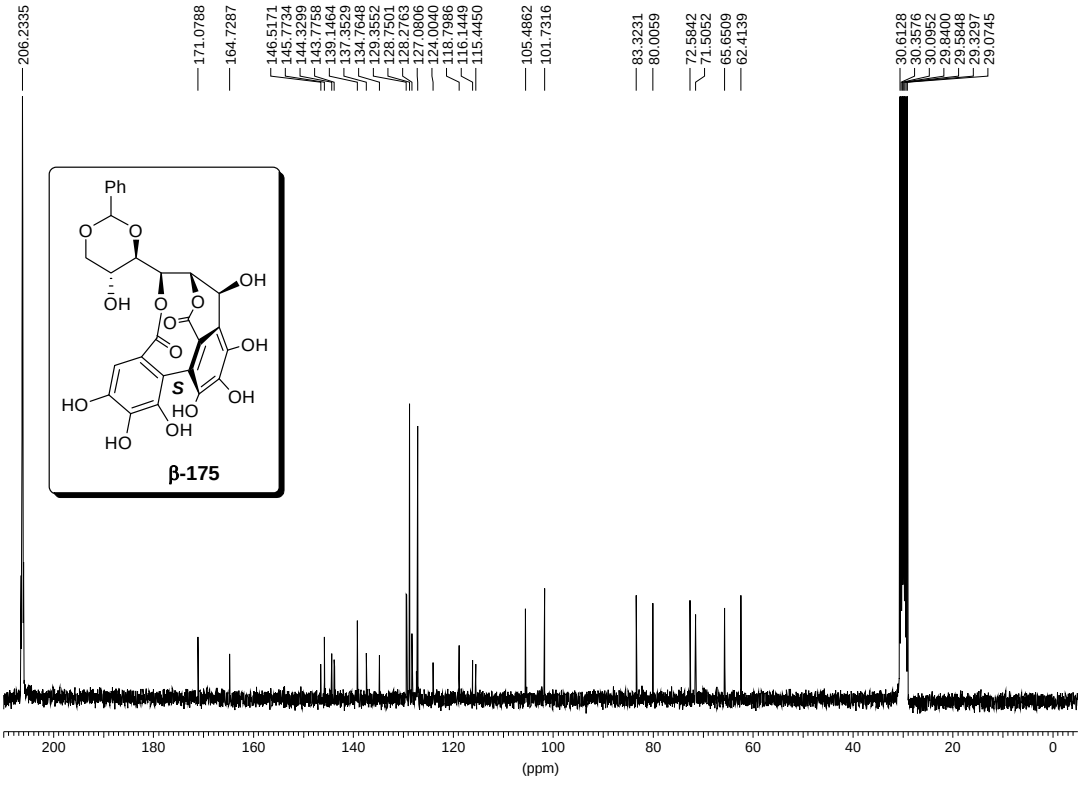
Peak Nr.	Data Point	Frequency	PPM	Intensity	%Int.
1	15550	2006.69	6.6861	279459936	61.2
2	15561	2004.61	6.6791	252330240	55.3
3	15716	1975.34	6.5816	456465440	100
4	17565	1626.16	5.4182	51362940	11.3
5	17613	1617.10	5.3880	147604976	32.3
6	17626	1614.64	5.3798	115376216	25.3
7	17664	1607.47	5.3559	64191152	14.1
8	18141	1517.39	5.0558	45616348	10
9	18192	1507.75	5.0237	100948552	22.1
10	18241	1498.50	4.9928	144097792	31.6
11	18284	1490.38	4.9658	115671168	25.3
12	18343	1479.24	4.9287	72438264	15.9
13	18362	1475.65	4.9167	68811464	15.1
14	18394	1469.61	4.8966	62368660	13.7
15	18413	1466.02	4.8846	63635248	13.9
16	18659	1419.56	4.7298	62225960	13.6
17	18702	1411.44	4.7028	61699752	13.5
18	18710	1409.93	4.6977	59720888	13.1
19	18753	1401.81	4.6707	42138240	9.2
20	19858	1193.14	3.9754	29158396	6.4
21	19874	1190.11	3.9653	25065348	5.5
22	19887	1187.66	3.9572	30927706	6.8
23	19910	1183.32	3.9427	48879336	10.7
24	19925	1180.48	3.9332	40120480	8.8
25	19950	1175.76	3.9175	35408164	7.8
26	19963	1173.31	3.9093	38805584	8.5
27	20008	1164.81	3.8810	105108928	23
28	20026	1161.41	3.8697	64711076	14.2
29	20057	1155.56	3.8502	114569416	25.1
30	20085	1150.27	3.8326	66980280	14.7
31	20101	1147.25	3.8225	111336448	24.4
32	20114	1144.79	3.8143	114539872	25.1
33	20127	1142.34	3.8061	119413872	26.2
34	20135	1140.83	3.8011	134122096	29.4
35	20149	1138.18	3.7923	83508336	18.3
36	20171	1134.03	3.7785	65394692	14.3
37	20186	1131.19	3.7690	81843072	17.9
38	20198	1128.93	3.7615	67006344	14.7
39	20233	1122.32	3.7394	34472640	7.6
40	20260	1117.22	3.7225	35517668	7.8
41	20550	1062.45	3.5400	30443886	6.7
42	20563	1060.00	3.5318	32279918	7.1
43	20576	1057.54	3.5236	33061712	7.2

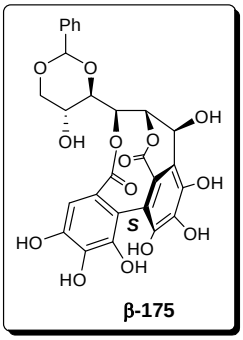
44	20599	1053.20	3.5091	28330512	6.2
45	20613	1050.56	3.5003	27167082	6
46	20627	1047.91	3.4915	25284098	5.5
47	20640	1045.46	3.4834	19067768	4.2
48	20659	1041.87	3.4714	17118906	3.8
49	22895	619.61	2.0645	160898816	35.2
50	22907	617.34	2.0569	220025312	48.2
51	22918	615.27	2.0500	271195904	59.4
52	22930	613.00	2.0424	187959200	41.2
53	22942	610.73	2.0349	93564776	20.5

