Towards the Synthesis of Proanthocyanidins: Half a Century of Innovation

Abstract

Results emanating from the synthesis of proanthocyanidins played a crucial role in defining the constitution, regiochemistry, and absolute configuration of this complex but fascinating group of plant secondary metabolites. The initial efforts, commencing in 1966, were focused on structure elucidation of, especially, the procyanidins, profisetinidins, and prorobinetinidins. However, over the past 12 years the emphasis has shifted to the synthesis of the bioactive procyanidins and some of their derivatives at a scale that would permit assessment of their pharmacological properties. With a few exceptions, the vast majority of these synthetic protocols involve the formation of the interflavanyl bond by acid/Lewis acid activation at C-4 of a flavan-3,4-diol or its equivalent, and subsequent trapping of the incipient C-4 carbocation by the nucleophilic centers of a flavan-3-ol (catechin). This review represents the first comprehensive chronicle depicting the development of the subject of proanthocyanidin synthesis.

Introduction

The first reports dealing with the isolation and structure elucidation of naturally occurring proanthocyanidins (syn. condensed tannins) were documented in the early 1960s. These early contributions and achievements by pioneers like Forsyth and Roberts, Dreves and Roux, Freudenberg and Weinges, Swain, Geissman, Mayer, Sebaghi, Petler, Brown, and several others were covered in a comprehensive 1972 review [1]. The accuracy of the initial structural assignments needs to be judged in terms of the sophistication of the instrumentation available at the time. Thus, it soon became evident that the complexity of a proanthocyanidin structure would require utilization of the full array of tools at the disposal of the natural product chemist in order to address the subtleties of the structure elucidation of this fascinating class of natural products. Prevalent among these methods was the potential of synthetic protocols to complement physical methods like nuclear magnetic resonance (NMR) and circular dichroism (CD) spectroscopy, and mass spectrometric (MS) measurements. Therefore, it came as no surprise that the first synthesis of a procyanidin derivative was attempted as early as 1966 [2], such a synthesis being based on the premise that proanthocyanidins were biosynthetically formed via the condensation of a flavan-3,4-diol and a flavan-3-ol as the incipient electrophile and nucleophile, respectively [3, 4]. The development of synthetic methods for the production of proanthocyanidins was initially used as an analytical tool [2, 5–14] in the quest to assign their constitution and absolute configuration. The emphasis recently shifted to synthesis as a means to access sufficient amounts of free phenolic material in order to probe the bioactivity and pharmacological effects of, especially, the procyanidins [15]. Herein we present a concise review of the evolution of proanthocyanidin synthetic methodologies beginning with the pioneering efforts of Geissman and Yoshimura [2] and concluding with the current state-of-the-art protocols supported by modern day chromatographic and spectroscopic/spectrometric techniques.

Discussion

The first synthesis of a procyanidin derivative 3 is credited to the pioneering work of Geissman and Yoshimura [2]. Mild acid-catalyzed condensation of the leucocyanidin (flavan-3,4-diol) analogue 1 and free phenolic catechin (2) (a flavan-3-ol fol-
lowed by methylation and acetylation, afforded the procyanidin derivative 3 (Fig. 1). Structure elucidation of 3 was based on 1H NMR data acquired at 60 MHz and hence not comprehensive. However, these results did demonstrate the feasibility of utilizing a flavan-3,4-diol and a flavan-3-ol as the extender and starter units, respectively, to synthetically access proanthocyanidins. Weinges and his collaborators [5, 6] utilized a Grignard-type coupling reaction between the 8-lithio derivative of catechin (5) and the taxifolin derivative 4 (Fig. 2) to produce an intermediate 4-hydroxyprocyanidin. Hydrogenolysis to reductively remove the 4-hydroxy group and the benzyl protecting group, and subsequent acetylation afforded the perceived procyanidin B-3 derivative 6.

