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Review

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Synthesis of A-type Proanthocyanidins and their Analogues. A Comprehensive Review

Alfonso Alejo-Armijo, Sofía Salido, and Joaquín Altarejos*

Departamento de Química Inorgánica y Orgánica, Facultad de Ciencias Experimentales, Universidad de Jaén, Campus de Excelencia Internacional Agroalimentario, ceiA3, 23071 Jaén, Spain

KEYWORDS: Organic synthesis; condensed tannins; A-type proanthocyanidins (PACs); analogues to A-type PACs; 2,8-dioxabicyclo[3.3.1]nonane skeleton.

ABSTRACT: Proanthocyanidins (PACs) are oligomers or polymers composed of units of flavanols. A-type proanthocyanidins are a subclass of PACs characterized by the presence of at least a double linkage between two consecutive monomers of flavanol. These A-type PACs are found in some fruits and spices and possess potential health benefits as a result of their interesting biological activities, and consequently their isolation and synthesis have given rise to great interest in the past. This review summarizes the synthetic efforts made to obtain both naturally occurring A-type PACs and their structurally simplified analogues. Most of the synthetic protocols reported involve the addition of a π-nucleophilic molecule over a molecule with two electrophilic carbons, such as a chalcone, a flavylium salt or a flavanol derivative, among others. Synthesis of A-type PACs remains an issue at a very early stage of development, compared to that of PACs with single linkages between monomers (B-type PACs), but the advances that are taking place in the last years point to a significant development of the subject in the near future.

INTRODUCTION

Proanthocyanidins (PACs), also known as condensed tannins, are secondary metabolites formed by the union of monomers of flavanol (Figure 1). They are widely distributed throughout nature. In fact, they comprise the most abundant class of plant phenolics after lignins[1] and represent the second main phenolic compounds in human diet.[2] In that sense, they have also been detected and in some cases isolated from several foods and drinks such as fruits, cereals, legumes, nuts, cocoa, wine, beer or tea.[3,4,5]

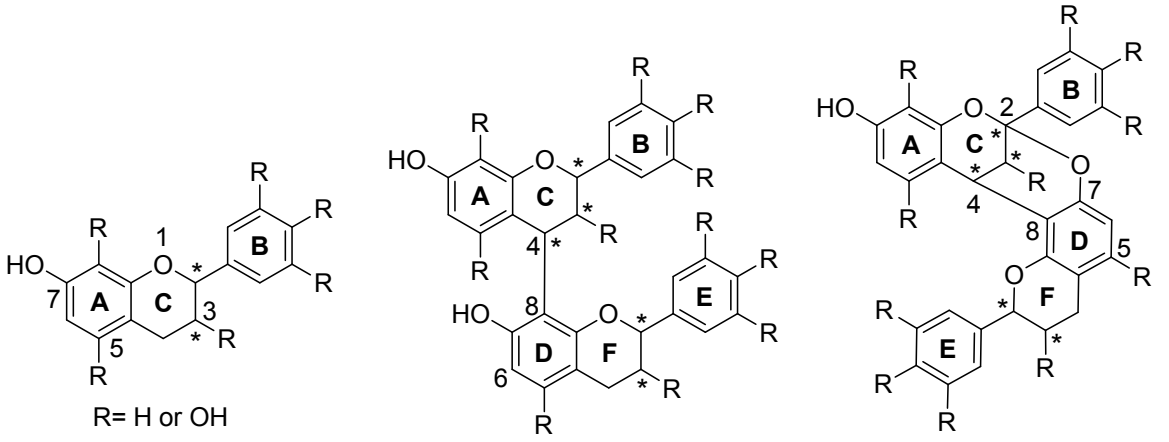


Figure 1. Chemical structure of flavanols and dimeric proanthocyanidins (PACs).

The chemical nature of PACs is related to the number (polymerization degree) and the structural class of flavanols that comprise them, which basically depends on its degree of hydroxylation, the stereochemistry at their chiral centers, and location and type of the interflavan linkage.[6,7] In terms of their polymerization degree PACs are classified into dimers, trimers, tetramers or oligomers. In that way, A-type and B-type PACs are dimers and C-type PACs are

trimers. According to the interflavan linkage, B-type and C-type PACs present only a single linkage between C-4 of the upper monomer and C-6 or C-8 of the lower unit. On the other hand, A-type PACs are more complex because they present an additional ether linkage between C-2 of the upper monomer and 7-OH of the lower moiety (or 5-OH, if present in the specific PAC structure), obtaining a bicyclic structure of 2,8-dioxabicyclo[3.3.1]nonane.[7,8] Moreover, in terms of stereochemistry of the upper monomer, the 3,4-*trans* configuration generally predominate over the 3,4-*cis* one[7] (Figure 1).

PACs are widespread oligomeric or polymeric end products biosynthesized in plant kingdom *via* the flavonoid pathway.[1,9,10] Despite the well-understood biosynthesis of flavanols, the mechanism of their polymerization remains unknown.[9,11] In fact, several hypotheses have been proposed,[9] although it seems that plant flavonoid carbocations play a vital role in the polymerization process, particularly for B-type PACs.[12] On the other hand, the biosynthesis of A-type PACs is less understood, but there are some evidences that point to a possible biosynthesis of A-type PACs through the oxidation of B-type ones.[13,14]

The recent interest on the isolation and synthesis of this kind of metabolites and their analogues is due to its potential and, in some cases, evidenced biological activities, such as antioxidant, cardioprotective, neuroprotective, immunomodulatory, antiadhesion, anticancer and antimicrobial activities, among others.[15,16,17,18,19] Particularly, A-type PACs showed interesting antibacterial and antiviral properties, due to the inhibition of both bacterial adhesion[20] and virus replication.[21] These important antiadhesion properties of A-type PACs have been applied to the treatment of urinary tract infections.[22,23] Moreover, A-type PACs could be very useful to reduce cardiovascular complications in type 2 diabetes mellitus as a consequence of their antihyperglycemic activities[24], their selective inhibition of α-amylase[25] and their ability for the

reduction of platelet hyperaggregability.[26] From a synthetic point of view, the synthesis of B-type PACs has been developed and optimized in depth over the years, being also reviewed several times recently.[27,28,29,30,31] On the contrary, the synthesis of A-type PACs is a topic at a very early stage and is still underdeveloped, maybe due to its higher chemical complexity.

This review will provide an overview of the synthesis of A-type PACs and their analogues. The first section deals specifically with the synthesis of this kind of metabolites through B-type PACs or from flavanol's monomers. The second section deals with the synthetic efforts performed over the last 40 years on the formation of analogues with the bicycle core characteristic of A-type PACs.

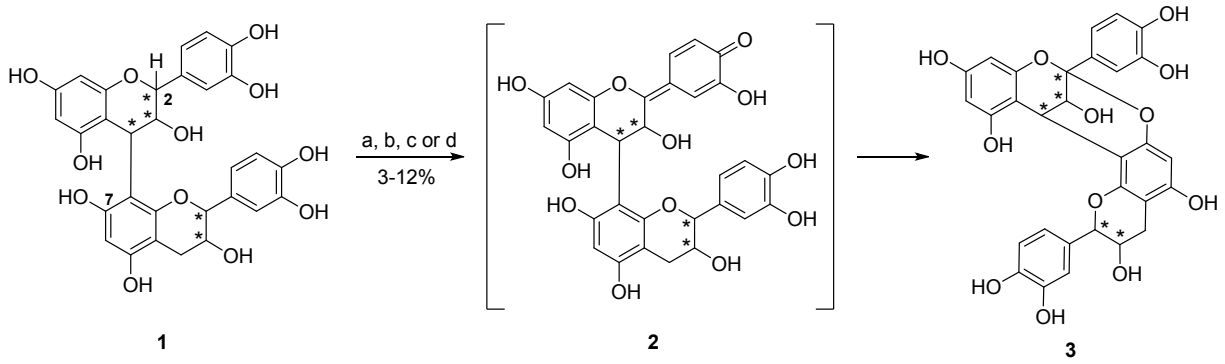
SYNTHESIS OF A-TYPE PROANTHOCYANIDINS

Synthesis of A-type PACs *via* Oxidation of B-type PACs. From a biosynthetic point of view the mechanism for the formation of the double interflavan linkage of A-type PACs remains unclear.[9] Several authors have proposed that A-type PACs are formed from the corresponding B-type one through the oxidation of C-2 of the upper monomer. This assumption allowed the design of the first syntheses of A-type PACs[32,33,34] (Scheme 1). In the initial attempts, the conversion between B-type (**1**) and A-type (**3**) PACs was carried out using oxidizing agents such as $H_2O_2/NaHCO_3$,[34] $O_2/NaHCO_3$[33] and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical[32] (Scheme 1). In all cases, the conversion was achieved with low yields (3−12%).

The proposed mechanisms involved the oxidative removal of a hydrogen atom[32] or a hydride anion[33] at C-2 as the initial step, formation of a quinone intermediate (**2**) and the nucleophilic attack of the hydroxyl group at C-7 of the lower unit to C-2 of the upper moiety (Scheme 1).[32,33]

In 2007, it was observed the conversion of B-type to A-type PACs by HPLC–MS through enzymatic oxidation using lacasse (EC 1.10.3.2) as a catalyst (no yield reported)[14] (Scheme 1). This result suggested that the conversion of B-type to A-type PACs in plants might also involve an enzyme-catalyzed oxidation reaction and not only a radical-driven process as previously suggested by Kondo *et al*.[32]

Scheme 1. Synthesis of A-type PACs by Chemical or Enzymatic Oxidation of B-type PACs[a]



1 **B-type proanthocyanidin** **2** **quinone intermediate** **3** **A-type proanthocyanidin**

[a]Reagents and conditions: (a) H_2O_2, $NaHCO_3$, EtOH, r.t., 13 h;[34] (b) O_2, $NaHCO_3$, H_2O, 40 ºC, 6.5 h;[33] (c) DPPH, EtOH, H_2O;[32] (d) acetate buffer, phosphate buffer, lacasse EC 1.10.3.2.[14]