ANA179-B / acetone / 400 MHz



ANA179-B / acetone / 400 MHz

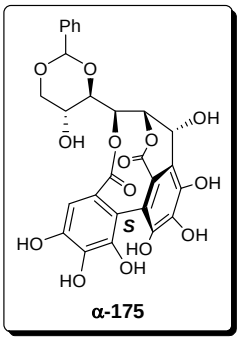




β-175

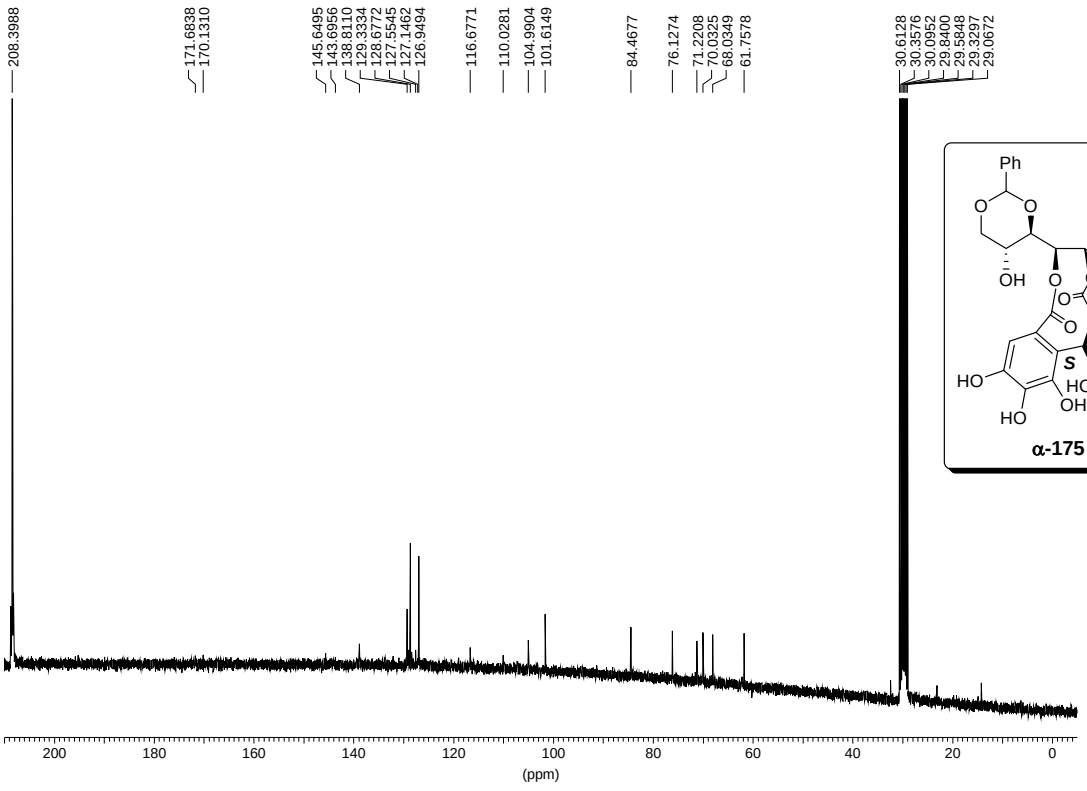
Peak Nr.	Data Point	Frequency	PPM	Intensity	%Int.
1	9842	2255.59	7.5154	83780016	14.7
2	9855	2253.13	7.5072	88762080	15.5
3	9884	2247.65	7.4889	126962656	22.2
4	9891	2246.33	7.4845	116567704	20.4
5	10085	2209.70	7.3625	46358536	8.1
6	10111	2204.79	7.3461	135128160	23.7
7	10142	2198.93	7.3266	189180032	33.1
8	10149	2197.61	7.3222	181031024	31.7
9	11594	1924.73	6.4130	203252112	35.6
10	12825	1692.26	5.6384	173118112	30.3
11	13686	1529.66	5.0967	93945376	16.5
12	14061	1458.84	4.8607	104625480	18.3
13	14070	1457.14	4.8550	102711144	18
14	14170	1438.26	4.7921	53510536	9.4
15	14184	1435.62	4.7833	93811312	16.4
16	14198	1432.97	4.7745	55814192	9.8
17	15060	1270.19	4.2321	38857048	6.8
18	15081	1266.22	4.2189	48893200	8.6
19	15110	1260.74	4.2007	50507156	8.8
20	15131	1256.78	4.1874	37358292	6.5
21	15487	1189.55	3.9634	35888828	6.3
22	15501	1186.90	3.9546	37642384	6.6
23	15533	1180.86	3.9345	43406800	7.6
24	15547	1178.22	3.9257	40813856	7.1
25	15853	1120.43	3.7332	12089353	2.1
26	15877	1115.90	3.7180	11817798	2.1
27	15906	1110.42	3.6998	23249874	4.1
28	15931	1105.70	3.6841	22490648	3.9
29	15955	1101.17	3.6690	21114428	3.7
30	15978	1096.82	3.6545	41492704	7.3
31	16030	1087.00	3.6218	29009736	5.1
32	16082	1077.18	3.5891	11316653	2
33	18505	619.61	2.0645	229480384	40.2
34	18517	617.34	2.0569	418512128	73.3
35	18528	615.27	2.0500	571044416	100
36	18540	613.00	2.0424	421937472	73.9
37	18551	610.92	2.0355	238229760	41.7