The first synthesis of free phenolic procyanidins emanated from the work of Haslam and his collaborators [7, 8]. Their approach (Fig. 3) involved the generation of 4β-benzylthio-epicatechin (7) and 4α-benzylthiocatechin (8) via acid-catalyzed thiolysis [9] of the procyanidin polymers of Salix caprea and Crataegus monogyna, respectively. Under acidic conditions, the 4-benzylthioethers 7 and 8 equilibrate with their C-4 carbocations 9 and 10, respectively. These reactive intermediates are subsequently trapped separately by catechin (2) to afford procyanidins B-1 (12) and B-3 (14), respectively, and by epicatechin (11) to give procyanidins B-2 (13) and B-4 (15), respectively. In contrast to the synthetic derivatives 3 and 6, the structures of procyanidins B-1 – B-4 were properly elucidated and shown to be identical to the naturally occurring analogues.

Our own work in the proanthocyanidin field commenced in the late 1960s in Bloemfontein, South Africa, when we turned to the investigation of the polyphenolic profile of the large variety of hardwood species in Southern Africa. The proanthocyanidin pool in these sources is dominated by 5-deoxy analogues, i.e., the profisetinidins and prorobinetinidins, and is of considerable complexity as far as heterogeneity of the interflavanyl bonds and configurational diversity of the heterocyclic rings are concerned. Thus, it came as no surprise that the structures of the first profisetinidin-type tri- [10] and tetra-flavonoid [11] (Fig. 4) of undefined absolute configuration were incorrectly assigned. This prompted us to embark on a systematic program of synthesis of, especially, the profisetinidins and prorobinetinidins [12], knowing well that others would follow suit as far as the synthesis of the other classes of proanthocyanidins, especially the procyanidins, was concerned.

Our approach, similar to that of Geissman and Yoshimura [2], was based on the utilization of a flavan-3,4-diol or its equivalent as a potential C-4 electrophile and a flavan-3-ol, e.g., catechin (2), as nucleophile to form the interflavanyl bond (Fig. 5) in, e.g., a (4→8)-linked proanthocyanidin 20. Such an approach was feasible because of the commercial availability of the flavan-3-ol catechin (2) and the natural availability of three flavan-3,4-diols: fisetinidol-4α-ol (21) from Acacia mearnsii (Black Wattle), its enantiomer ent-fisetinidol-4β-ol from Quebracho (Schinopsis spp.), and epioritin-4β-ol (25) from Acacia auriculiformis [13]. Under mild aqueous acidic conditions, fisetinidol-4α-ol (21) and phloroglucinol (22) condensed to afford a mixture of fisetinidol-(4α→2)-phloroglucinol (23) and fisetinidol-(4β→2)-phloroglucinol (24) (Fig. 6) [12, 13]. Under similar conditions, epioritin-4β-ol (25) and phloroglucinol (22) exclusively gave the epioritin-(4β→2)-phloroglucinol adduct 26, such selectivity being effected by the α-axial 3-hydroxy group in a C-4 carboxation intermediate of type 19 [12, 13].

Subsequently, we focused on the application of a similar protocol to synthesize the naturally occurring profisetinidin-type biflavonoids that occur abundantly in the commercially important bark extract of Black Wattle. Thus, acid-catalyzed condensation of fisetinidol-4α-ol (21) and catechin (2) afforded a mixture of fiseti-

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**Fig. 1** The first synthesis of a procyanidin derivative 3.

**Fig. 2** Synthesis of procyanidin derivative 6 via a Grignard-type coupling.
nidol-(4α→8)-catechin (27), fisetinidol-(4β→8)-catechin (28), and fisetinidol-(4α→6)-catechin (29) (Fig. 7) [14, 15]. The structures of the two (4→8)-linked analogues 27 and 28 were shown to be identical to the corresponding natural products from Black Wattle bark, with regards to both structure and absolute configuration. Although the fisetinidol-(4β→6)-catechin (30) could not be identified in the initial work, its formation was confirmed in a subsequent study [16].