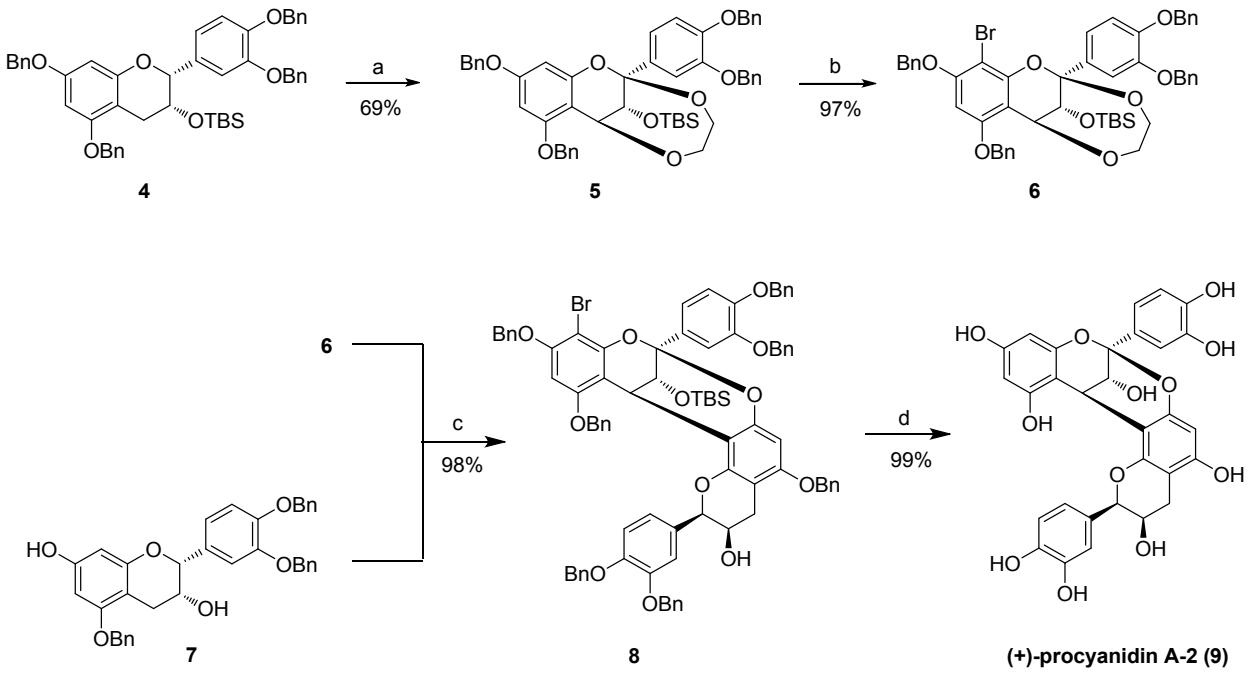
The hypothesis suggested by Kondo *et al.*[32] and Osman and Wong[14] was checked in 2014 by Chen *et al.*,[13] who studied in depth the oxidative conversion of B-type into A-type PACs. In this study, the temperature, pH value and four oxidant catalysts (DPPH, O^{2-}, polyphenol oxidase and xanthine oxidase) were investigated. Results showed that the conversion was significantly affected by temperature and pH, but not by the type of reagent employed to achieve the oxidation. Therefore, it remains unclear what kind of mechanism (free radical-driven process or enzyme-catalyzed free radical reaction) prevails in plant kingdom. However, the isolation and characterization of several oxidation products during the study performed by Chen *et al.*[13] have allowed to corroborate that PACs oxidation mechanism proceeds through a quinone methide as previously suggested by Kondo *et al.*[32] and Osman and Wong.[14]

All the efforts made during the last 20 years for understanding the biosynthesis of A-type PACs in plant kingdom have been inconclusive due to the fact that both oxidation mechanisms of B-type PACs are able to produce A-type PACs in biological conditions. Moreover, in all cases reaction yields of B-type PACs into A-type ones are still low, which is a handicap for using these bioinspired methodology as a worthy synthetic approach for A-type PACs synthesis. On the other hand, it means at the same time that there would still be scope for making progresses within this strategy.

Synthesis of A-type PACs from Flavanol's Monomers. During the last few years, this synthetic strategy has been employed by two different research groups to properly achieve the synthesis of natural A-type PACs.[35,36] One of them, Suzuki-Ohmori's group (Ito *et al.*,[36]) described the first synthesis of an A-type PAC in good yield: (+)-procyanidin A-2 (**9**) (Scheme

2). The DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) oxidation of a fully protected (–)-epicatechin (**4**) in the presence of ethylene glycol afforded the double electrophile key intermediate **5**, which was brominated in C-8 to suppress self-reactions in following reactions, giving the bromide derivative **6**. Finally, Lewis acid activation of **6** by $BF_3{\cdot}Et_2O$ in the presence of the proper nucleophile (**7**) and subsequent removal of hydroxyl protecting groups and debromination afforded (+)-procyanidin A-2 (**9**) in a 59% overall yield.

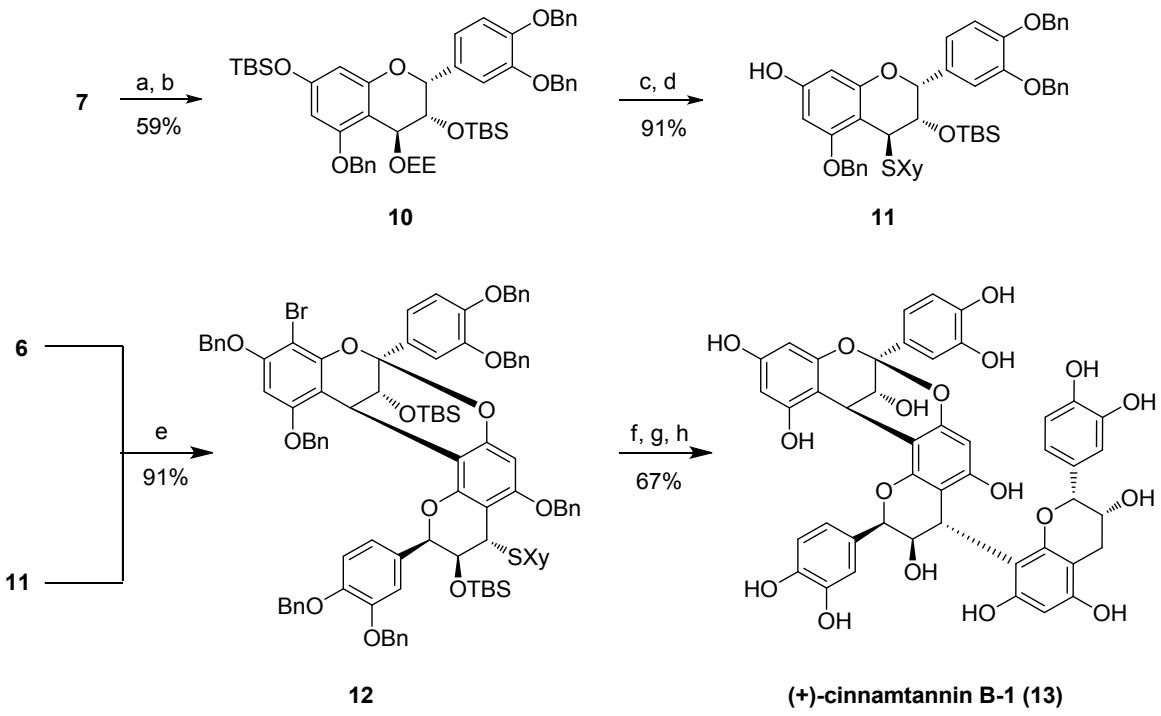
Scheme 2. Ito's Synthesis of (+)-Procyanidin A-2 (9) [a]



[a]Reagents and conditions: (a) DDQ, $(CH_2OH)_2$, DCM, reflux, 8 h; (b) *N*-bromosuccinimide, DCM, –10 ºC, 1 h; (c) $BF_3{\cdot}OEt_2$, DCM, –78 ºC → –30 ºC, 4 h; (d) *n*-Bu_4NF, THF, 8 h; then H_2, 5% $Pd(OH)_2/C$, 1 h.[36]

This synthetic methodology has also been applied to achieve in a 33% overall yield the first synthesis of (+)-cinnamtannin B-1 (**13**) (Scheme 3), a trimeric PAC with an A-type interflavan linkage between the top and middle monomers, which has many interesting biological properties.[37,38,39,40] Before achieving its synthesis, (+)-cinnamtannin B-1 had exclusively been obtained from natural sources such as laurel wood[41,42] and *Cinnamomum* sp.,[43] among others.

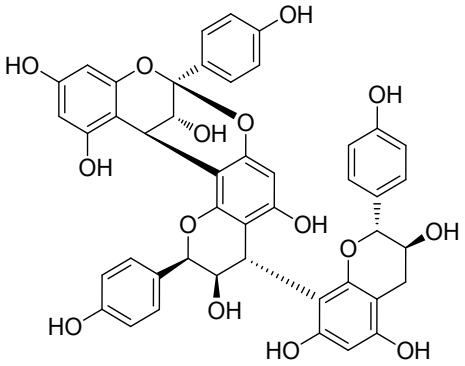
Scheme 3. Ito's Synthesis of (+)-Cinnamtannin B-1 (13) [a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMF, r.t., 24 h; (b) DDQ, 2-ethoxyethanol, DCM, r.t., 1.5 h; (c) $BF_3{\cdot}OEt_2$, 2,6-xylyl-1-thiol, DCM, –78 ºC → –70 ºC, 1.5 h; (d) *n*-Bu_4NF, HOAc, THF, 0 ºC. (e) $BF_3{\cdot}OEt_2$, DCM, –78 ºC → –30 ºC, 4 h; (f) **4**, I_2, Ag_2O, molecular sieves (4 Å), DCM, –78 ºC → –40 ºC, 2 h; (g) *n*-Bu_4NF, THF, reflux, 16 h; (h) H_2, 5% $Pd(OH)_2/C$, THF, MeOH, H_2O, r.t., 2 h. EE= 2-ethoxyethyl. Xy=2,6-xylyl.[36]

146

147 This synthetic work described by Ito *et al.*[36] has been used by the same research team in
148 the synthesis of the trimeric A-type PAC selligueain A in a 44% overall yield[44] (Figure 2).



