Towards the Synthesis of Proanthocyanidins: Half a Century of Innovation

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- synthesis
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- profisetinidins
- flavan-3,4-diols
- catechins
- condensed tannins

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, Drewes and Roux, Freudenberg and Weinges, Swain, Geissman, Mayer, Seshadri, Pelter, 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-

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lowed by methylation and acetylation, afforded the procyanidin derivative **3** (**Fig. 1**). Structure elucidation of **3** was based on ^{1}H 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 4*β*-benzylthio-epicatechin (**7**) and 4*α*-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- **16** [10] and tetra-flavonoid **17** [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 **18** as a potential C-4 electrophile **19** 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-4*α*-ol (**21**) from *Acacia mearnsii* (Black Wattle), its enantiomer *ent*-fisetinidol-4*β*-ol from Quebracho (*Schinopsis* spp.), and epioritin-4*β*-ol (**25**) from *Acacia auricultriformis* [13].

Under mild aqueous acidic conditions, fisetinidol-4*α*-ol (**21**) and phloroglucinol (**22**) condensed to afford a mixture of fisetinidol-(4*α* → 2)-phloroglucinol (**23**) and fisetinidol-(4*β* → 2)-phloroglucinol (**24**) (**Fig. 6**) [12,13]. Under similar conditions, epioritin-4*β*-ol (**25**) and phloroglucinol (**22**) exclusively gave the epioritin-(4*β* → 2)-phloroglucinol adduct **26**, such selectivity being effected by the *α*-axial 3-hydroxy group in a C-4 carbocationic intermediate of type **19** [12,13].

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

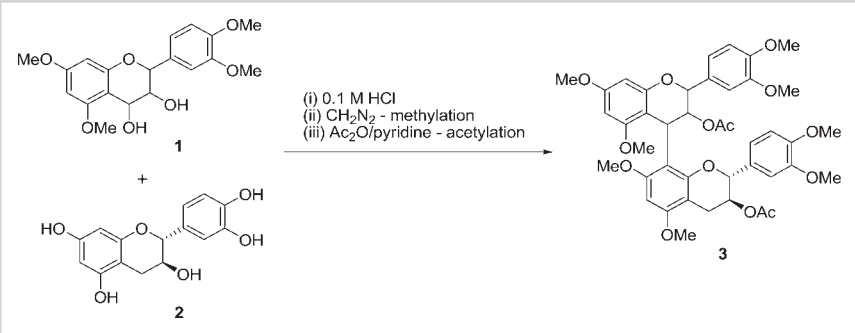

Fig. 1 The first synthesis of a procyanidin derivative **3**.

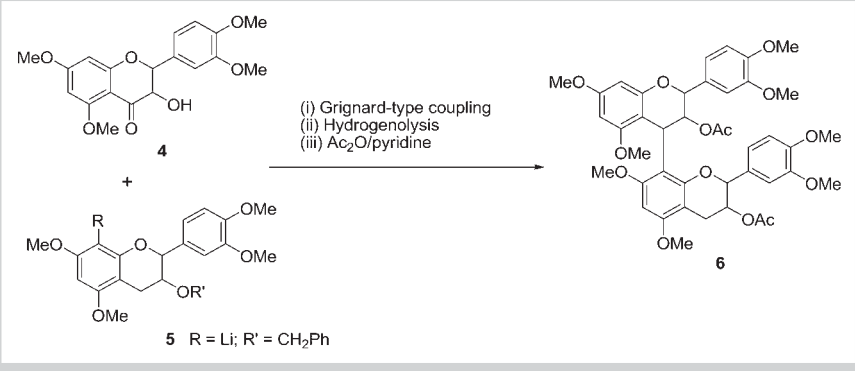

Fig. 2 Synthesis of procyanidin derivative **6** via a Grignard-type coupling.