The protocol of acid-catalyzed condensation of a flavan-3,4-diol and a flavan-3-ol to effectively and predictably form the interflavanyl bond was extended to include the synthesis of a comprehensive array of dimeric 5-deoxy proanthocyanidins. Flavan-3,4-diols employed included: ent-fisetinidol-4β-ol (ent-21) [15, 17], robinetinidol-4α-ol (31) [15], mopanol A (32) [18], guiboutinidol-4α-ol (33) [19], butiniflavan-4-ols (34) [20], cassiaflavan-4-ols (35) [21], and epioritin-4β-ol (25) and epimesquitol-4β-ol (36) [22]. The flavan-3-ols employed included: catechin (2) [15–17] and epicatechin (11) [15], gallocatechin and epigallocatechin (37 and 38) [20, 21], and fisetinidol (39) and ent-epifisetinidol (40) [19] (Fig. 8). It should be emphasized that the 5,7-dihydroxyflavan-3-ols, e.g., catechin (2), capture C-4 electrophiles originating from 5-deoxyflavan-3,4-diols, e.g., fisetinidol-4α-ol.
at both C-6 and C-8. In contrast, 5-deoxyflavan-3-ols, e.g., fisetinidol (39), capture the same C-4 electrophile regioselectively at C-6.

Availability of the synthetic 4-arylflavan-3-ols generated as in Fig. 6 permitted us to formulate a simple circular dichroic (CD) rule to define their absolute configuration at C-4 [12, 13, 23, 24]. The rule was also applicable to the biflavanoids [14, 15] and has been used extensively to define the absolute configuration at C-4 (C-ring) of the full array of naturally occurring dimeric proanthocyanidins.

Having established the regiochemistry of the coupling between fisetinidol-4α-ol (21) and catechin (2) (Fig. 7), and in view of the coupling positions “defined” for the profisetinidin triflavanoid 16 from Colophospermum mopane, we next used the fisetinidol-(4α → 8)- and (4β → 8)-catechins (27 and 28) (Fig. 7) as nucleophiles to capture the C-4 carbocation derived from fisetinidol-4α-ol (21) (Fig. 9) [25, 26]. This culminated in the formation of four angular profisetinidin triflavanoids 41–44. These compounds were shown to be identical to the four analogues isolated from the heartwood of Black Wattle [27]. The CD data of the all-trans and all-cis analogues 41 and 44, respectively, were crucial to the assignment of the absolute configuration at C-4 of both the C- and I-rings of these compounds. The four triflavonoids in which the chain extender units were derived from ent-fisetinidol-4β-ol were synthesized in a similar fashion and shown to be identical to the four naturally occurring analogues isolated from Rhus lancea [17]. Two of these structures are shown as 45 and 46 in Fig. 10.

An interesting feature of the regiochemistry of the coupling process is that C-6 of the phloroglucinol D-ring, rather than C-6 of the resorcinol A-ring, of the biflavanoid 27 acted as the preferential nucleophilic center. This contrasted with the general belief of a “linear” condensation mode for the formation of profisetinidin triflavanoids [10]. In addition, the structure and absolute configuration of fisetinidol-(4α → 8)-catechin-(6 → 4α)-fisetinidol (41) were shown to be identical to the analogue from Colophosper-
mum mopane that was assigned structure 16 [10]. This was a gratifying experience that also provided a solid foundation to further unravel the considerable complexities of the naturally occurring classes of proanthocyanidins with 5-deoxy extender and 5,7-dihydroxy starter flavanoid units.

At the tetraflavanoid level, the key issue was to define whether C-6 of the A- or G-ring in a triflavanoid precursor of type 41 would be preferred in the chain extension process. In order to add the third fisetinidol/ent-fisetinidol structural moiety, we therefore used the four trimers 41–44 and their diastereoisomers, e.g., 45 and 46, synthesized by employing ent-fisetinidol-4β-ol (ent-21) in an acid-catalyzed condensation with catechin (2). Utilization of the all-trans triflavanoid 41 with fisetinidol extender units afforded the all-trans tetraflavanoid 47, with the third fisetinidol moiety regioselectively added to C-6 of the A-ring of precursor 41 [Fig. 11] [28]. The same regioselectivity was observed when the synthetic triflavanoids 42–44 were subjected to the same treatment. The structures of the resulting four tetraflavanoids...