149 **selligueain A**

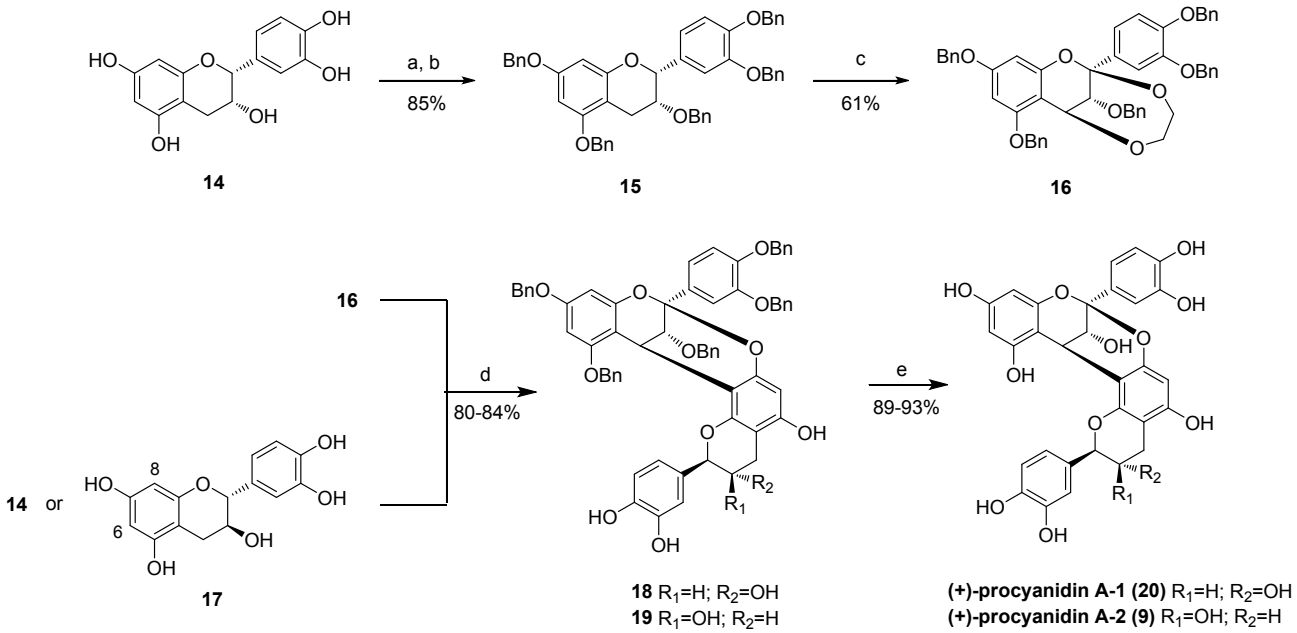
150 **Figure 2**. Chemical structure of selligueain A.

151

152 More recently, in 2019, the same research group could significantly simplify their
153 previous synthetic procedure achieving the synthesis of (+)-procyanidins A-1 and A-2 (46% and
154 42% overall yields, respectively) using free flavan units (**14** and **17**) as nucleophiles (Scheme
155 4).[45] The direct use of **14** or **17** and the non-bromo capped substrate **16** (compare Schemes 2 and
156 4) allowed an important reduction of synthetic steps. Furthermore, two minor secondary products
157 were also formed (6–9%) in the procedure due to the nucleophilic attack of the C-6 of flavanols
158 **14** or **17** to the electrophilic moiety **16**. These authors have studied and explained for the first
159 time the origin of the more nucleophilic character of C-8 compared to C-6 in nucleophilic units
160 such as flavanols **14** or **17**.[45]

161

Scheme 4. Improved Synthesis of (+)-Procyanidins A-1 (20) and A-2 (9) [a]



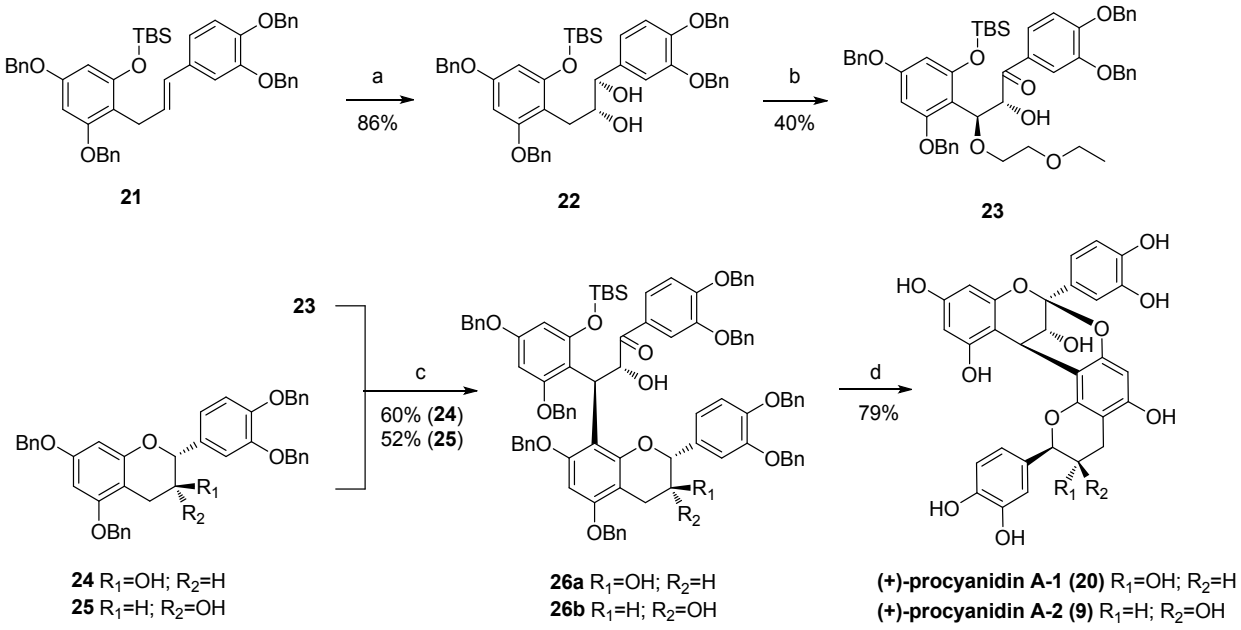
[a]Reagents and conditions: (a) Ac_2O, DMAP, pyridine, r.t., 17 h; (b) NaH, BnCl, H_2O, n-Bu_4NI, DMF, 15 ºC, 40 h; (c) DDQ, $(CH_2OH)_2$, DCM, reflux, 3 h; (d) CSA (camphorsulfonic acid), EtOH, dioxane, r.t., 24 h; (e) H_2, ASCA-2®, THF, MeOH, H_2O, r.t., 3 h.[45]

In 2015, a second research group (Sharma and col.[35]) reported other interesting synthesis of A-type PACs (Scheme 5). In this case, the synthetic procedure was started with the synthesis of diol **22** *via* a Sharpless asymmetric dihydroxylation of the 1,3-diphenylpropene derivative **21**, which was previously prepared according to their previous experience.[46] Compound **22** was then converted into the double electrophile key intermediate **23** by two sequential benzylic oxidations using DDQ as oxidizing agent. The coupling reaction between **23** and the fully protected (+)-catechin (**24**) or (–)-epicatechin (**25**) using bentonite K-10 as a solid acid catalyst afforded compounds **26a** or **26b**, which after subsequent removal of the phenolic protecting groups led to

177 (+)-procyanidin A-1 (**20**) or (+)-procyanidin A-2 (**9**) in a 16% or 14% overall yield, respectively.
178 This novel stereoselective methodology was further extended to the synthesis of other six
179 additional A-type PAC stereoisomers.[35]

180

181 **Scheme 5. Sharma's Synthesis of A-type (+)-Procyanidins A-1 (20) and A-2 (9)** [a]



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183

184 [a]Reagents and conditions: (a) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, r.t.→ 0 ºC, 24 h; (b) DDQ, DCM, r.t., 4 h;
185 then DDQ, 2-ethoxyethanol, DCM, r.t., 72 h; (c) Bentonite K-10, DCM, 0→ 4 ºC, 6 h; (d) *n*-Bu_4NF, DCM, HOAc,
186 THF, 0→ 4 ºC, 3 h; then H_2, EtOAc, 20% $Pd(OH)_2/C$, 1.5 h.[35]

187

188 These methodologies reported for the synthesis of A-type PACs from monomers
189 overcome, at the moment, the bioinspired methods based on B-type PAC oxidations and open the
190 possibility to achieve the synthesis of diverse and even more complex nature-identical A-type
191 PACs. In these syntheses the oxidation step with DDQ and the coupling reaction between

monomers are the key steps, which might be further optimized in order to ensure improved overall reaction yields. However, and despite these syntheses have clearly been a milestone, it remains to see whether they will be the practical way of obtaining natural A-type PACs in larger amounts to address more ambitious biological activities. On the other hand, efforts made over many years to synthesize natural A-type PACs have enabled to explore different pathways that have led to the synthesis of many structurally-simplified analogues to A-type PACs, which open up new possibilities as shown in the following section.

SYNTHESIS OF A-TYPE PROANTHOCYANIDIN ANALOGUES

It is known that the interest and applications of natural products are occasionally limited by their poor availability and sometimes complex chemical structures what, in some cases, makes their syntheses not economically viable. For that reason, the structural simplification of natural bioactive products (natural product-mimetic scaffolds) would become a good alternative approach to search for new potential biologically active products. In that sense, the complexity of the bicyclic structure of A-type PACs and consequent synthetic difficulty have resulted in an increased number of scientific contributions in the synthesis of (simplified) analogues to A-type PACs. This section will review the synthetic approaches to obtain analogues to A-type PACs. The most closely structurally-related analogues to natural PACs have a core of 2,8-dioxabicyclo[3.3.1]nonane and their syntheses have been performed using different types of starting materials such as chalcones and flavylium salts, among others (Figure 3).