ANA184-C / acetone / 300 MHz

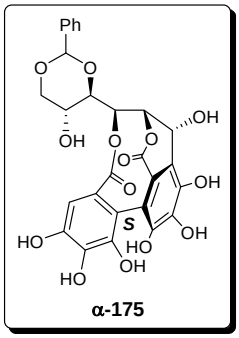


α-175

ANB129-D / acetone / 300 MHz



α-175

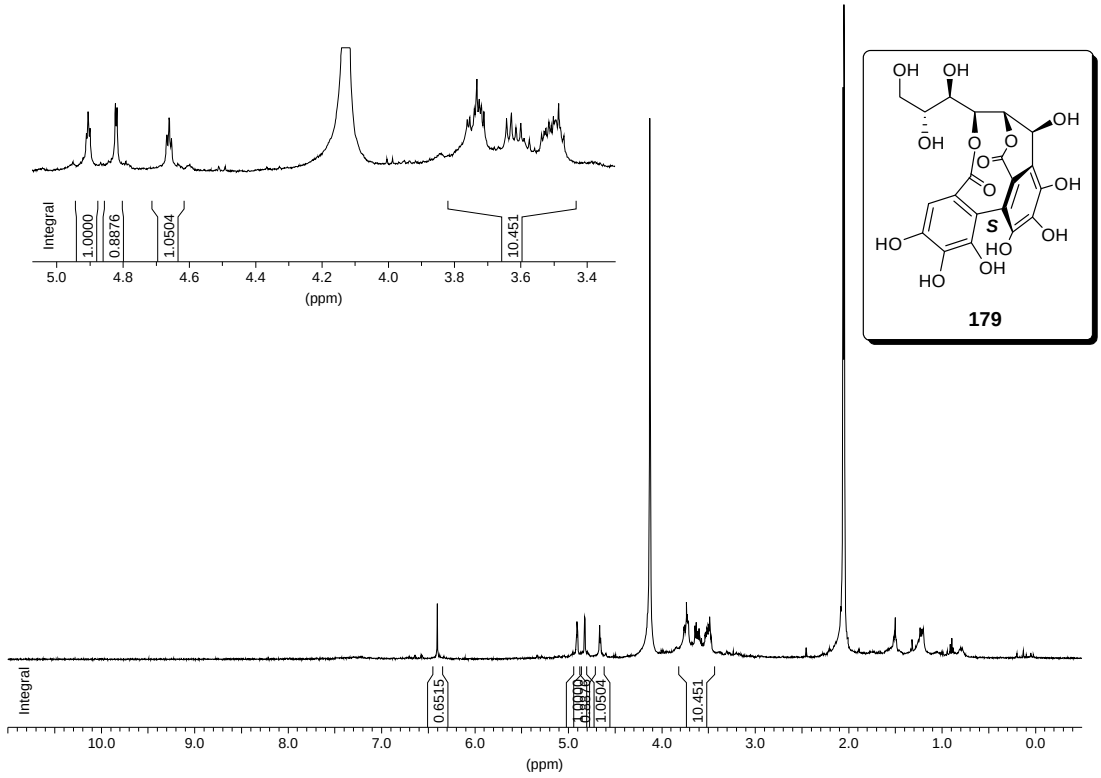


α-175

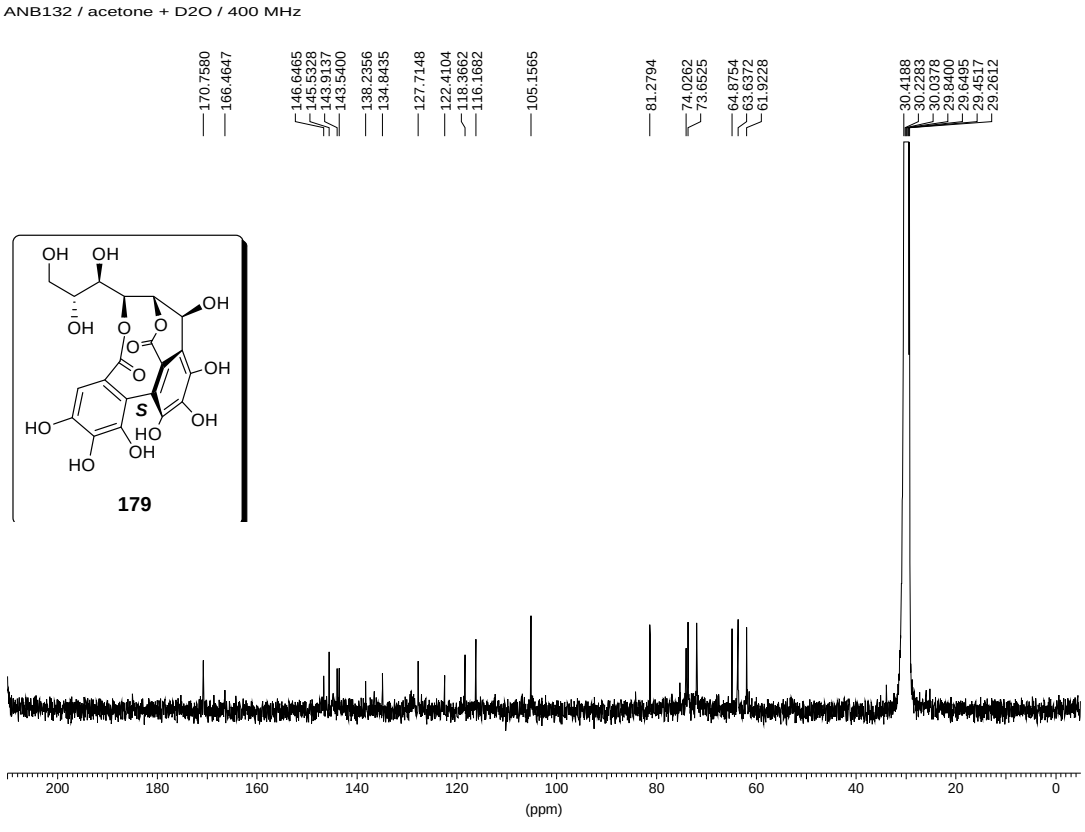
Peak Nr.	Data Point	Frequency	PPM	Intensity	%Int.
1	17111	3016.90	7.5398	3596144	0.9
2	17143	3009.07	7.5202	12237014	2.9
3	17153	3006.63	7.5141	11713036	2.8
4	17176	3001.00	7.5001	15038347	3.6
5	17182	2999.53	7.4964	12964499	3.1
6	17195	2996.36	7.4885	5326320	1.3
7	17412	2943.29	7.3558	11310963	2.7
8	17420	2941.34	7.3510	11084601	2.7
9	17434	2937.91	7.3424	19861324	4.8
10	17463	2930.82	7.3247	26064110	6.3
11	17480	2926.66	7.3143	10438850	2.5
12	17487	2924.95	7.3100	9489064	2.3
13	18920	2574.54	6.4343	20277984	4.9
14	20241	2251.51	5.6270	17216606	4.1
15	20271	2244.18	5.6086	9134295	2.2
16	20290	2239.53	5.5970	8909749	2.1
17	20681	2143.92	5.3581	6376718	1.5
18	20692	2141.23	5.3513	10607604	2.5
19	20702	2138.78	5.3452	5839642	1.4
20	21295	1993.78	4.9828	5547512	1.3