Fig. 7 Synthesis of the four regio-isomeric profisetinidin biflavanoids 27–30.

Fig. 8 Flavan-3,4-diols, flavan-4-ols, and flavan-3-ols utilized in the synthesis of a comprehensive series of dimeric 5-deoxy proanthocyanidins.
were identical to the corresponding natural products from the heartwood of Black Wattle [28]. The four diastereoisomeric triflavanoids with ent-fisetinidol chain extender units, e.g., compounds 45 and 46, were similarly subjected to acid-catalyzed condensation with ent-fisetinidol-4β-ol. Again, the third ent-fisetinidol unit was added regioselectively at C-6 of the ABC moiety to produce four diastereoisomeric tetraflavanoids, e.g., 48 (Fig. 11) [29]. The four synthetic compounds were shown to be identical to the four naturally occurring analogues obtained from *Rhus lancea* [11, 29]. In addition, compound 48 was identical to the first tetraflavanoid that was assigned structure 17 almost fifteen years earlier. This work dealing with the synthesis of the tri- and tetraflavanoids abundantly demonstrates the necessity of a synthetic approach in order to unequivocally assign the composition and absolute configuration of these complex compounds.

A range of catechin-(4α→8) and (4α→6)-catechin procyanidin bi- and triflavanoids, as well as the first di- and trimeric procyanidins with (4β→8)-interflavanyl linkages, could be accessed by replacing the 5-deoxyflavan-3,4-diols with a mixture of catechin-4α- and 4β-ols (49) (leucocyanidins), using catechin (2) and epicatechin (11) as starter units. Some of these analogues are shown in Fig. 12 [15, 30, 31], e.g., all-trans-(4α→8)-linked procyandin (50), catechin-(4β→8)-epicatechin (51), and the all-trans trimer 52 with mixed regiochemistry.

When considering the synthesis of the biologically important procyanidins, it became evident early on that synthetic access would be hampered by the unavailability of 5-oxyflavan-3,4-di-ol-type precursors like 1, 7, 8, and 49. Thus, we developed a
method to oxygenate the tetra-O-methyl ethers 53 and 54 of catechin (2) and epicatechin (11), respectively, in ca. 50% yield using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol (Fig. 13) [32]. The 4-methoxyflavan-3-ols 55 and 56 could then serve as the extender units to procyanidins possessing both catechin and epicatechin moieties.

In order to improve the utility of the C-4 oxygenated catechin and epicatechin derivatives towards the synthesis of free phenolic procyanidins, Kozikowski and his coworkers used the O-benzyl protected epicatechin derivative 57 and DDQ to synthesize the 4-O-(hydroxyethyl)flavan-3-ol analogue 58 (Fig. 13) [33]. This reaction was performed using ethylene glycol in dichloromethane as the nucleophile in place of methanol in chloroform, as these conditions resulted in a cleaner reaction with a higher overall yield of the C-4 oxygenated product [34]. Following the requisite synthetic manipulations, the free phenolic procyanidins were made readily available via mild deprotection using catalytic hydrogenation [33].

One of the complications of the formation of the interflavanyl bond in procyanidins under acidic conditions is the instability of this bond under the very conditions required for its formation. We addressed this problem by activating 4β-thiobenzylepicatexitin (7) with the thiophilic Lewis acid silver tetrafluoroborate (AgBF₄), thereby coupling it with free phenolic catechin (2) or epicatechin (11). This permitted formation of the interflavanyl bond in procyanidins under essentially neutral and extremely mild (0 °C) conditions (Fig. 14) [35], and afforded procyanidins B-1 (12) and B-2 (13) in up to 50% isolated yields.