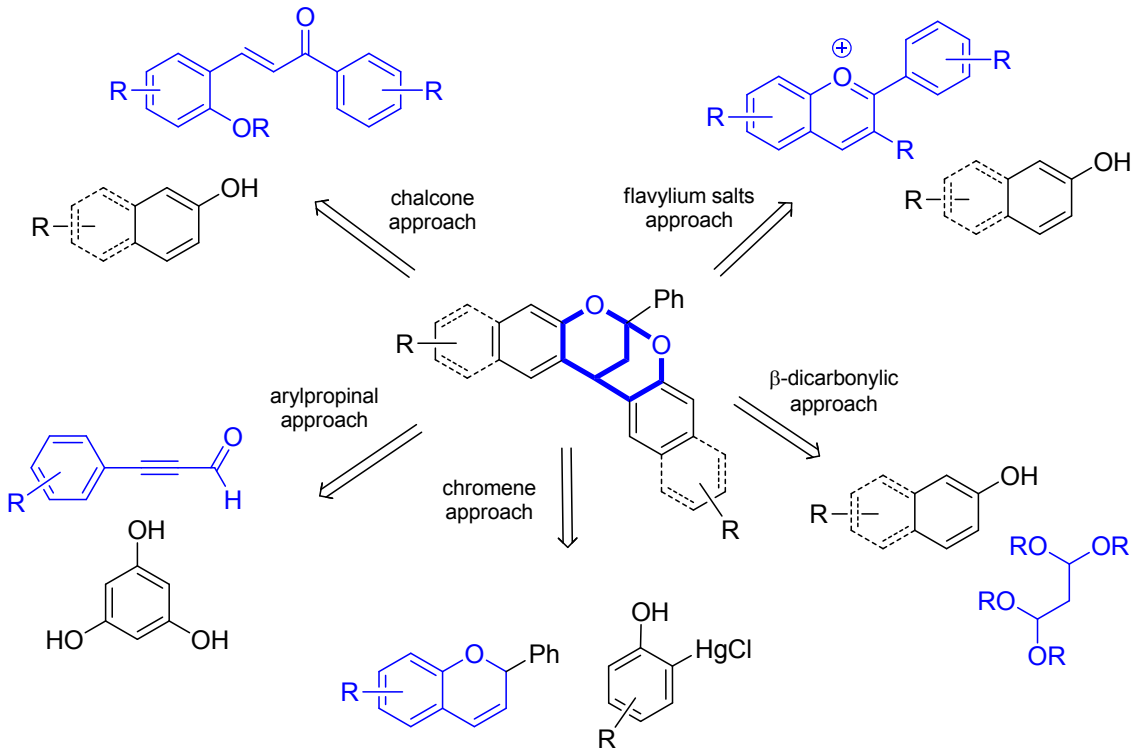
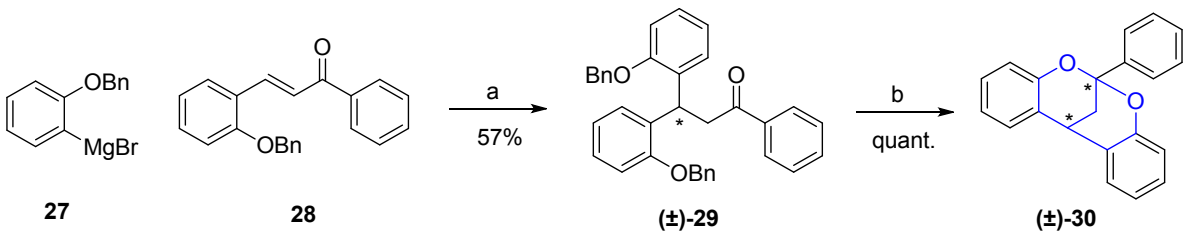


Figure 3. Building blocks for the synthesis of analogues to A-type PACs.

Synthesis of A-type PAC Analogues through Chalcones. The first synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives through chalcones was performed by Weinges and Theobald in 1971[47] (Scheme 6). In this synthetic procedure the nucleophilic addition of the protected phenolic organomagnesium bromide **27** to chalcone **28** afforded, after the removal of protective groups, the 2,8-dioxabicyclo[3.3.1]nonane derivative (±)-**30** in a moderate yield (57%).

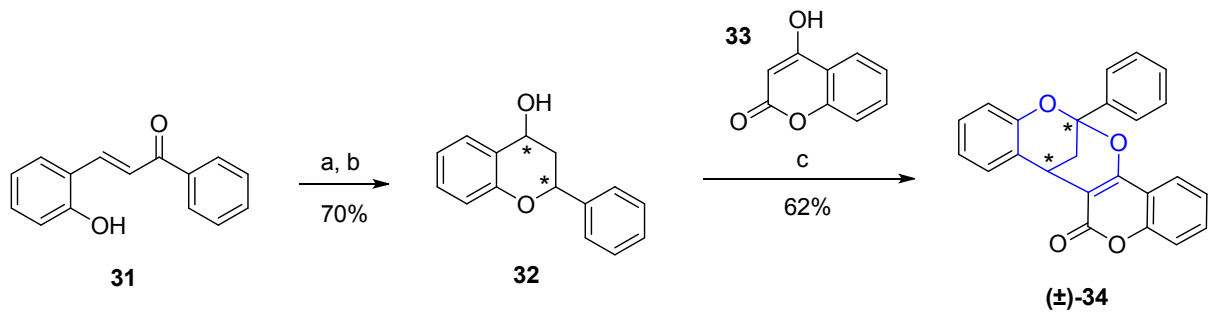
Scheme 6. First Synthesis of a 2,8-Dioxabicyclo[3.3.1]nonane Core through Chalcones [a]



[a]Reagents and conditions: (a) Toluene. (b) P_2O_5.[47]

Weinges and Theobald's synthesis did not have much impact and chalcones were unused as starting material to prepare PAC analogues for a long period of time. In 2005, chalcones were used again by Chen *et al*.[48] who synthesized the 2,8-dioxabicyclo[3.3.1]nonane derivative (±)-**34** in a three-step methodology through 2-hydroxychalcone (**31**) with a moderate overall yield (43%) (Scheme 7). First, 2-hydroxychalcone (**31**) (prepared from 2-hydroxyacetophenone) was cyclized by refluxing with phosphoric acid in ethanol and then reduced with $NaBH_4$ to afford the cyclic alcohol **32**. Finally, condensation of alcohol **32** with 4-hydroxycoumarin (**33**) in $AlCl_3$ at 130–140 ºC allowed the synthesis of the bicyclic compound (±)-**34**.

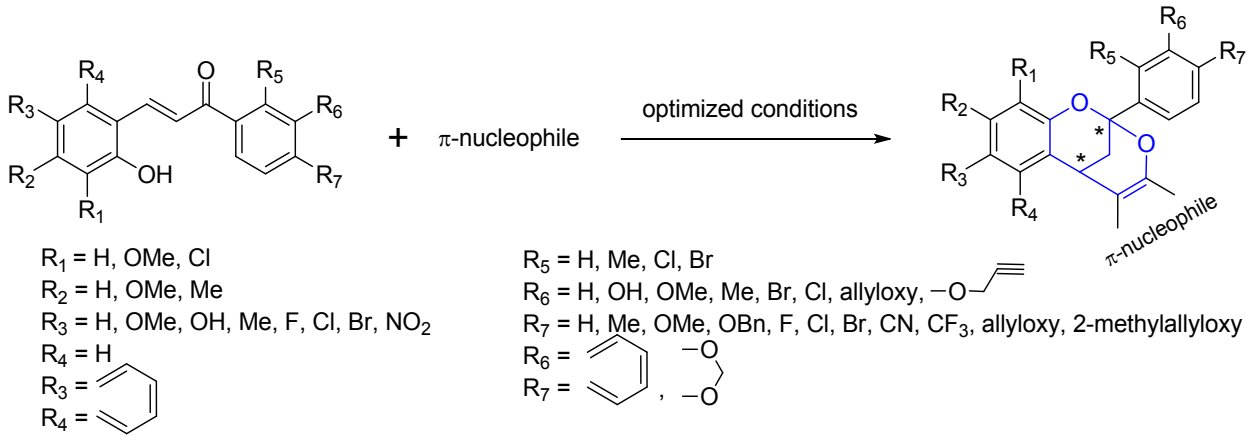
Scheme 7. Chen's Methodology to Synthesize A-type PAC Analogues [a]

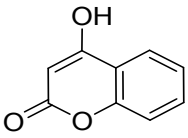


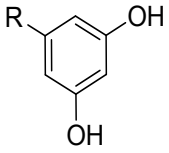
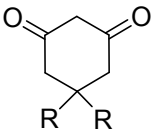
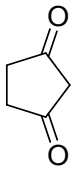
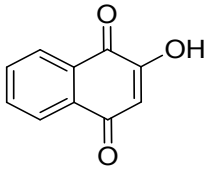
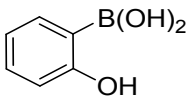
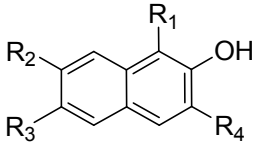
[a]Reagents and conditions: (a) H_3PO_4, EtOH, reflux, 3 h; (b) $NaBH_4$, MeOH, r.t., 48 h; (c) $AlCl_3$, 130–140 ºC, 0.5 h.[48]

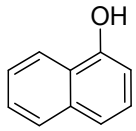
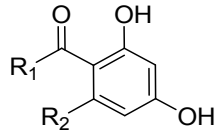
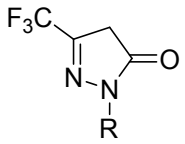
More recently, a large number of synthetic procedures have been reported in a brief period of time (2013–2019) to achieve the synthesis of A-type PAC analogues through chalcones.[49,50,51,52,53,54,55,56,57,58,59,60,61] In all these studies, the optimization of the experimental conditions for the coupling reaction between a given chalcone and the π-nucleophile has carefully been performed selecting the proper set of catalyst, solvent and temperature for each individual reaction (Table 1).

Table 1. Optimized Conditions to Synthesize A-type PAC Analogues through Addition of π-Nucleophiles to Chalcone



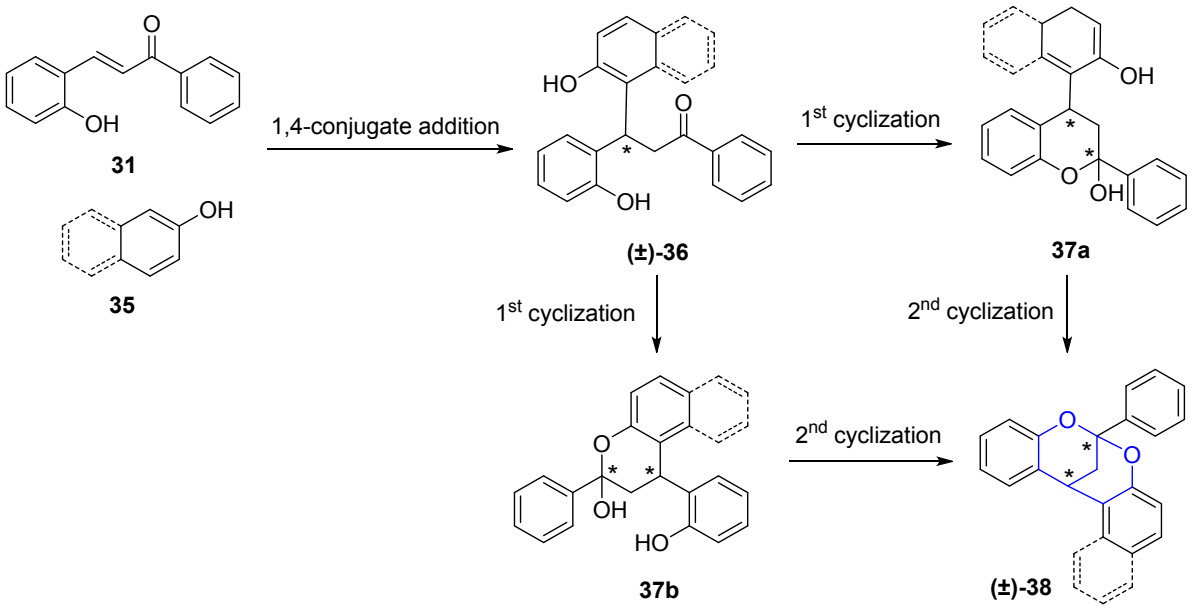
π-Nucleophile	Optimized conditions	Yield	Ref.
	TsOH or HCl (aq), CH_3CN, r.t., hν	16–85%	49
	Amberlyst-15, toluene, reflux, 6–12 h	53–69%	51
	4-Pyrrolidinopyridine, $CHCl_3$, reflux, 24 h	34–71%	54
	I_2, EtOH, H_2O, reflux,	85–94%	58