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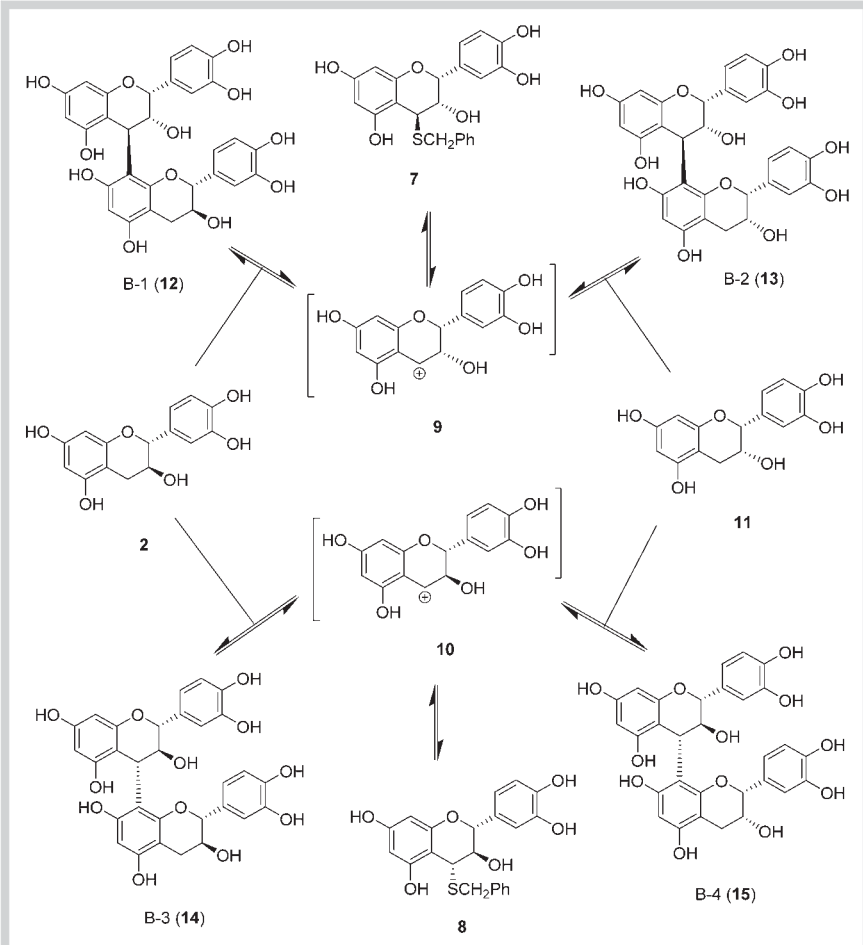

Fig. 3 Synthesis of free phenolic procyanidins B-1 – B-4.

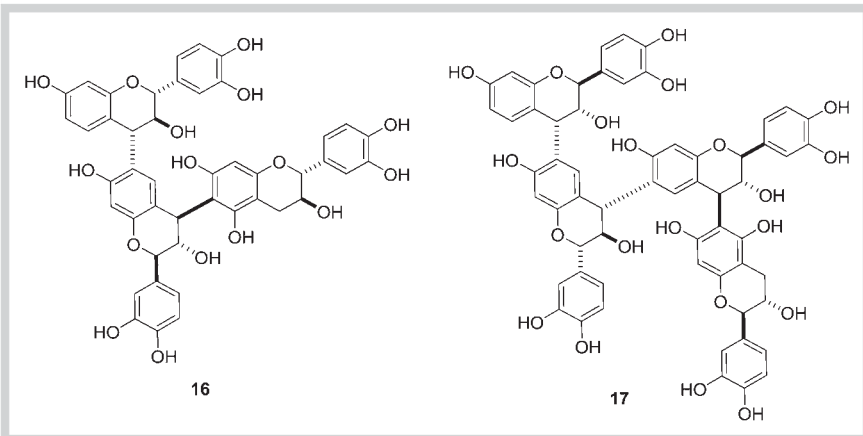

Fig. 4 Proposed structures of the first tri- and tetraflavanoid **16** and **17** profisetinidins.