The protection of phenolic hydroxy groups of flavan-3-ols with the benzyl functionality often results in disappointingly low yields.
yields ([36], and cited references). In view of the importance of
the phenolic per-O-benzyl ethers of catechin and epicatechin as
building blocks for synthetic procyanidins, we addressed the
problem of low yields by capitalizing on the increased acidity of
the 4′-hydroxy group of both catechin (2) and epicatechin (11)
compared to that of the remaining hydroxy groups [36]. Thus,
treatment of catechin (2) and epicatechin (11) with 4.25 molar
equivalents of sodium hydride and 5 molar equivalents of benzyl
chloride in dry dimethylformamide under N2 at −78°C led to rap-
id formation of the 4′-O-benzyl ethers 59 and 60 (Fig. 15), via a
process that can be kinetically controlled. These 4′-O-benzyl de-
rivatives are stable under basic conditions and are not susceptible
to C-ring racemization reactions or to the extensive rearrange-
ment reactions via B-ring quinone methides that may form when
the 4-hydroxy group is unprotected (see reference [36] for a de-
tailed explanation). When the reaction mixture is allowed to rise
to ambient temperatures, the 4′-O-benzyl ethers 59 and 60 are
susceptible to clean benzylation of the remaining phenolic hy-
droxy functions to give the per-O-benzyl ethers 61 and 57 in 98
and 90% isolated yields.

In 1999, Kozikowski and his collaborators published the first [34]
of a series of papers [33,37] and patents [38–40] aimed at the de-
velopment of synthetic strategies for a variety of natural and non-
natural procyanidins which had exhibited significant biological
activities. The 3-O-bis-gallate 64 of procyanidin B-2 (13), a cancer
cell growth inhibitor, was synthesized via the procedures out-
lined in Fig. 16. TiCl4-induced coupling of tetra-O-benzylepica-
techin (57) with the leucocyanidin derivative 58 (Fig. 12), af-
forded the procyanidin B-2 per-O-benzyl ether 62 (53% yield).
Procyanidin B-2 (13) was available via catalytic hydrogenation
of 62 using 20% Pd(OH)2/C as a catalyst. Galloylation of 62 using
tri-O-benzylgalloyl chloride in pyridine/dimethylaminopyridine
(DMAP)(cat) gave the per-O-benzylprocyanidin B-2 diester 63
in near quantitative yield. Hydrogenation over 20% Pd(OH)2/C gave
procyanidin B-2 bis-3-O-gallate (64) in 90% yield. When the TiCl4
used to induce coupling between 57 and 58 was replaced by the
commercial acidic clay mineral Bentonite K-10, it led to the al-
most exclusive formation (90% isolated yield) of per-O-benzy-
procyanidin B-2 (62), without the formation of artifacts like trimeric
and/or (4 → 6)-regiosomeric forms of 62 [37]. The biologi-
cal activities of the procyanidin bis-gallate 64 were reviewed by
Kozikowski and collaborators [34].

Kozikowski and coworkers [37] utilized the AgBF4-catalyzed reac-
tion [35] of 4-[(2-benzothiazolyl)-thio]epicatechin (65) with the
fully protected procyanidin B-2 derivative 56 to generate a mix-
ture of tri- through octamers (67–72) (Fig. 17). This mixture was separable by HPLC using a Waters µBondapack C18 column
with a solvent gradient consisting of water, ethyl acetate, and
acetonitrile. Subsequent deacetylation (40% aqueous tetra-n-bu-
tylammonium hydroxide) and debenzylation (Pearlman’s cata-
lyst) afforded the free phenolic forms of procyanidins 67–72, that
is, trimer through octamer. Replacement of the dimeric starter
unit 66 in Fig. 17 with the trimeric procyanidin 67 also afforded

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**Fig. 14** Synthesis of procyanidins B-1 (12) and B-2 (13) under neutral conditions.

**Fig. 15** High-yield process for the phenolic per-O-benzylation of catechin (2) and epicatechin (11).

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access to the free phenolic forms of nonamer (73), decamer (74), and undecamer (75).