	2–5 h		
	Toluene, reflux, 6 h	72–93%	61
 R = H, OH	TsOH or HCl (aq), CH_3CN, r.t., hν	50–81%	49
	$CeCl_3$, NaI, CH_3CN, reflux, 2–4 h	79–95%	56
 R = H, Me	TsOH or HCl (aq), CH_3CN, r.t., hν	49–99%	49
	Amberlyst-15, toluene, reflux, 6–12 h	55–73%	51
	Toluene, reflux, 6 h	71–87%	61
	Amberlyst-15, toluene, reflux, 10–12 h	60–72%	52
	Amberlyst-15, toluene, reflux, 6–10 h	62–70%	51
	n-PrOH, reflux, 6–12 h	68–88%	61
	$Pd(PhCN)_2Cl_2$, $AgBF_4$, toluene, r.t., 24 h	41–97%	59
 R_1 = H, Br R_2 = H, Br, CN, OMe R_3 = H, Br, OMe R_4 = H, CONHPh	$[Yb(CH_3CN)_9][AlCl_4]_3$ PhCl, reflux, 72 h	46–91%	50
	Amberlyst-15, toluene, reflux, 8–14 h	60–71%	51
	Camphorsulfonic acid, toluene, reflux, 12 h	41–85%	57
	AgOTf, toluene, reflux, 18 h	36–72%	60

	Amberlyst-15, toluene, reflux, 12–14 h	40–44%	51
 R_1 = OMe, OEt, Me, Et, CH_2Ph, Ph R_2 = OH,Me, H	Diammonium diacetate, toluene, reflux, 8 h	71–90%	55
	p-Toluenesulfonic acid, toluene, reflux, 6 h	75–87%	55
 R = H, Ph	*p*-Xylene, reflux, 4 h	58–84%	53

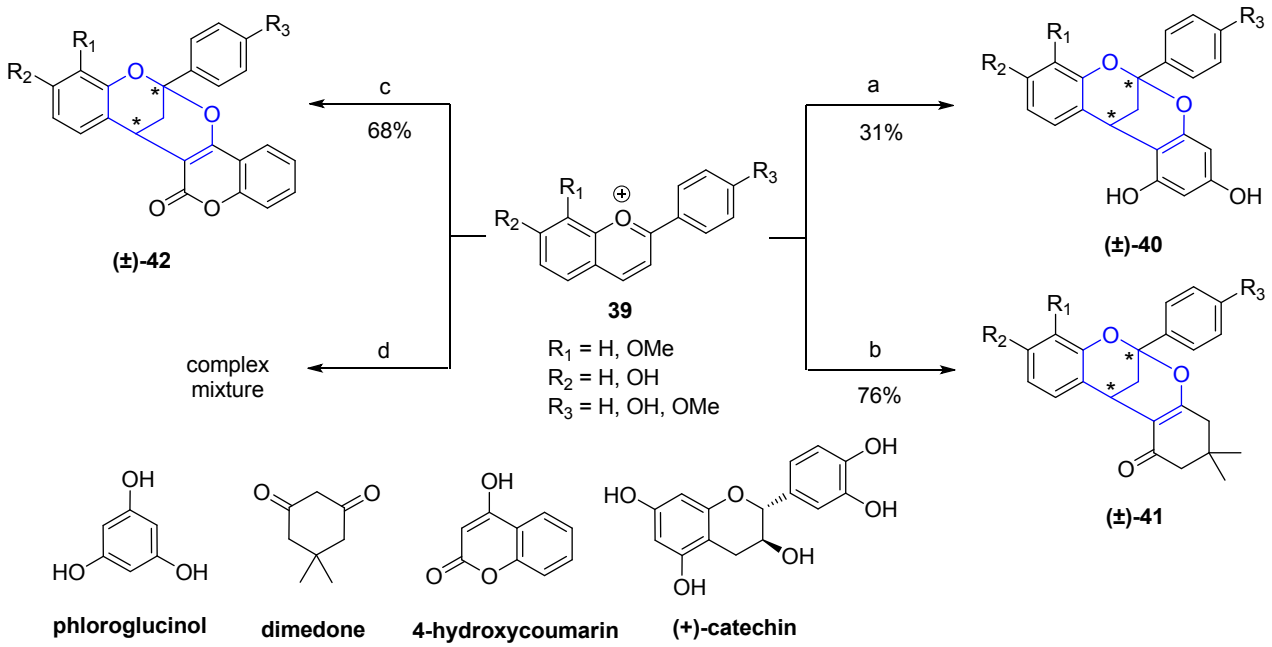
The main differences between all these procedures lie in the electrophilic activation of the α,β-unsaturated ketone and the reaction solvent used. In this sense, the activation has been performed by Lewis acid,[50,56,58,59,60] by Brönsted acid,[49,51,52,55,57] by organobases[54] and also without any catalyst.[53,61] It seemed that the reaction started with a 1,4 conjugate addition between 2-hydroxychalcone (**31**) and the corresponding π-nucleophile (**35**), affording the key intermediate (±)-**36**, which quickly evolved to the target bicyclic compound (±)-**38** through a double intramolecular cyclization (Scheme 8).[55,59,60]

Scheme 8. Mechanism Proposal for the Conjugated Addition of π-Nucleophiles to Chalcones and Subsequent Double Intramolecular Cyclization



Synthesis of A-type PAC Analogues through Flavylium Salts. The first synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives from flavylium salts was performed by Jurd's group (Scheme 9).[62,63,64,65] They observed that heating flavylium salts (**39**) with different π-nucleophiles such as phloroglucinol,[64] dimedone[65] or 4-hydroxycoumarin[62] in a methanol-water mixture at pH 5.8, mainly afforded molecules with a 2,8-dioxabicyclo[3.3.1]nonane core ((±)-**40**, (±)-**41** and (±)-**42**) in 31%, 76% and 68% yields, respectively. Unfortunately, when this methodology was applied to other π-nucleophiles such as (+)-catechin, a complex mixture was afforded instead.[63,64]

Scheme 9. First Syntheses of the 2,8-Dioxabicyclo[3.3.1]nonane Core through Flavylium Salts [a]



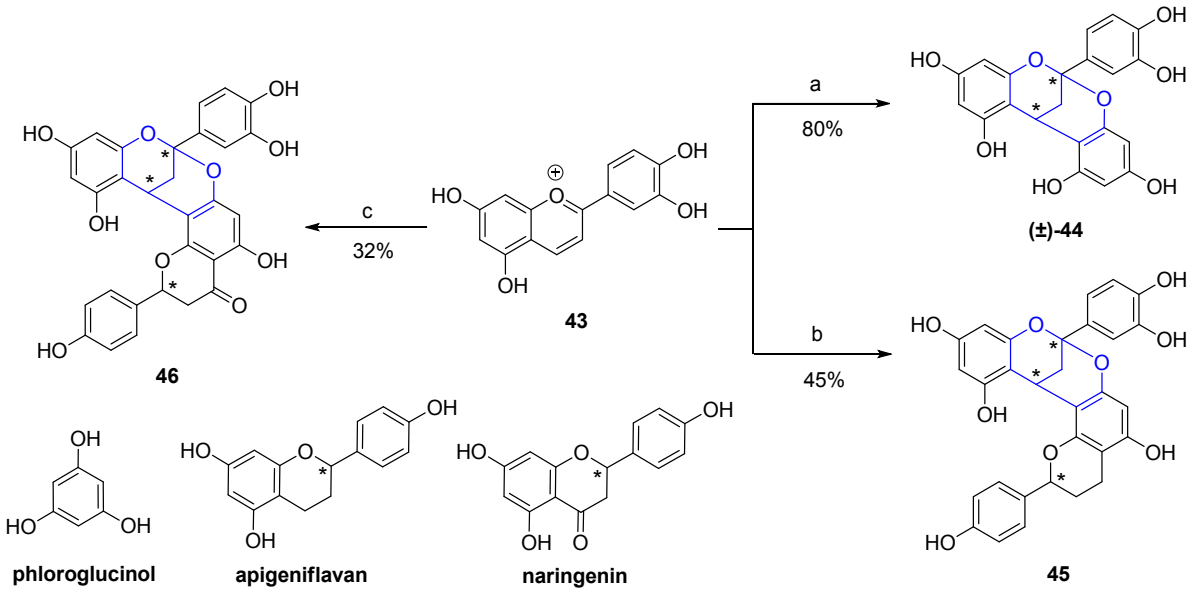
[a]Reagents and conditions: (a) Phloroglucinol, MeOH, aqueous buffer pH 5.8, 70 ºC, 5 min;[64] (b) Dimedone, MeOH, aqueous buffer pH 5.8, reflux, 10 min;[65] (c) 4-Hydroxycoumarin, HOAc, HCl (aq.), reflux, 5 min;[62] (d) (+)-Catechin, HOAc, H_2O, 50 ºC, 1 h.[62,63]

In 1984, Bishop and Nagel[66] were able to improve the synthetic methodology described previously by Jurd's group, achieving the synthesis of a 2,8-dioxabicyclo[3.3.1]nonane derivative using malvidin-3,5-diglucoside as flavylium salt and (+)-catechin as the π-nucleophile unit in low yield (29%). More recently, Cheynier's group used malvidin-3-glucoside and (–)-epicatechin as starting materials to achieve the synthesis of the corresponding 2,8-dioxabicyclo[3.3.1]nonane derivative also in low yield (11%).[67]

295 However, the important observations reported by Jurd's group and Bishop and Nagel
296 during their research were unnoticed until 2006, when Selenski and Pettus were able to improve
297 previous results using microwave radiation (MW).[68] In this case, the microwave heating at 150
298 ºC of a 3:1 mixture of phloroglucinol and flavylium salt in methanol-water mixtures at pH 5.8
299 afforded the bicyclic compound (±)-**44** in a 80% yield (Scheme 10). Selenski also tested other π-
300 nucleophiles such as flavans and flavanones, affording the bicyclic compounds **45** and **46** in 45%
301 and 32% yields, respectively, as mixtures of diastereomers.