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], guibourtinidol-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

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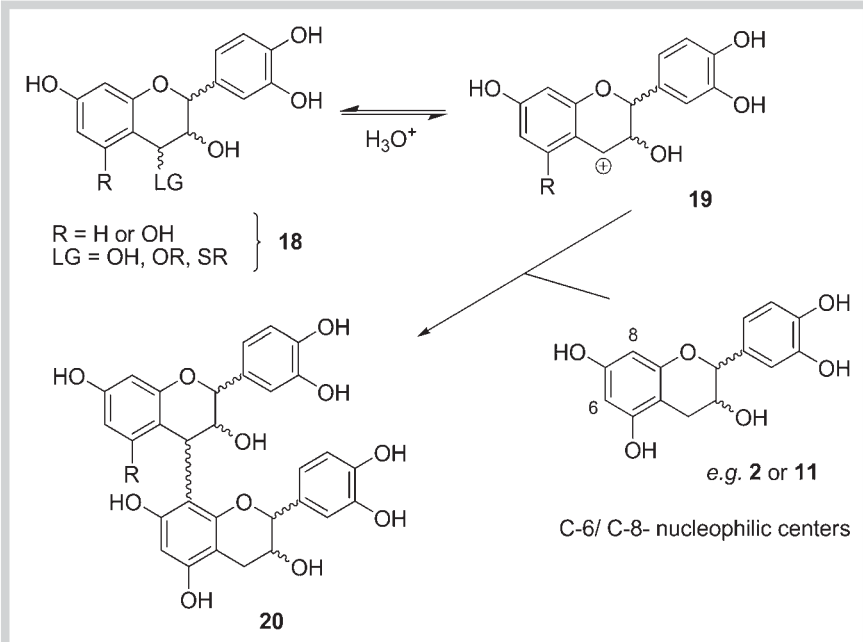

Fig. 5 Perceived synthesis of proanthocyanidins via flavan-3,4-diols and flavan-3-ols.

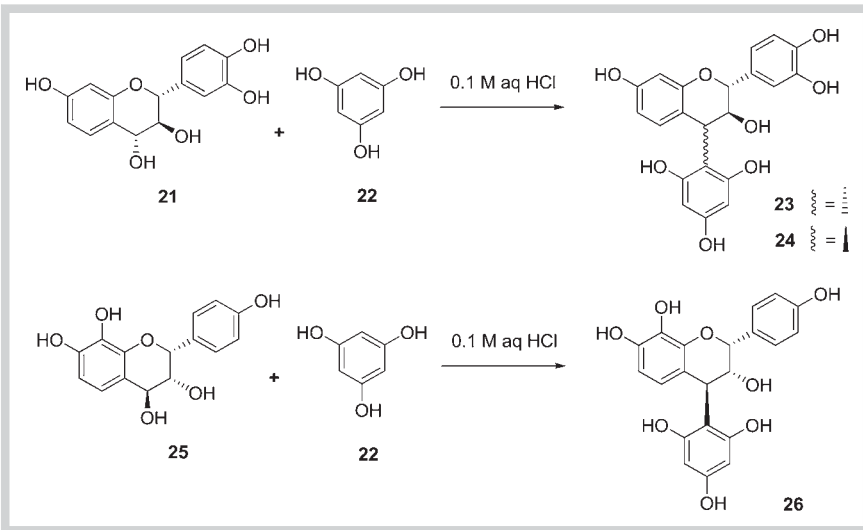

Fig. 6 Synthesis of 4-arylflavan-3-ols via acid-catalyzed condensation of a flavan-3,4-diol and phloroglucinol.

(**21**), 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-*

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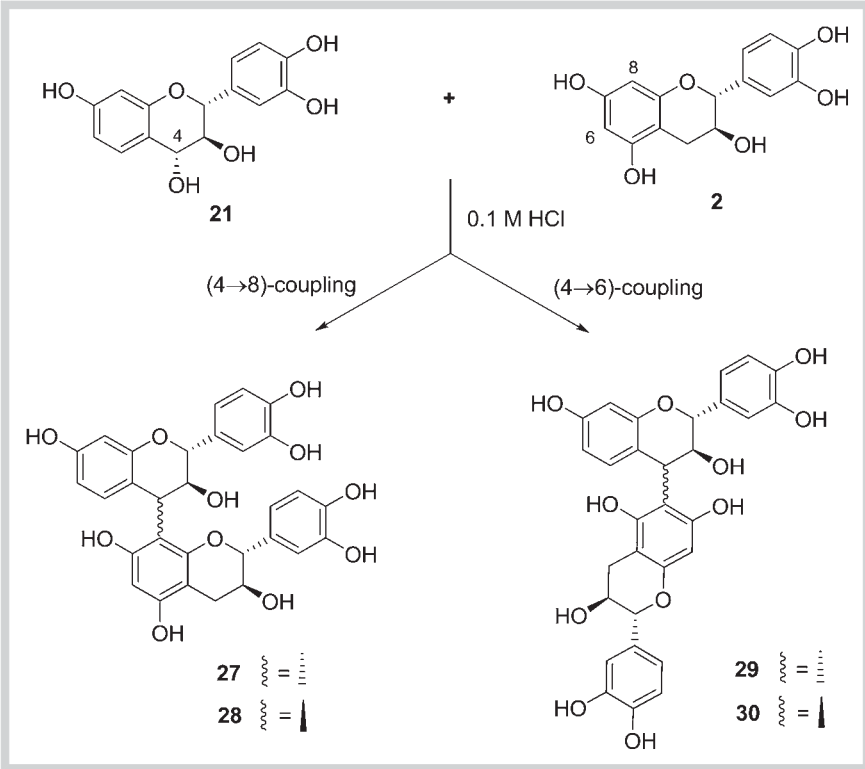