The synthetic procedures shown in Figs. 16 and 17 gave access to 10–100 mg quantities of some of the procyanidins, allowing assessment of their in vitro biological activities [34, 37–40]. In order to fully develop their potential clinical applications, and to address pharmacological and toxicological issues, Sharma and collaborators [41] recently developed the process scale-up conditions necessary for the multigram synthesis of procyanidin B-1 (12) and the 3,3-bis-O-gallate (64) of procyanidin B-2 (13). Notable differences from the procedures shown in Fig. 16, and for the methodology to transform catechin (2) into the much more expensive epicatechin (11) [34], included the benzylation of catechin, refinement of the workup procedure for the Dess-Martin
oxidation of per-O-benzylcatechin (61), substituting TiCl₄ with Bentonite K-10 clay for the interflavanyl coupling process, and most significantly, using an ethyl acetate/water mixture for the catalytic debenzylation step. This biphasic solvent system permitted preferential dissolution of the per-O-benzylprocyanidin, e.g., 62, in the organic layer, and of the free phenolic compound, such as 13, in the aqueous layer.

In their “enabling synthetic strategy by orthogonal activation and C(8) protection,” Ohmori and coworkers [42] used penta-O-benzyl-4β-O-acetylcatechin 76, penta-O-benzyl-4β-thiophenylcatechin 78, and their C-8 bromo derivatives 77 and 81 to synthesize procyanidin B-3 (14) derivatives, e.g., 80, and the trimeric bis[catechin-(4α→8)]-catechin derivative 86 (Fig. 18). Utilization of the 8-bromo-4β-acetoxy catechin 77 or the 4β-phenylsulphide 78 permitted the usage of near equimolar quantities of the electrophilic and nucleophilic moieties. This approach offers an advantage over methods requiring the usage of an excess of the nucleophile in order to limit both self-condensation of the electrophile and random oligomerization of the initially formed procyanidin.

The principle of “soft activation” of the C-4 thiophenyl leaving group in 81 by AgBF₄ or N-iodosuccinimide (NIS), and “hard activation” of the C-4 acetoxy nucleofuge in 77 by BF₃·OEt₂ to synthesize catechin-related di- and trimeric procyanidins is demonstrated in Fig. 18. Procyanidin B-3 (14) was formed either by soft activation of the C-4 phenylsulphide 78 with AgBF₄ or NIS in the presence of penta-O-benzylcatechin (85) (1:3 molar ratio) (Fig. 18), or by hard activation of the C-4 acetate 76 with BF₃·OEt₂ in the presence of 85 (1:3 molar ratio) and subsequent deprotection of the O-benzyl groups. However, application of the hard activation procedure employing the 8-bromoacetate 77 and the 4-phenylsulphide 78 as coupling moieties (1:1.2 molar ratio), or of the soft activation method using the 8-bromophenylsulphide 81 and the C-4 acetate 76 (1:1.3 molar ratio), afforded access to the 8-bromoprocyanidin B-3 analogues 79 and 82 with the requisite C-4 thiophenyl or acetoxy leaving groups, respectively, for further synthetic elaboration. The dimeric 8-debromo analogues 80 and 83 were similarly available by replacing 77 with 76, and 81 with 78 in the appropriate coupling processes. The dimeric 8-bromophenylsulphide 79 and 8-bromoacetate 82 were subjected to the same protocol using penta-O-benzylcatechin.
(85) as the nucleophile to access the trimeric derivative 86 in good yield. As usual, the free phenolic bis-[catechin-(4α→8)]-catechin was readily available via successive debromination and debenzylation procedures.

Much effort has been devoted to the synthesis of 13C- and 14C-labeled catechins and procyanidins. Labeled procyanidin B-3 (14), procyanidin B-6 [catechin-(4α→6)-catechin], procyanidin C-2 (bis-[catechin-(4α→8)]-catechin), and a related polymer of high radio-purity were obtained when [U-14C]phenylalanine or [1-14C]acetate was fed to willow tree shoots [43]. Similar incorporation of [1-13C]phenylalanine into cell suspension cultures of Vitis vinifera [44] afforded the 13C-labeled anthocyanins, cyanidin-3-O-β-D-glucopyranoside, peonidin-3-O-β-D-glucopyranoside, and malvidin-3-O-β-D-glucopyranoside. Nay and his collaborators synthesized rac-4-[13C]catechin [45], enantiopure 4-[13C]catechin, and 4-[13C]epicatechin [46, 47], and gram quantities of 4-[13C]procyanidin B-3 [48, 49].