302

303 **Scheme 10. Selenski's Methodology to Synthesize A-type PAC Analogues** [a]



304

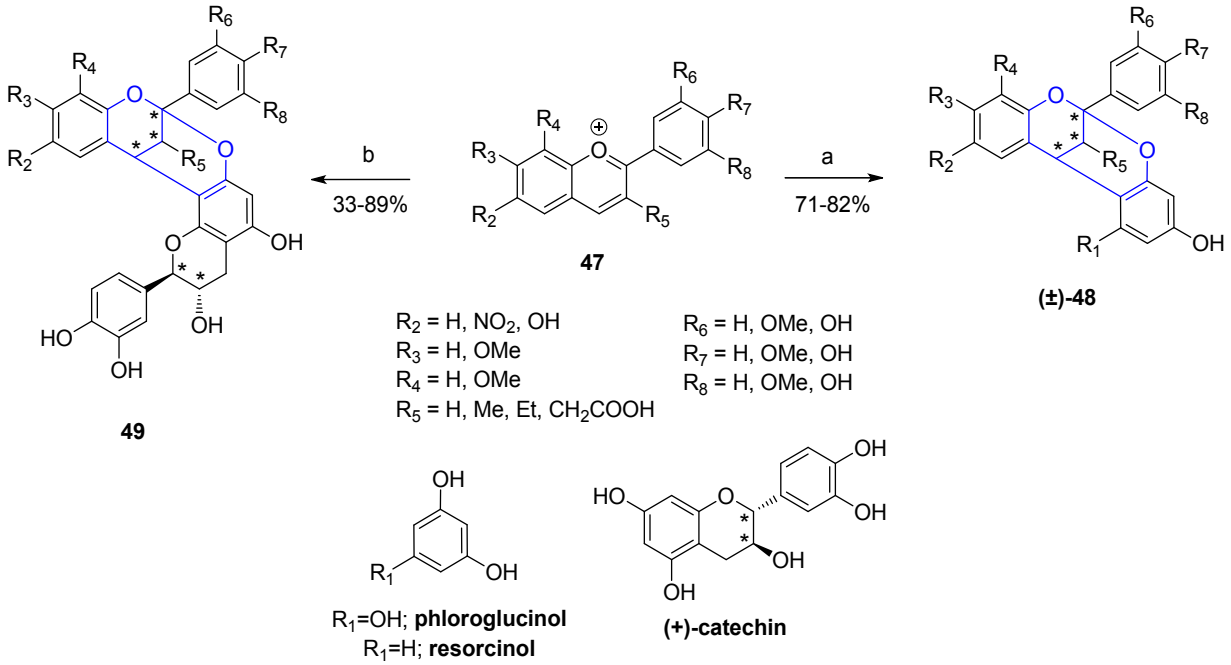
305

306 [a]Reagents and conditions: (a) Phloroglucinol, MeOH, aqueous buffer pH 5.8, 150 ºC, MW, 1 h; (b) Apigeniflavan,
307 MeOH, aqueous buffer pH 5.8, 150 ºC, MW, 2 h; (c) Naringenin, MeOH, aqueous buffer pH 5.8, 120 ºC, MW, 20
308 h.[68]

309 One year later, in 2007, Kraus' group reported a methodology to synthesize 2,8-
310 dioxabicyclo[3.3.1]nonane derivatives through flavylium salts with low electronic density in

absolute methanol at 50 ºC[69,70] (Scheme 11). The presence of an electron withdrawing group (such as $–NO_2$) or at least the absence of electron donating groups (such as –OH) in the A-ring of flavylium salts was found to be essential to achieve the synthesis of 2,8-dioxabicyclic compounds in higher yield (81% yield (R_2=NO_2) versus 47% yield (R_2=OH) in compound **49**; Scheme 11). Moreover, it was also very important to keep anhydrous conditions to ensure high yields in the reaction.[70] With this methodology, it was possible to achieve the synthesis of a great variety of 2,8-dioxabicyclo[3.3.1]nonane derivatives ((±)-**48** and diastereomeric mixtures of **49**) in moderate to high yields (33–89%).

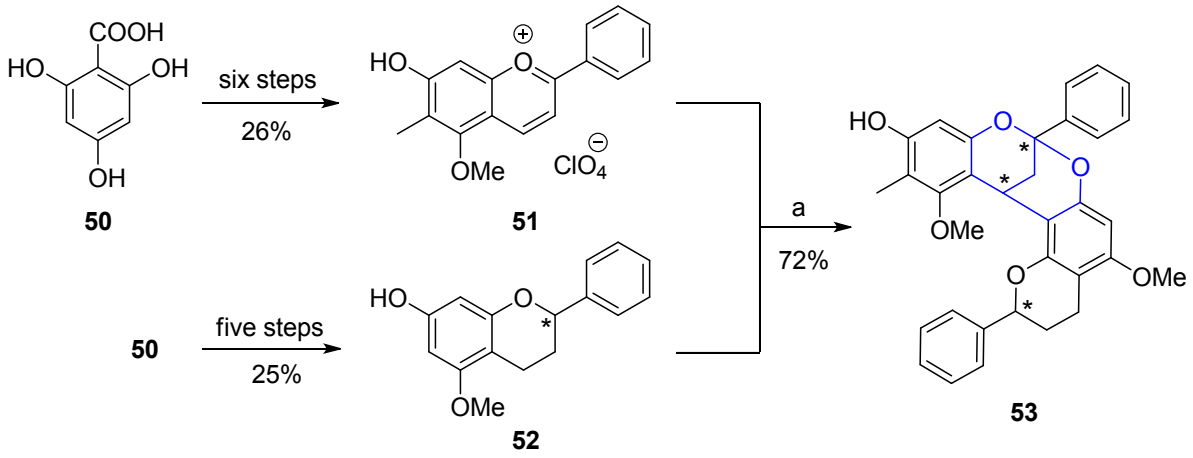
Scheme 11. Kraus' Methodology to Synthesize A-type PAC Analogues [a]



[a]Reagents and conditions: (a) Phloroglucinol or resorcinol, MeOH, 50 ºC, 1–24 h; (b) (+)-Catechin, MeOH, 50 ºC, 1–24 h.[69,70]

Recently, in 2017, the flavylium salt methodology has been applied to achieve the synthesis of other natural products (dracoflavans C-1 and C-2) structurally related to A-type PACs.[71] Synthesis of the flavylium salt **51** was performed in a six-step methodology with a 26% overall yield from **50**. For its part, the nucleophile moiety **52** was also synthesized from **50** in five steps with a 25% overall yield (Scheme 12). Finally, the coupling reaction between both moieties was performed in acetonitrile-water mixtures at pH 5.8 (inspired on the previously described solvent conditions of Selenski and Pettus)[68] at 110 ºC in a closed vial.[71] That afforded a diastereomeric mixture of dracoflavans C-1 and C-2 (**53**) in a 72% yield with a d.r. of 56:44 ratio (Scheme 12), which is almost identical to the ratio in which these two diastereomers have been found in nature.

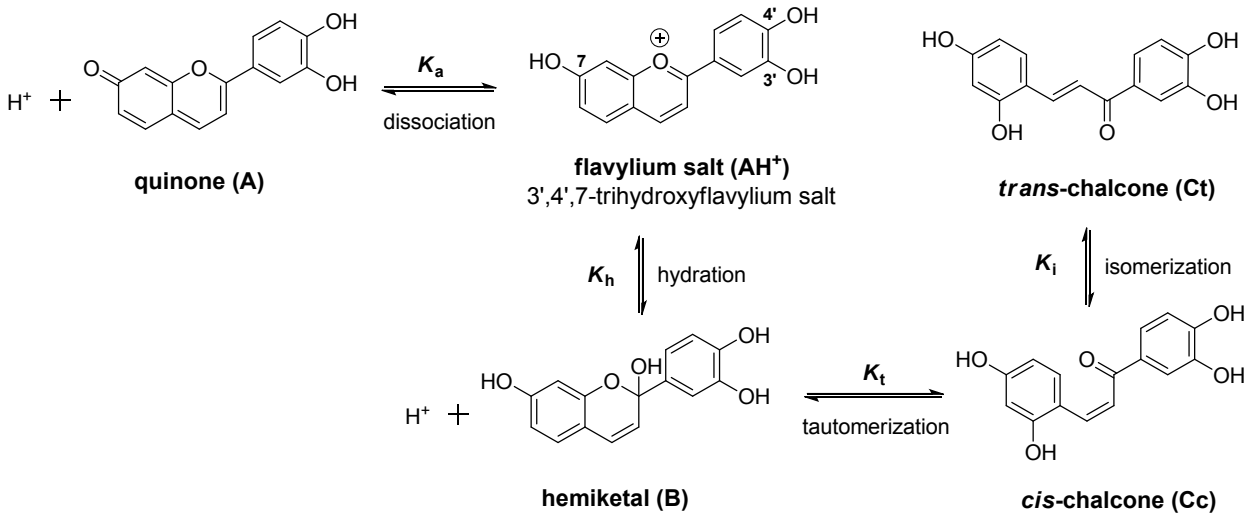
Scheme 12. Synthesis of Dracoflavans C-1 and C-2 (53) [a]



[a]Reagents and conditions: (a) MeOH, aqueous buffer pH 5.8, 110 ºC, 2 h.[71]

More recently, our research group has prepared A-type PAC analogues through the nucleophilic addition of several π-nucleophiles to flavylium salts.[72,73] We have focused on the study of the electronic features that flavylium salts should fulfil to be suitable starting materials for the synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives. In that way, the synthesis of several flavylium salts (*via* acid catalyzed aldolic condensation between salicylic aldehyde and acetophenone derivatives) and the study of their thermodynamic and kinetic properties[74] have been described, allowing us to propose that the thermodynamic stability of flavylium salts, which is determined by the constant K'_a (Scheme 13), could be related to the electronic density of the salt.[72,74] Flavylium salts are involved in a very complex pH-dependent multistate of chemical reactions (Scheme 13). At acid pH values flavylium salt (AH^+) is the most stable species, but when the pH increase, different species start to appear, such as quinoidal base (A), by a proton transfer reaction; hemiketal (B), by a hydration reaction; *cis*-chalcone (Cc), by a non-classic tautomerization process of B; and finally *trans*-chalcone (Ct), by a isomerization of Cc. Despite the complexity of this system, it can be simplified by considering a single acid-base equilibrium involving the species AH^+ and a conjugate base CB which englobes all the other species (Scheme 13). This global chemical reaction is controlled by the global thermodynamic constant K'_a, defined by a linear combination of all the equilibrium constants of every single chemical process where AH^+ is involved: (*i*) proton transfer (K_a), (*ii*) hydration (K_h), (*iii*) tautomerization ($K_h \times K_t$), and (*iv*) isomerization ($K_h \times K_t \times K_i$).[75]

Scheme 13. Multistate of Reversible Chemical Reaction of Flavylium Salts Exemplified for 3',4',7-Trihydroxyflavylium Cation in Acidic to Moderately Acidic Solutions