21	21306	1991.09	4.9761	6388929	1.5
22	21313	1989.37	4.9718	6552925	1.6
23	21324	1986.68	4.9651	5855504	1.4
24	22527	1692.51	4.2299	4471856	1.1
25	22547	1687.62	4.2177	5451362	1.3
26	22569	1682.24	4.2042	5585897	1.3
27	22588	1677.60	4.1926	5120827	1.2
28	23221	1522.81	3.8058	3077296	0.7
29	23257	1514.00	3.7838	5100854	1.2
30	23294	1504.96	3.7612	8316235	2
31	23304	1502.51	3.7551	7995297	1.9
32	23326	1497.13	3.7416	4639209	1.1
33	23345	1492.48	3.7300	4230922	1
34	23365	1487.59	3.7178	6085204	1.5
35	23385	1482.70	3.7056	5734215	1.4
36	23403	1478.30	3.6946	4745713	1.1
37	23422	1473.66	3.6829	5832350	1.4
38	23476	1460.45	3.6499	8703358	2.1
39	23518	1450.18	3.6243	9085879	2.2
40	23557	1440.64	3.6004	4438933	1.1

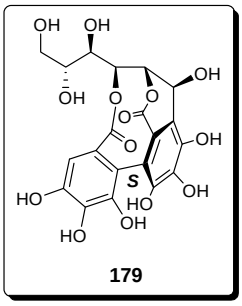
41	26075	824.91	2.0616	155258672	37.2
42	26084	822.71	2.0561	234060080	56.1
43	26094	820.27	2.0500	416900224	100
44	26102	818.31	2.0451	226217600	54.3
45	26111	816.11	2.0396	106353888	25.5