Saito and his coworkers [50] began their synthetic studies of procyanidins by refining the conditions involving the TiCl4-induced coupling of 3-O-acetyltetra-O-benzyl-4β-methoxycatechin (87) (Fig. 19) and tetra-O-benzylcatechin (61) in order to enhance the stereoselective formation of the (4α→8)-interflavanyl bond in procyanidin B-3 (14) [50]. The Lewis acid trimethylsilyl trifluoromethane sulphonate (TMSOTf) was used to induce a high degree of stereoselectivity in the formation of the (4α→8)-interflavanyl bond in a gram-scale synthesis of octa-O-benzylprocyanidin B-3 using tetra-O-benzylcatechin (61) and per-O-benzyl-4β-O-(2-hydroxyethyl)catechin (88) as nucleophile and electrophile, respectively.

Fig. 19 C4 Oxygen-ated catechin analogues as electrophiles in procyanidin synthesis.

Fig. 20 Synthesis of octa-O-benzylcatechin-(4β→8)-catechin 87.
In contrast to the classical approach of interflavanyl bond formation in proanthocyanidins via an intermolecular coupling process, Saito and his coworkers [51] developed a protocol that focused on an intramolecular bond-forming process (Fig. 20). Esterification of tetra-O-benzylcatechin (61) with succinic or glutaric anhydrides gave the succinate (89) or glutarate (90), respectively. Intermolecular esterification of these esters with the C-4 protected leucocyanidin derivative 88 using dicyclohexylcarbodiimide (DCC) afforded the heterodimeric esters 91 and 92. These were subjected to stereoselective intramolecular interflavanyl bond formation using TMSOTf to afford the dimeric esters 93 and 94. Ester hydrolysis (K₂CO₃ in methanol) gave the C-3 esters 95 and 96 which were reduced by diisobutylaluminium hydride to give the octa-O-benzyl ether of the C-4 (C-ring) diastereomer 97 of procyanidin B-3 (14) in good overall yield.

The protocol shown in Fig. 20 also gave access to the octa-O-benzyl ethers of procyanidins B-1 (12), B-2 (13), and B-4 (15) [52,53]. The ability of procyanidins B-1 – B-4 and some of their derivatives to inhibit the Maillard reaction was also reported [53]. Substitution of the glutaric ester linker in the heterodimeric ester of type 92 with an azelaic acid [HOOC-(CH₂)₇-COOH] unit gave highly stereoselective access to procyanidin B-3 (14) [54]. Saito group [55] also used TMSOTf-induced intermolecular coupling of tetra-O-benzyl-4β-O-(2-ethoxyethyl)catechin (88) and tetra-O-benzylcatechin (61) or their 3-O-gallates, to obtain procyanidin B-3 (14), its 3-O-gallate 98, and the bis-O-gallate 99 (Fig. 21). Among these compounds, the bis-O-gallate 99 showed the most potent antioxidant and radical scavenging activity. Although showing the weakest antioxidant and radical scavenging activity, the mono-O-gallate 98 exhibited the highest inhibition of mammalian DNA polymerase alpha [55]. TMSOTf also effectively induced the stereoselective intermolecular coupling of electrophiles 101 and 102 (Fig. 21) with octa-O-benzylprocyanidin B-1 – B-4 nucleophiles, and of the dimeric electrophile 100 with the catechin and epicatechin tetra-O-benzyl ethers 61 and 57, respectively, to give ready access to a series of trimeric procyanidin derivatives [56]. The usual deprotection methods afforded procyanidin C-1 (bis-[epicatechin-(4β→8)]-epicatechin), procyanidin C-2 (bis-[catechin-(4α→8)]-catechin), bis-[epicatechin-(4β→8)]-catechin, and epicatechin-(4β→8)-catechin-(4α→8)-epicatechin.