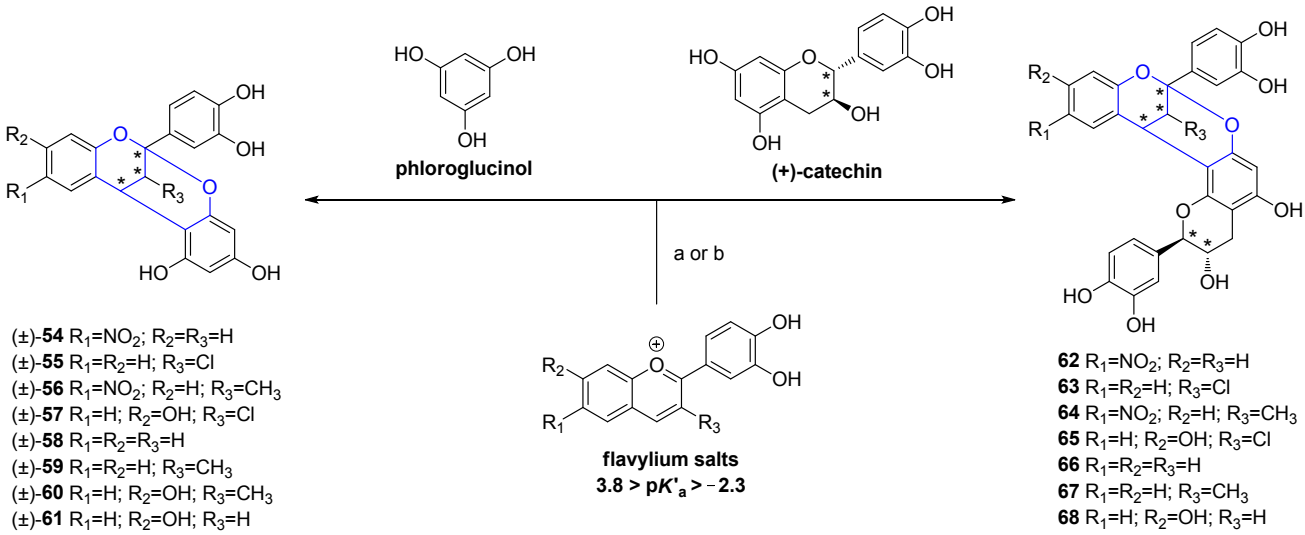


global chemical reaction $\mathbf{AH^+ + H_2O} \overset{K'_a}{\rightleftharpoons} \mathbf{CB}$ $\quad$ **[CB] = [A] + [B] + [Cc] + [Ct]**

global thermodynamic constant $K'_a = K_a + K_h + K_h \times K_t + K_h \times K_t \times K_i$

Our further studies allowed us to correlate the reactivity between a flavylium salt with π-nucleophiles (i.e. phloroglucinol, (+)-catechin) with the constant K'_a of the flavylium salt and hence validate our initial hypothesis (Scheme 14).[72] It was observed that when flavylium salts have a pK'_a value of 1.3 or lower, Kraus' conditions (methanol, 50 ºC) may be useful to achieve the synthesis of bicyclic derivatives. However, for flavylium salts with a pK'_a value of 2.8 or higher, a microwave methodology should be used in order to achieve, in some cases, the reaction between these flavylium salts and the nucleophiles (Scheme 14).[72]

Scheme 14 Synthesis of A-type PAC Analogues through Flavylium Salts with different pK'_a [a]

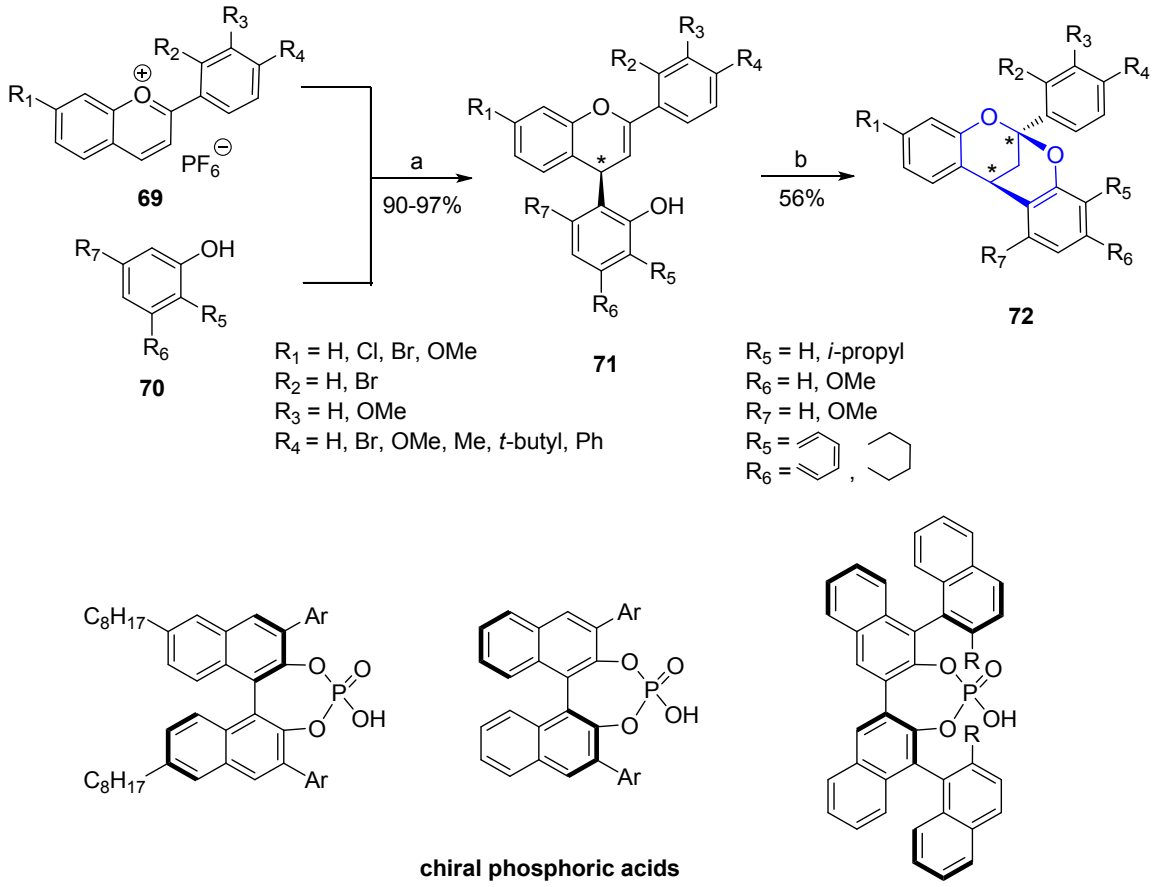


[a]Reagents and conditions: (a) MeOH, 50 ºC, 24 h; (b) MeOH, 100 ºC, MW, 1 h.[72]

In addition, our research group has evaluated the antimicrobial and antibiofilm properties of a selection of 2,8-dioxabicyclo[3.3.1]nonane derivatives previously synthesized by us (**54**, **55**, **61**, **66**)[73] and compared with the values obtained for two natural PACs ((+)-procyanidin B-2 and (+)-cinnamtannin B-1), also isolated by us from laurel wood,[76] and for commercial (+)-procyanidin A-2. This study improved the knowledge about the structural features that may have some influence on the antimicrobial and antibiofilm activities of A-type PAC analogues against foodborne pathogens: (*i*) the presence of electron-withdrawing groups at rings A or C instead of hydroxyl groups enhance activities (**54**, **55**, **66** *vs* **61**); (*ii*) the smaller size of the bottom monomer also enhances the effectiveness of the derivatives (**54**, **55**, **61** *vs* **66**). In all cases, the synthetic analogues were found to show higher antimicrobial activities than natural PACs, but further analyses should be performed with a large number of compounds to get a more rational and accurate structure–activity relationship.

In all the synthetic methodologies of A-type PACs analogues described up to now (through chalcones or flavylium salts), the addition of the π-nucleophilic unit to the electrophilic substrate takes place in a non-stereoselective manner leading to mixtures of enantiomers or diastereomers. In order to overcome this problem, Yang *et al.*[77] reported in 2016 a catalytic enantioselective synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives through chiral flavylium salts. The asymmetry was induced by the flavylium salt (benzopyrylium hexafluorophosphate) in the presence of a chiral anion (Scheme 15). Thus, the flavylium salt underwent an *in situ* chiral anion phase-transfer (CAPT) catalysis using several chiral phosphoric acids as catalysts. In the medium, CAPT of an insoluble benzopyrylium cation generates a soluble chiral benzopyrylium ion pair allowing its asymmetric reaction with the phenolic nucleophile **70**. As a result, the key 4-substituted flavene **71** was formed with high enantioselectivity. Then, the final cyclization was performed using *p*-toluenesulfonic acid (*p*-TSA) to achieve the bicyclic structure **72** in around 50% overall yield with up to 94% e.e.

Scheme 15. Catalytic Enantioselective Synthesis of A-type PAC Analogues [a]



414

415 [a]Reagents and conditions: (a) Chiral phosphoric acid, Na_3PO_4, toluene, r.t., 2–12 h; (b) *p*-TSA, DCM, r.t., 1–2 h.[77]

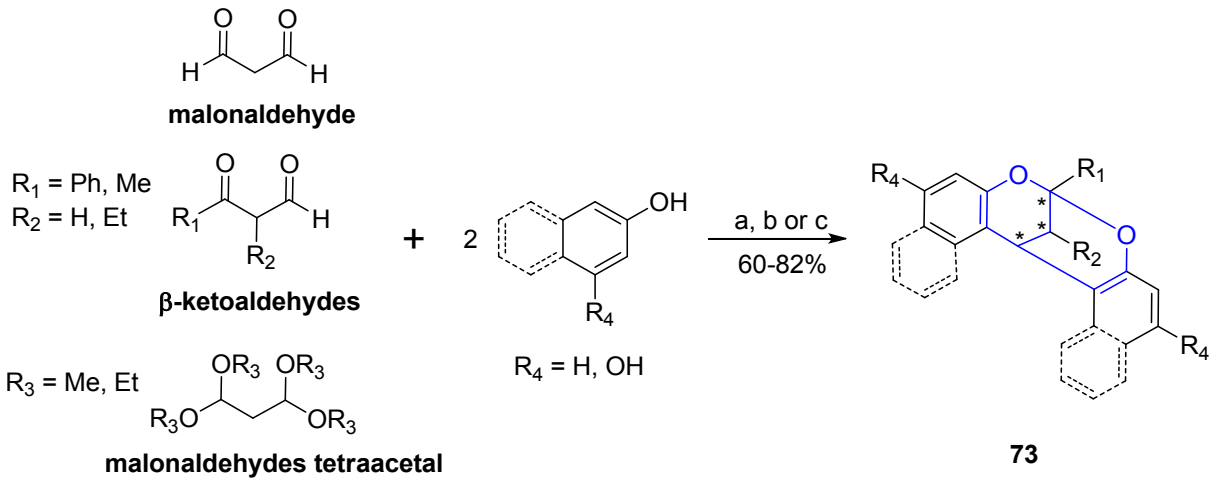
416

417 The synthesis of A-type PACs analogues using flavylium salts as starting material has
418 emerged as a versatile way to prepare many molecules functionalized in almost all carbons of the
419 skeleton even at C-3 of ring C. However, the method still fails in the introduction of hydroxyl or
420 oxygenated groups at that position, which would be required to also get natural A-type PACs
421 from flavylium salts. Despite this drawback, the fact that an asymmetric version has recently
422 been reported makes the flavylium salts' methodology very robust to get many enantiomerically-
423 pure analogues. Taking into account that the only study to evaluate the antimicrobial activity of
424 some analogues in comparison to related natural A-type PACs[73] has shown improved properties
425 for the former, it means that an interesting research area would be opened to explore as many

biological activities as possible on big collections of analogues, both racemates and pure enantiomers.