ANB132 / acetone + D2O / 400 MHz



ANB132 / acetone + D2O / 400 MHz

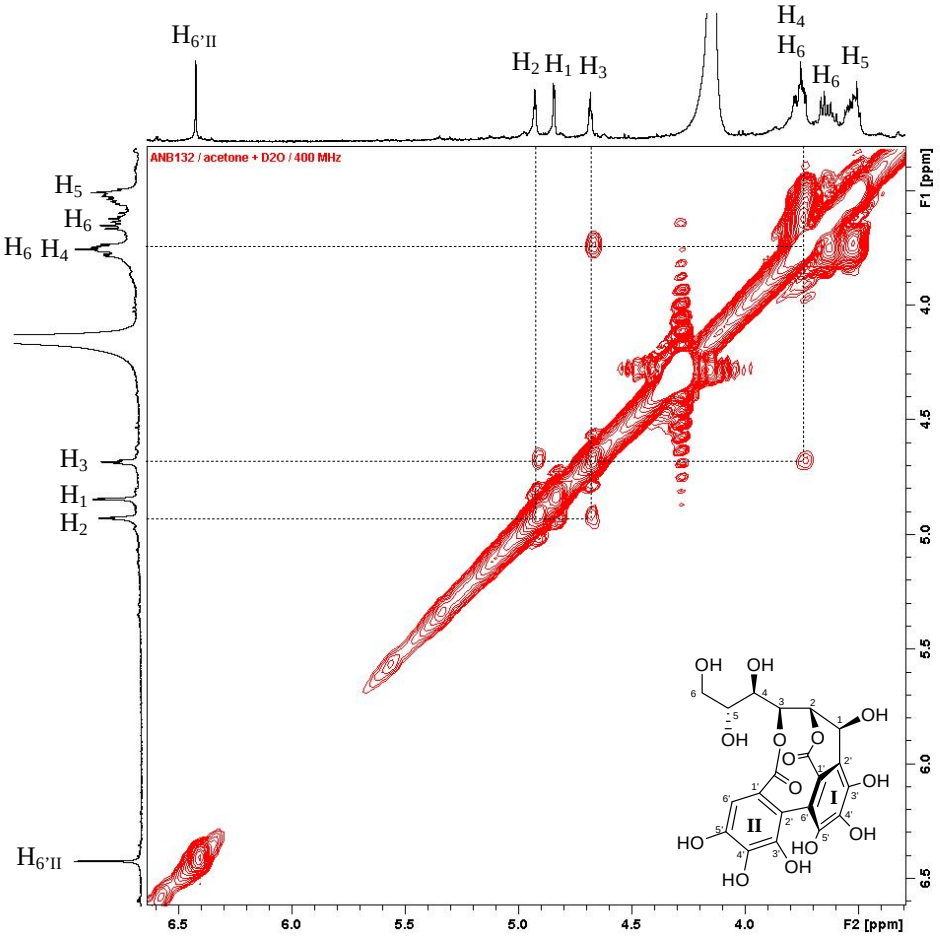




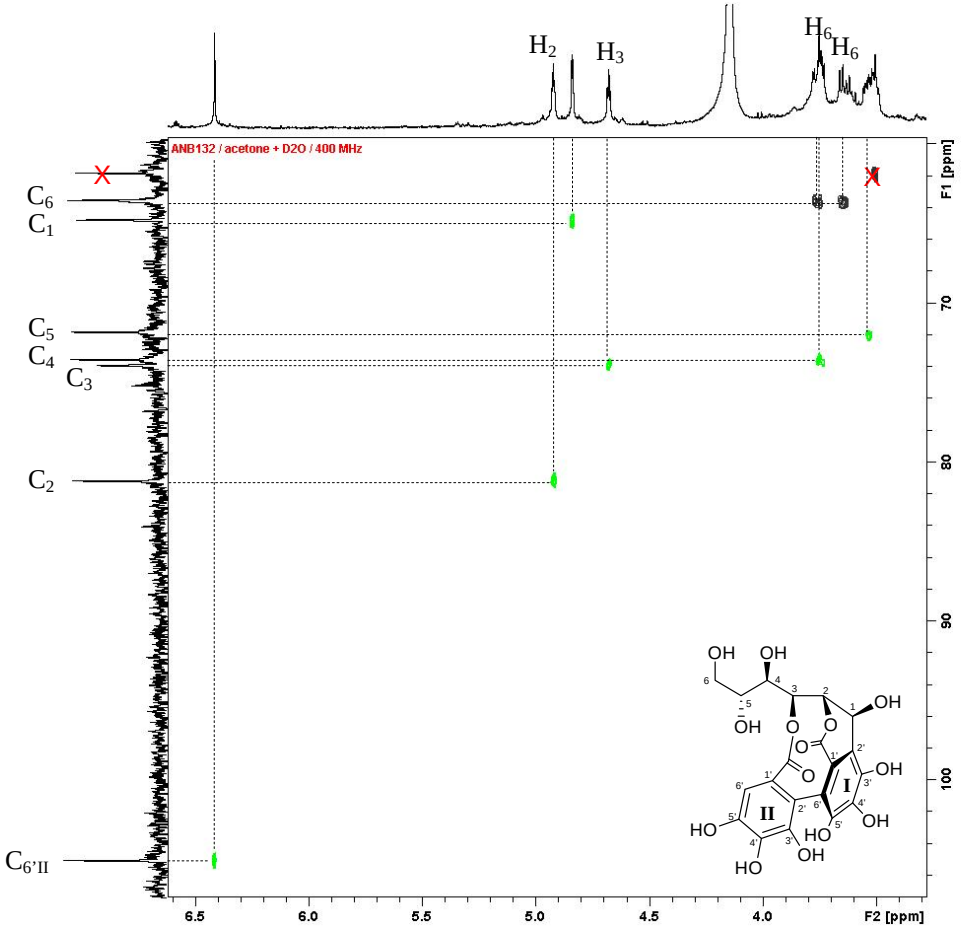
179

Peak Nr.	Data Point	Frequency	PPM	Intensity	%Int.
1	16002	2560.63	6.3995	22883876	7
2	18360	1964.93	4.9107	10237276	3.1
3	18369	1962.65	4.9050	15560459	4.7
4	18378	1960.38	4.8994	11419893	3.5
5	18499	1929.81	4.8230	17527060	5.3
6	18506	1928.04	4.8185	16507023	5
7	18745	1867.67	4.6676	9755505	3
8	18756	1864.89	4.6607	14021730	4.3
9	18767	1862.11	4.6538	8864376	2.7
10	19601	1651.42	4.1272	222677824	67.8
11	20180	1505.14	3.7616	13581372	4.1
12	20193	1501.86	3.7534	14200167	4.3
13	20214	1496.55	3.7402	16280302	5
14	20226	1493.52	3.7326	23618884	7.2
15	20239	1490.24	3.7244	18645908	5.7
16	20248	1487.96	3.7187	17111658	5.2
17	20260	1484.93	3.7111	15595108	4.7
18	20369	1457.40	3.6423	13916445	4.2
19	20391	1451.84	3.6284	15279323	4.6
20	20414	1446.03	3.6139	11579298	3.5
21	20437	1440.22	3.5994	12751497	3.9
22	20452	1436.43	3.5899	9024115	2.7
23	20478	1429.86	3.5735	8695014	2.6
24	20535	1415.46	3.5375	10052471	3.1
25	20548	1412.18	3.5293	10712378	3.3
26	20557	1409.90	3.5236	11441523	3.5
27	20571	1406.37	3.5148	13021095	4
28	20582	1403.59	3.5078	12278170	3.7
29	20592	1401.06	3.5015	14380900	4.4
30	20604	1398.03	3.4939	13495195	4.1
31	20618	1394.49	3.4851	17598772	5.4
32	20642	1388.43	3.4699	9592655	2.9
33	22874	824.56	2.0607	145909104	44.4
34	22882	822.54	2.0557	235314080	71.6
35	22891	820.27	2.0500	328625248	100
36	22900	817.99	2.0443	237550464	72.3
37	22909	815.72	2.0386	130078344	39.6