A combination of the methods developed by Tueckmantel et al. [34] and Ohmori et al. [42], i.e., protection at C-8 of 4β-O-(2-hydroxyethyl)catechin or epicatechin as their 8-bromo [103 or 105] or iodo [104 or 106] derivatives (Fig. 21), and TiCl₄-induced coupling with the per-O-benzylethers 61 and 57 of catechin and epicatechin, was employed to synthesize procyanidins B-1 – B-4 (12 – 15) in good yields [57]. Such an approach permitted the coupling of the two monomers in a stoichiometric ratio, and provided a considerable degree of regio- and stereocontrol of the (4→8) bond formation process, as well as the level of oligomerization. Significantly improved yields and less complicated reaction mixtures were obtained using the 8-bromo derivatives 103 and 105 in place of the 8-iodo analogues 104 and 106. The catalytic deprotection step of, e.g., the 8-bromoprocyanidin B-3...
derivative 107 (Fig. 21) using Pd(OH)$_2$/Et$_3$N [58, 59] led to concomitant reduction of the 8-bromo bond. The use of an excess of TiCl$_4$ to induce coupling of the electrophilic and nucleophilic units was improved upon by utilizing the rare earth metal Lewis acid ytterbium III triflate [Yb(OTf)$_3$] to catalyze the coupling of tetra-O-benzylcatechin (61) and tetra-O-benzylepicatechin (57), respectively, with the 4β-methoxyepicatechin derivative 108 [60, 61]. The customary deprotection steps afforded procyanidins B-1 (12) and B-2 (13). Procyanidins B-3 (14) and B-4 (15) were similarly accessed via equimolar Yb (OTf)$_3$-induced coupling of the catechin and epicatechin derivatives 61 and 57, respectively, with the 4β-methoxycatechin derivative 87, followed by the appropriate deprotection steps. The versatile protocol of Lewis acid induced coupling of phenolic O-protected C-4 functionalized catechin and epicatechin electrophiles like 108 with phenolic O-protected catechin and epicatechin nucleophiles like 57 was expanded to include the use of equimolar amounts of TMSOTf [62] to produce procyanidins up to the tetrameric level. In contrast the tris-(pentafluorophenyl)borane-catalyzed self-condensation of the protected flavan-3,4-diacetate 109 (Fig. 21) led to an intractable mixture that was shown by MALDI-TOF-MS analysis to contain procyanidins of undefined regio- and stereochemistry up to the pentadecameric level.

An innovative method [63] based on the oxidative coupling of tetra-O-methyl-3-oxo-catechin (110) and tetra-O-methylcatechin (53) was recently developed (Fig. 22). Treatment of a solution of 110 and 53 with AgBF$_4$ (4 molar equivalents) in THF afforded the 3-oxocatechin-(4β→8)-catechin 114 and traces of the (4α→8)-isomer. Reduction of 114 with sodium borohydride in alkaline medium gave the per-O-methyl ether of the C-4 (C-ring) diastereoisomer 115 of procyanidin B-3 (14). Formation of the 3-oxo analogue 114 may be explained in terms of an initial one-electron oxidation to give an A-ring radical cation 111. Proton loss affords the resonance-stabilized benzylic radical 112 and subsequent conversion into the benzylic carbocation 113 via a second one-electron oxidation step. Stereoselective trapping of carbocation 113 by tetra-O-methylcatechin (53) affords the (4β→8)-analogue 114 that can be converted into the C-4 diastereoisomeric derivative 115 of procyanidin B-3 (14) via metal halide reduction.

**Conclusion**

From its humble but pioneering beginnings in the middle 1960s, the subject of proanthocyanidin synthesis has developed to the extent that, today, the vast majority of naturally occurring free phenolic analogues are synthetically accessible on a scale that permits assessment of their pharmacological properties. We have attempted to comprehensively chronicle these early attempts as well as more recent exquisite state-of-the-art methods for inducing interfлавanyl bond formation of proanthocyanidin constituent units. This review should not only excite the proanthocyanidin...
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