Fig. 7 Synthesis of the four regio-isomeric profisetinidin biflavanoids **27**–**30**.

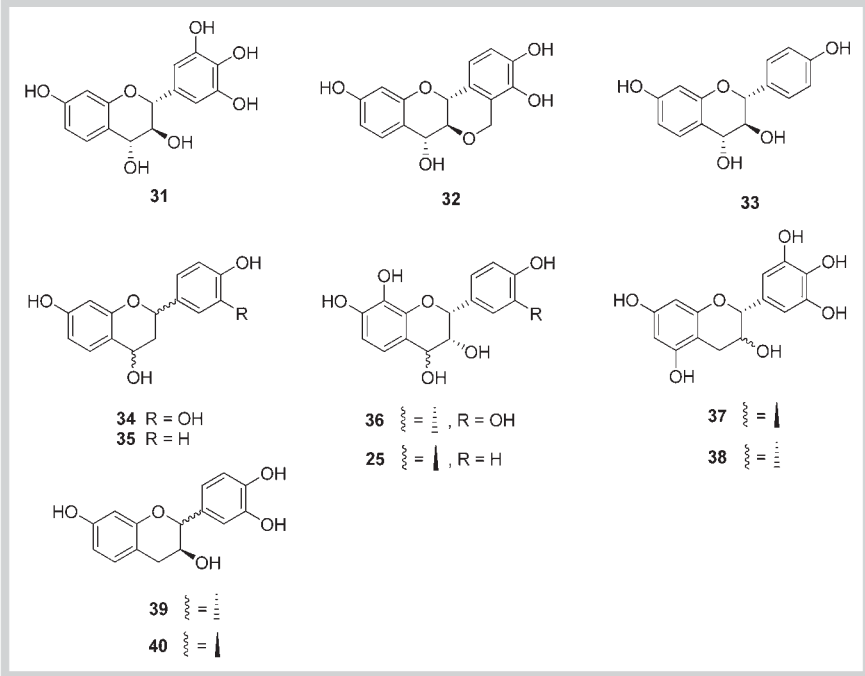

Fig. 8 Flavan-3,4-diols, flavan-4-ols, and flavan-3-ols utilized in the synthesis of a comprehensive series of dimeric 5-deoxy proanthocyanidins.

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-4*β*-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