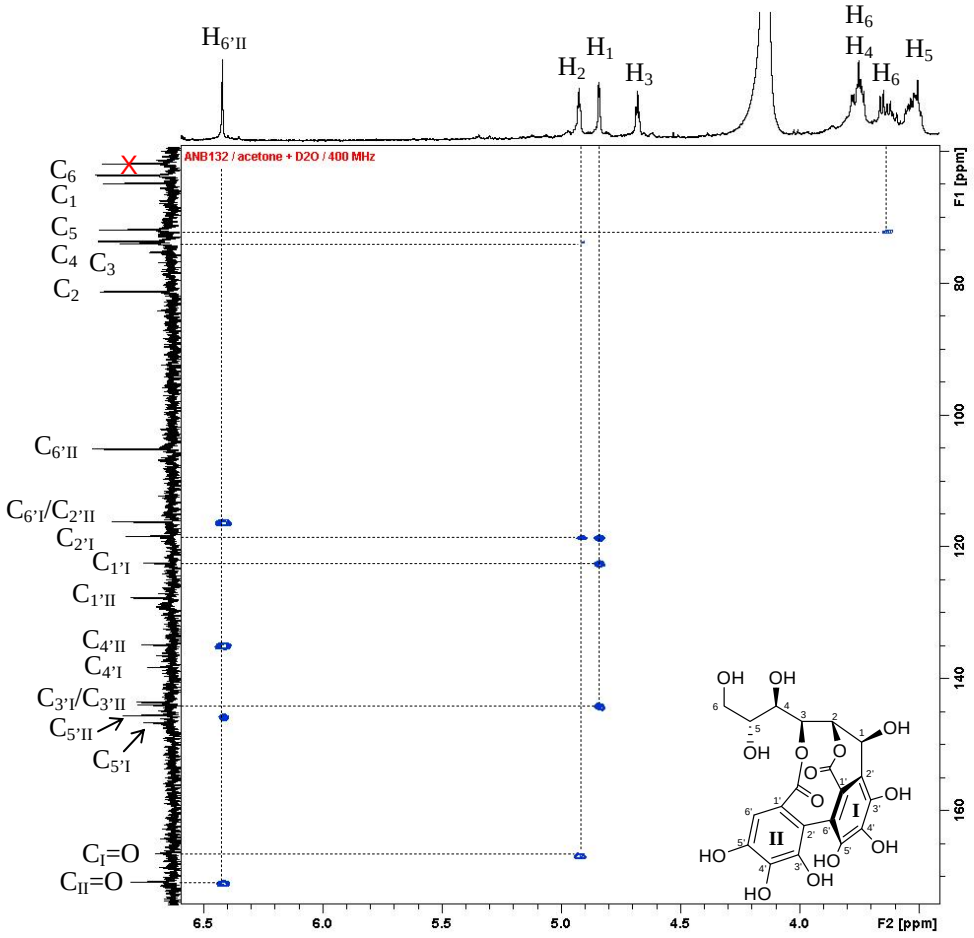
COSY ^{1}H-^{1}H of compound 179



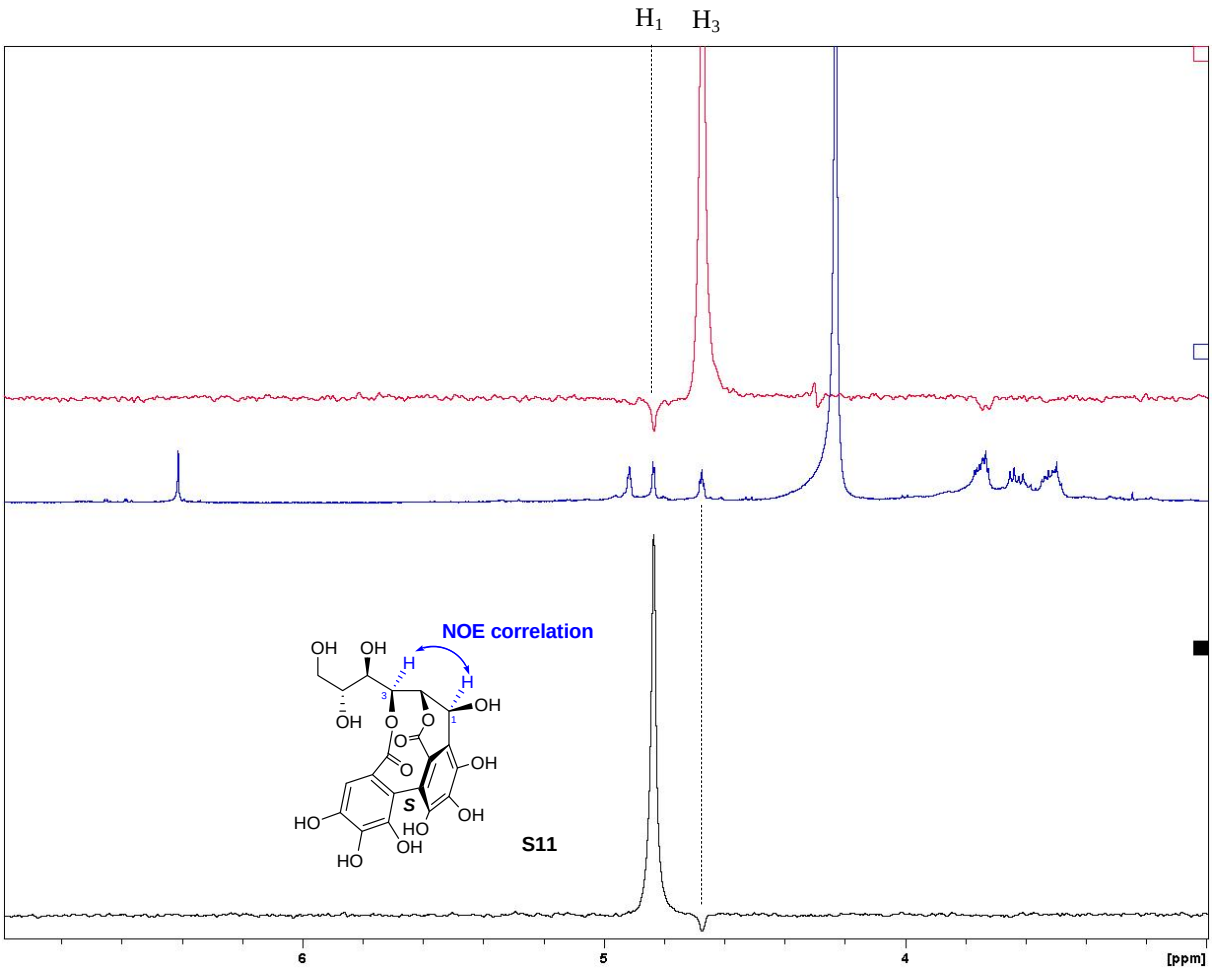
HSQC ^{1}H-^{13}C of compound 179



HMBC ^{1}H-^{13}C of compound 179



Selective ROESY of compound 179



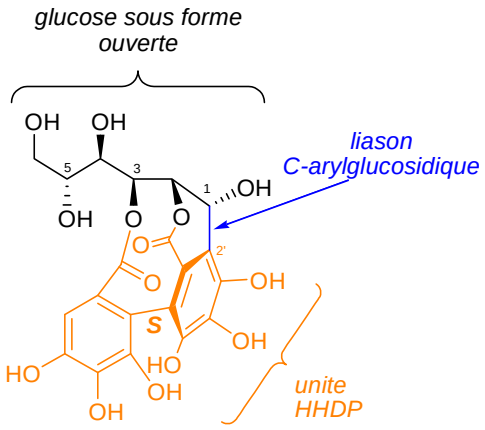
Résumé

Le sujet de cette thèse concerne le développement d'une méthodologie de synthèse d' ellagitannins C-arylglucosidiques, possibles agents chimiothérapeutiques contre le cancer. Les