Other Syntheses of A-type PAC Analogues. Other starting materials have also been used to achieve the synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives, such as β-dicarbonylic compounds[78,79,80,81,82,83,84,85,86,87,88] chromenes,[89,90,91] and arylpropinals[92] (Figure 3). The first substrates (1,3-dicarbonylic compounds) have been used by different research groups (Scheme 16) following similar experimental procedures: a mixture of two equivalents of the phenolic compound (usually naphtol or phenol) and one equivalent of the proper dicarbonylic compound (malonaldehyde,[78] β-ketoaldehydes[79,80] or malonaldehyde tetraacetal[81,82,83,84,85,86,87,88]) were reacted in the presence of Brönsted acids to afford the symmetric bicycles **73** in moderate to high yields (60–82%) (Scheme 16).

Scheme 16. Synthesis of Symmetric A-type PAC Analogues through β-Dicarbonylic Compounds [a]



446

447 [a]Reagents and conditions: (a) Malonaldehyde, HCOOH, 60 ºC, 4 h;[78] (b) β-Ketoaldehyde, HOAc, H_2SO_4, 50 ºC, 12

448 h;[79,80] (c) Malonaldehyde tetraacetal, trifluoroacetic acid, r.t., 48 h.[81,82,83,84,85,86,87,88]

449

450 The use of β-dicarbonylic compounds has the advantage of performing the synthesis of

451 the bicyclic core in just one step with moderate to high yield, but it is a methodology not

452 currently used due to its little scope that yields only symmetric A-type PACs analogues.

453 Chromenes provided the synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives ((±)-**76**)

454 but in low to moderate yield (9−56%).[89,90,91] The formation of several byproducts (**77**, **78**) could

455 limit its use as starting material (Scheme 17). Briefly, a Heck-oxyarylation of chromene

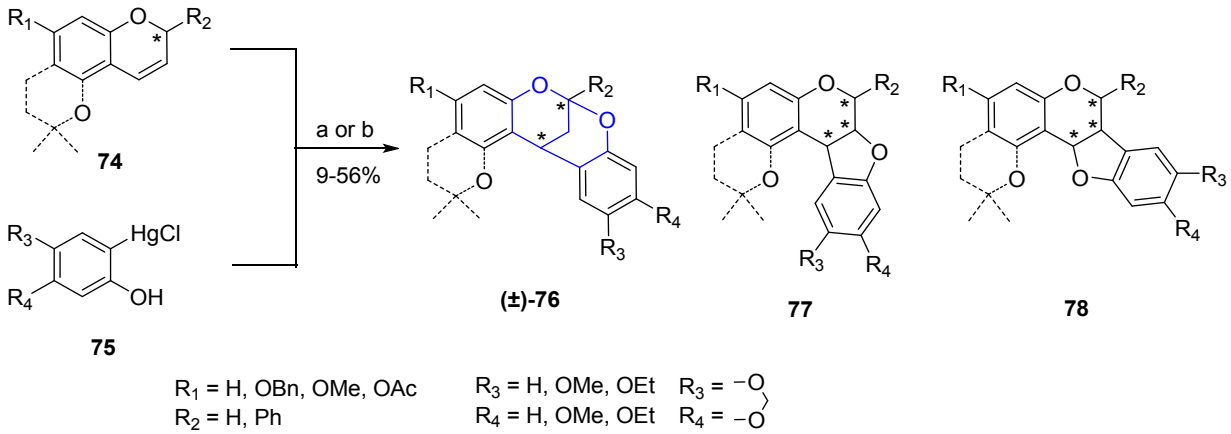
456 derivatives (**74**) and 2-chloromercuriphenols (**75**) catalyzed by Pd(II) salts allowed the formation

457 of phenylpterocarpans (**77**, **78**) and the corresponding 2,8-dioxabicyclic compounds ((±)-**76**) as

458 major products (Scheme 17).

459

460 **Scheme 17. Syntheses of A-type PAC Analogues through Chromenes** [a]



461

462 [a]Reagents and conditions: (a) Li_2PdCl_4, acetone, r.t., 5–24 h;[89,91] (b) $PdCl_2$, LiCl, acetone, r.t., 0.5 h.[90]

463

464 And finally, arylpropinals[92] (Scheme 18) have recently been employed for the synthesis
465 of 2,8-dioxabicyclo[3.3.1]nonane derivatives in moderate to high yields (54–82%). Kraus and
466 Geraskin observed that the addition of two equivalents of phloroglucinol to arylpropinal
467 derivatives yielded 2,8-dioxabicyclo[3.3.1]nonane derivatives in low yields (less than 25%),
468 although they were significantly improved up to 82% by the acetylation of crude reactions prior
469 purification (Scheme 18).[92]

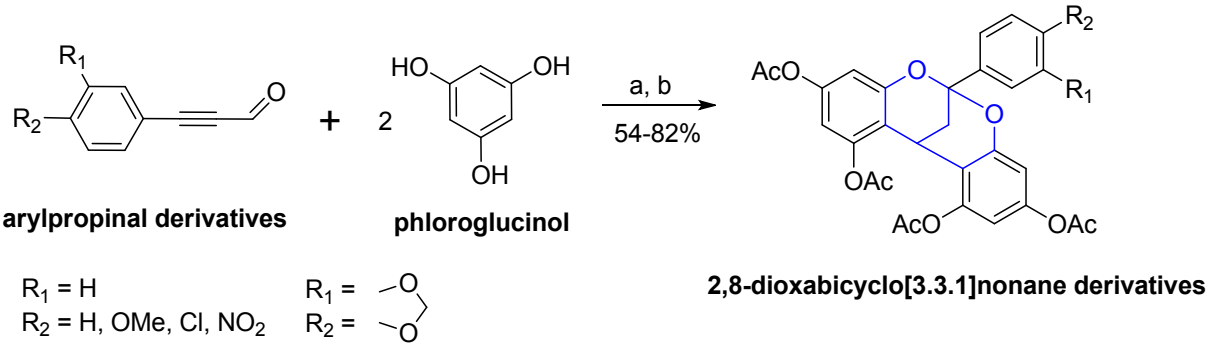
470

471

472

473

474 **Scheme 18. Syntheses of A-type PAC Analogues through Arylpropinal Derivatives** [a]



475

476 [a]Reagents and conditions: (a) *p*-TSA, CH_3CN, r.t., 12 h; (b) Ac_2O, pyridine, overnight.[92]

477

478 In conclusion, since Jurd's group reported in 1965 the synthesis of the 2,8-
479 dioxabicyclo[3.3.1]nonane skeleton of naturally occurring A-type PACs, many natural products
480 and synthetic chemists have been attracted by this outstanding topic due to the biological
481 activities and potential applications of this family of compounds and also by the intrinsic
482 difficulty to generate their characteristic C-3 oxygenated dioxabicyclic skeleton. However,
483 despite significant efforts made in the past, the first efficient synthesis of a natural (dimeric) A-
484 type PACs has been reported by Suzuki-Ohmori's group just few years ago. This means that
485 there is still margin in the near future for new syntheses of many other nature-identical PACs
486 with a higher degree of complexity to be described, in addition to dimers or trimers. This
487 forthcoming work would result, in principle, in the availability of larger amounts of A-type
488 PACs to address further and more ambitious biological studies on these molecules generally
489 found in human diet. Comparatively, a lot of work has been reported on the synthesis of
490 simplified analogues to A-type PACs, especially those with non-oxygenated groups at C-3 of the
491 C ring. All this work has led to a considerable number of molecules with certain structural
492 diversity on which, surprisingly, little work on biological activities has been reported in relation

493 to those described for natural A-type PACs. Taking into account that some analogues to A-type
494 PACs have shown higher activities than related natural ones (just few examples reported with
495 improved antimicrobial activities), it could mean that all this synthetic knowledge would open
496 the way to generate libraries of congeners for biological evaluation. Thus, according to the
497 outstanding biological properties of natural A-type PACs, one would expect to see considerably
498 more food (nutraceutics) and medicinal chemistry activities around this topic in the future.

499

AUTHOR INFORMATION

Corresponding Author

*Phone (Sofía Salido): 34-953-212746. E-mail: ssalido@ujaen.es

ORCID

Alfonso Alejo-Armijo: 0000-0001-8691-4628

Sofía Salido: 0000-0003-2319-7873

Joaquín Altarejos: 0000-0002-5532-8535

Notes

Authors declare no competing financial interest.

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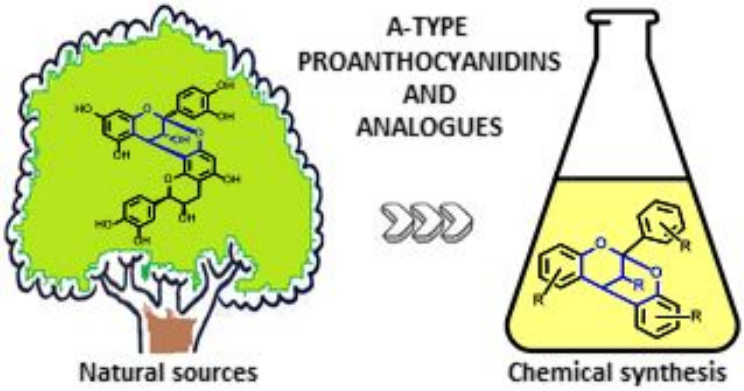
A-TYPE
PROANTHOCYANIDINS
AND
ANALOGUES
Natural sources
Chemical synthesis