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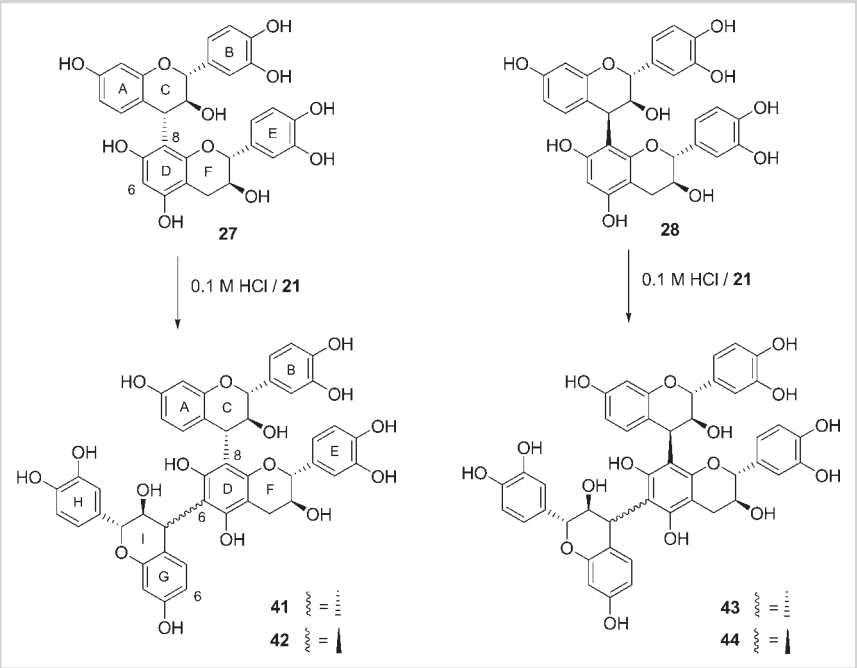

Fig. 9 Synthesis of the four angular profisetinidin triflavanoids **41**–**44** from the heartwood of Black Wattle.

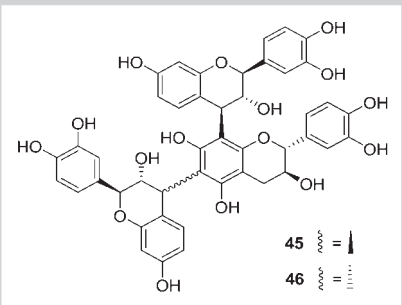

Fig. 10 Triflavonoids with *ent*-fisetinidol constituent units.

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-(4$\alpha \rightarrow$8) and (4$\alpha \rightarrow$6)-catechin procyanidin bi- and triflavanoids, as well as the first di- and trimeric procyanidins with (4$\beta \rightarrow$8)-interflavanyl linkages, could be accessed by replacing the 5-deoxyflavan-3,4-diols with a mixture of catechin-4α- and 4β-ols (**49**) (leucocyanidins), using catechin (**2**) and epicatechin (**11**) as starter units. Some of these analogues are shown in **Fig. 12** [15,30,31], e.g., all-*trans*-all-(4$\alpha \rightarrow$8)-linked procyanidin (**50**), catechin-(4$\beta \rightarrow$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-diol-type precursors like **1**, **7**, **8**, and **49**. Thus, we developed a

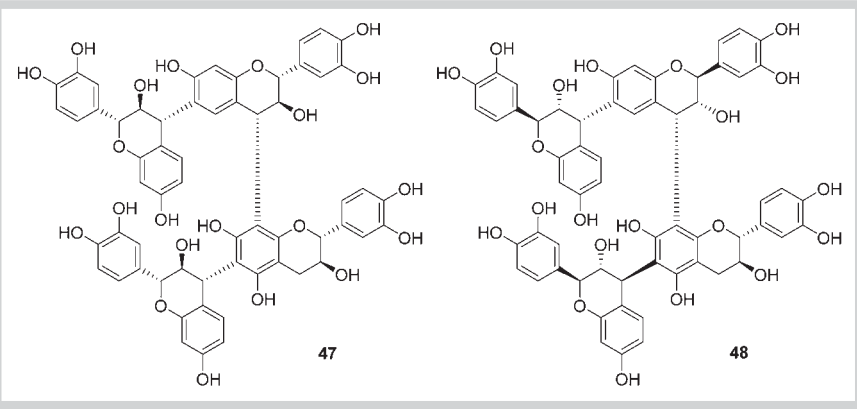

Fig. 11 Naturally occurring and synthetic profisetinidin-type tetraflavanoids.