ellagitannins C-arylglucosidiques sont des polyphénols bioactifs d'origine végétale, dérivés du métabolisme secondaire de l'acide gallique, et qui appartiennent à une sous-famille des tannins hydrolysables. La structure chimique de ces molécules est caractérisée par trois éléments structuraux clés :

un glucose sous forme ouverte,

une liaison C-arylglucosidique,

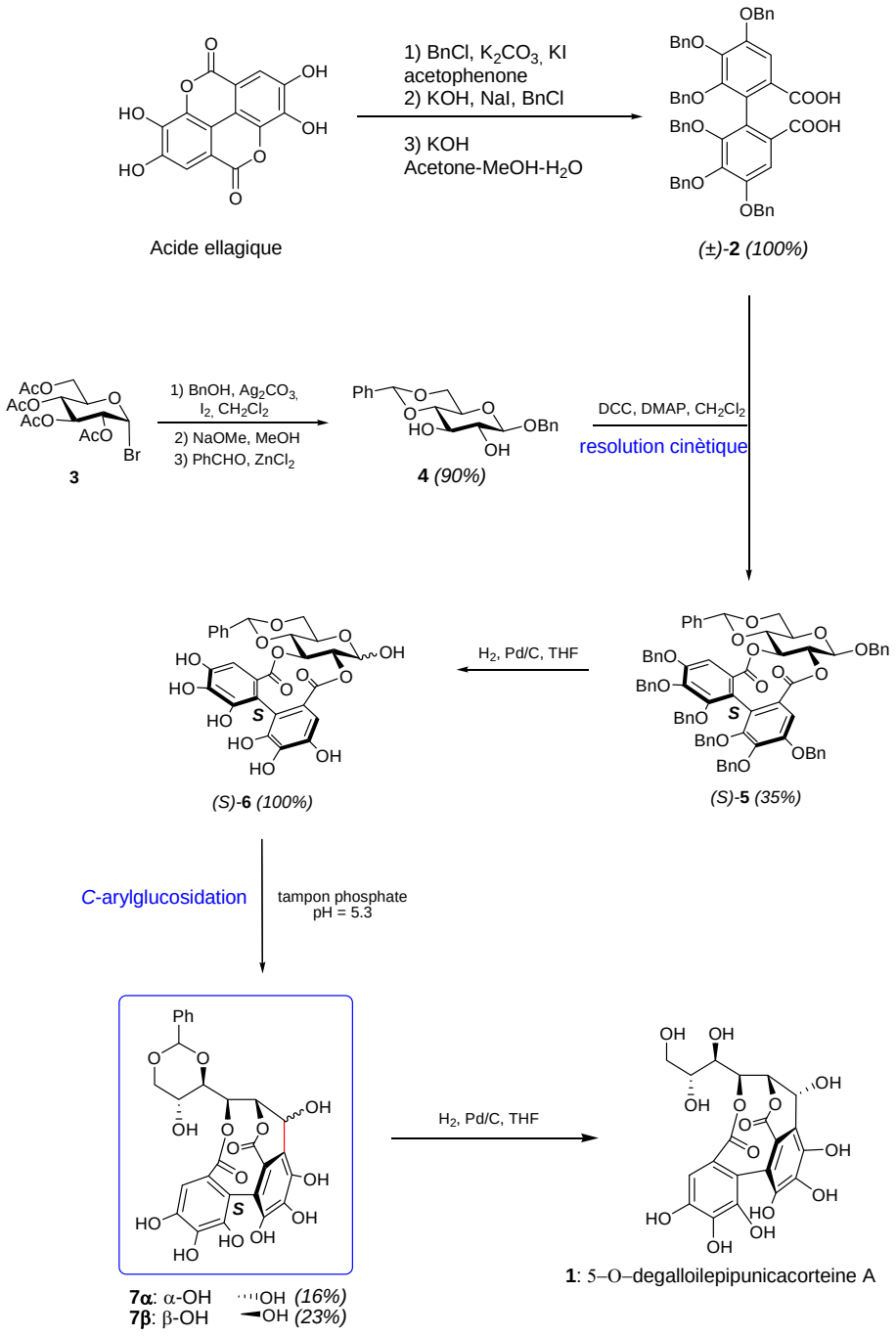
un motif de type 2,3- hexahydroxydiphenoyl (HHDP).