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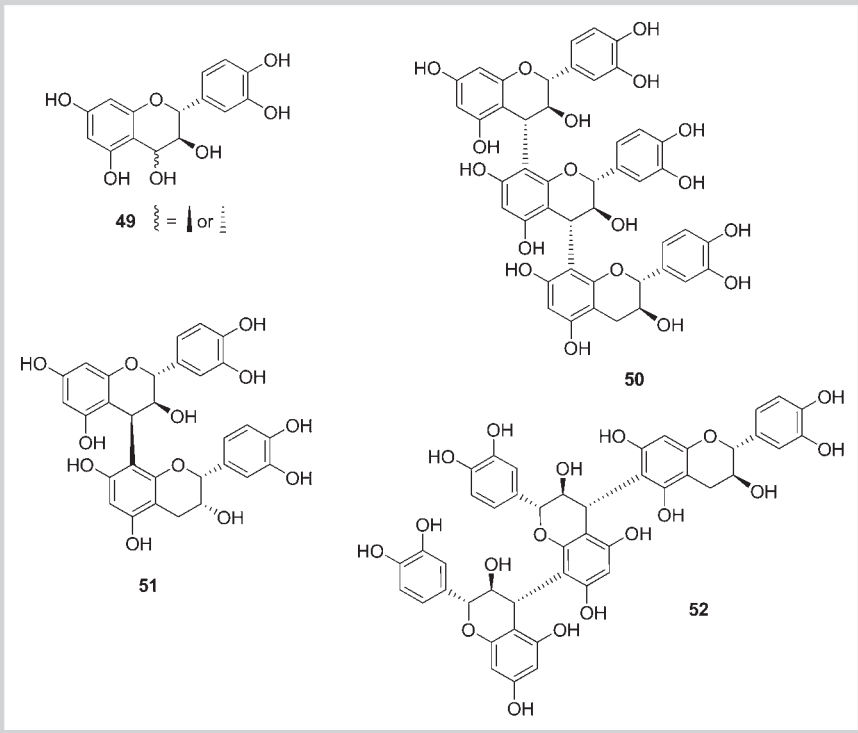

Fig. 12 Synthetically accessed procyanidins via leucocyanidins **49**.

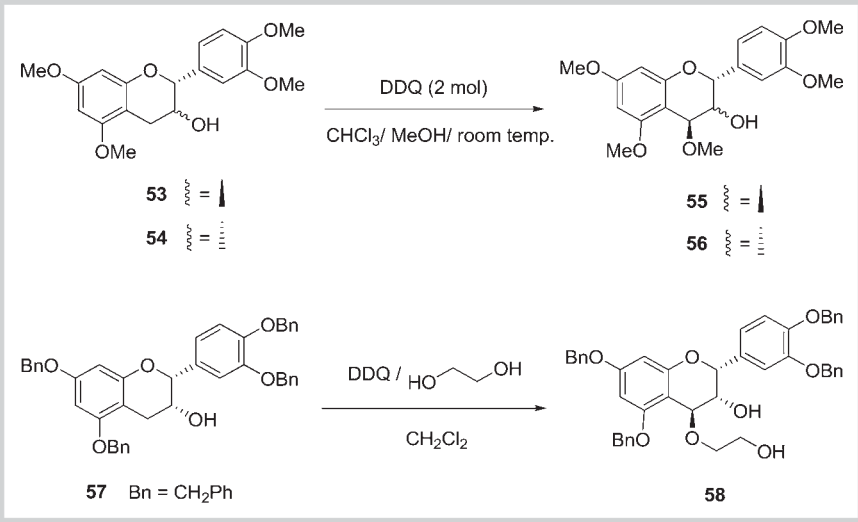

Fig. 13 C-4 oxygenation of catechin and epicatechin derivatives using DDQ.

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-thiobenzylepicatechin (**7**) with the thiophilic Lewis acid silver tetrafluoroborate ($AgBF_4$), 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

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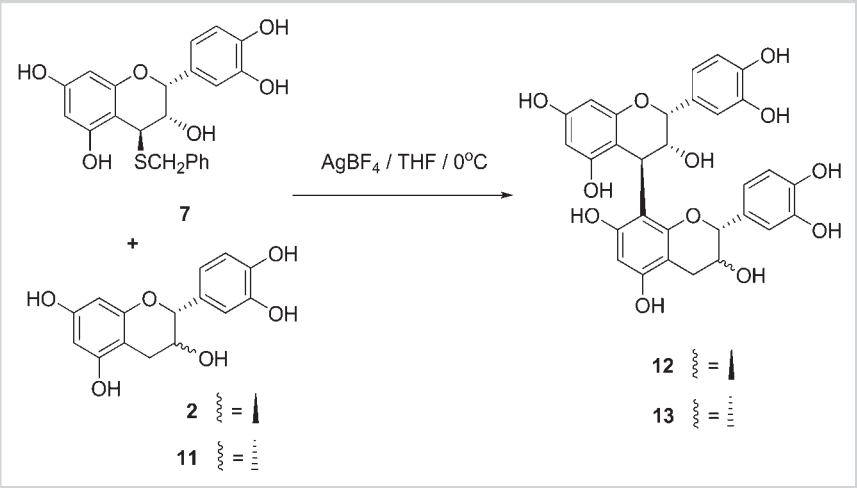