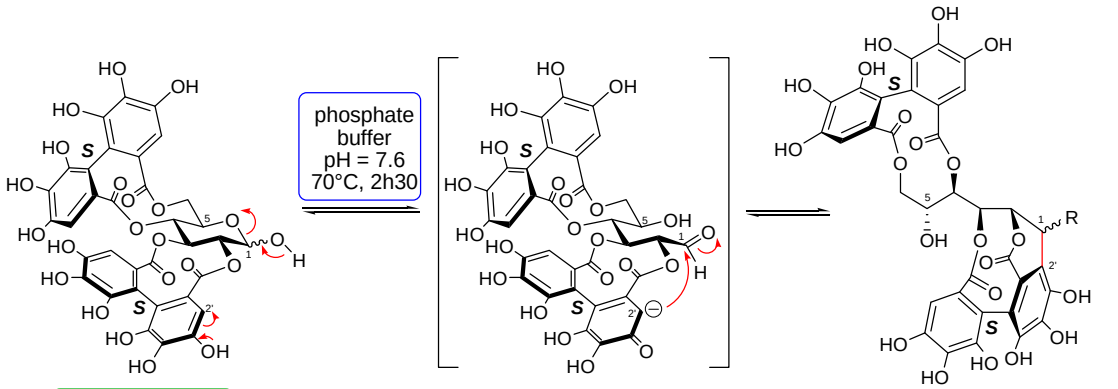
degalloyl epipunicacorteine A

Les unités HHBP et NHTP de type pyrogallol forment des cycles de dix et onze chaînons qui apportent à la structure un caractère rigide, stéréochimiquement très bien defini. La structure globulaire de ces molécules leur confère une aptitude certaine à interagir de manière spécifique avec des protéines d'intérêt pharmaceutique. Des études préliminaires ont montré que certains ellagitannins sont de puissant inhibiteurs de la topoisomérase II humaine, une enzyme ciblée par les chimiothérapies actuelles contre le cancer. La topoisomérase II intervient lors de la réplication de l'ADN, en éliminant les contraintes de torsion. Si la topoisomérase II est inhibée, la réplication ne peut plus se faire, bloquant ainsi la prolifération des cellules tumorales.

Forts de ces résultats préliminaires, nous avons concentré nos efforts sur le développement d'une stratégie de synthèse chimique de ces molécules afin de mieux comprendre leurs propriétés et réactivités chimiques, ainsi que leur mode d'action. Cela permettra in fine d'améliorer l'accès à des têtes de séries identifiées et de développer de nouvelles méthodologies pour la production d'analogues présentant des propriétés pharmacologiques améliorées. Dans le schéma suivant sont reportés les principaux résultats obtenus.



La construction stéréosélective de l'unité HHBP constitue l'étape décisive de toutes les synthèses d'ellagitannins décrites jusqu'à présent. Dans notre cas, l'intermédiaire **5** a été obtenu par une double estérification, en utilisant de la DMAP, du sucre **4** par l'acide racémique **2** (obtenu en 3 étapes en partant de l'acide ellagique naturel et commercial). Les diastéréoisomères S et R ont pu être isolés après chromatographie sur colonne. Le composé S-**5** a ensuite été engagé dans une hydrogénation afin d'obtenir avec un rendement quantitatif le composé S-**6**. En ce qui concerne l'étape clé de *C*-arylglucosidation de notre synthèse, les seuls travaux rapportés à ce jour dans la littérature sont ceux de Tanaka, qui a réalisé l'hémisynthèse de la casuariine et de son épimère en C-1 à partir de la pédunculagine en chauffant à 70°C pendant 2h30 dans une solution de tampon phosphate à pH 7.6.



8: Pedunculagine

9: R = β-OH, Stachyurine
5-*O*-degalloyl (34%)
10: R = α-OH, Casuariine (6%)

Tanaka avait proposé un mécanisme en deux étapes. Tout d'abord, une mutarotation du glucose provoquant l'ouverture du cycle pyranosique et la formation d'un intermédiaire aldéhydique. La deuxième étape du mécanisme est une aldolisation induite par un équilibre céto-énolique au niveau de l'unité HHBP, formant ainsi la liaison *C*-arylglucosidique attendue. Nous avons exploré des conditions similaires pour la *C*-arylglucosidation du composé couplé **6**. Les mêmes conditions que celles décrites par Tanaka ont été utilisées et conduisent à un mélange complexe de produits non analysables.

D'autres conditions opératoires ont été testées, impliquant des variations de la température, du temps de réaction, de la nature des solvants et du choix de bases organiques ou inorganiques. Malgré les nombreuses conditions testées, nous n'avons pas pu réaliser la *C*-arylglucosidation dans des conditions basiques. Il s'avère que les conditions basiques utilisées ne sont pas adaptées a nos composés, conduisant inéluctablement à leur dégradation. Cependant, la mutarotation du sucre peut être aussi induite sous des conditions

acides. Nous avons donc essayé la réaction dans un tampon phosphate à des pH acides. A l'aide de ces nouvelles conditions, le produit **7** a pu être isolé et des expériences RMN mono- et bidimensionnelle ont permi de confirmer la formation de la liaison *C*-arylglucosidique. Un seule étape de déprotection de l'épimère majoritaire a ensuite permis d'obtenir un premier membre de la classe des ellagitannins *C*-arylglucosidiques, à savoir l'épipunicacortéine A 5-O-desgalloylée (**1**).

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