Fig. 14 Synthesis of procyanidins B-1 (**12**) and B-2 (**13**) under neutral conditions.

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 N_2 at − 78 °C led to rapid formation of the 4′-*O*-benzyl ethers **59** and **60** (**Fig. 15**), via a process that can be kinetically controlled. These 4′-*O*-benzyl derivatives are stable under basic conditions and are not susceptible to C-ring racemization reactions or to the extensive rearrangement reactions via B-ring quinone methides that may form when the 4-hydroxy group is unprotected (see reference [36] for a detailed 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 hydroxy 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 development 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 outlined in **Fig. 16**. $TiCl_4$-induced coupling of tetra-*O*-benzylepicatechin (**57**) with the leucocyanidin derivative **58** (**Fig. 12**), afforded 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 $TiCl_4$ used to induce coupling between **57** and **58** was replaced by the commercial acidic clay mineral Bentonite K-10, it led to the almost exclusive formation (90% isolated yield) of per-*O*-benzylprocyanidin B-2 (**62**), without the formation of artifacts like trimeric and/or (4 → 6)-regioisomeric forms of **62** [37]. The biological activities of the procyanidin bis-gallate **64** were reviewed by Kozikowski and collaborators [34].

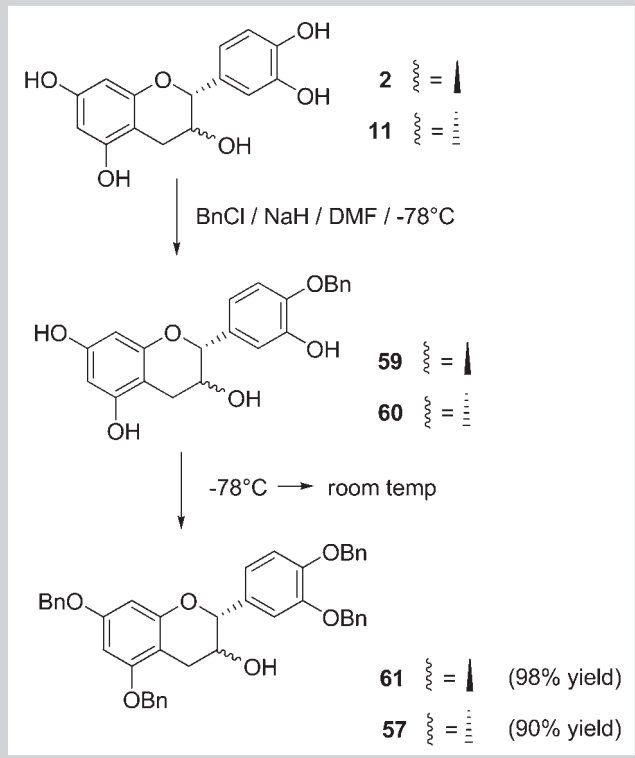

Fig. 15 High-yield process for the phenolic per-*O*-benzylation of catechin (**2**) and epicatechin (**11**).

Kozikowski and coworkers [37] utilized the $AgBF_4$-catalyzed reaction [35] of 4-[(2-benzothiazolyl)-thio]epicatechin (**65**) with the fully protected procyanidin B-2 derivative **56** to generate a mixture of tri- through octamers (**67**–**72**) (**Fig. 17**). This mixture was separable by HPLC using a Waters µBondapack C_{18} column with a solvent gradient consisting of water, ethyl acetate, and acetonitrile. Subsequent deacetylation (40% aqueous tetra-*n*-butylammonium hydroxide) and debenzylation (Pearlman's catalyst) 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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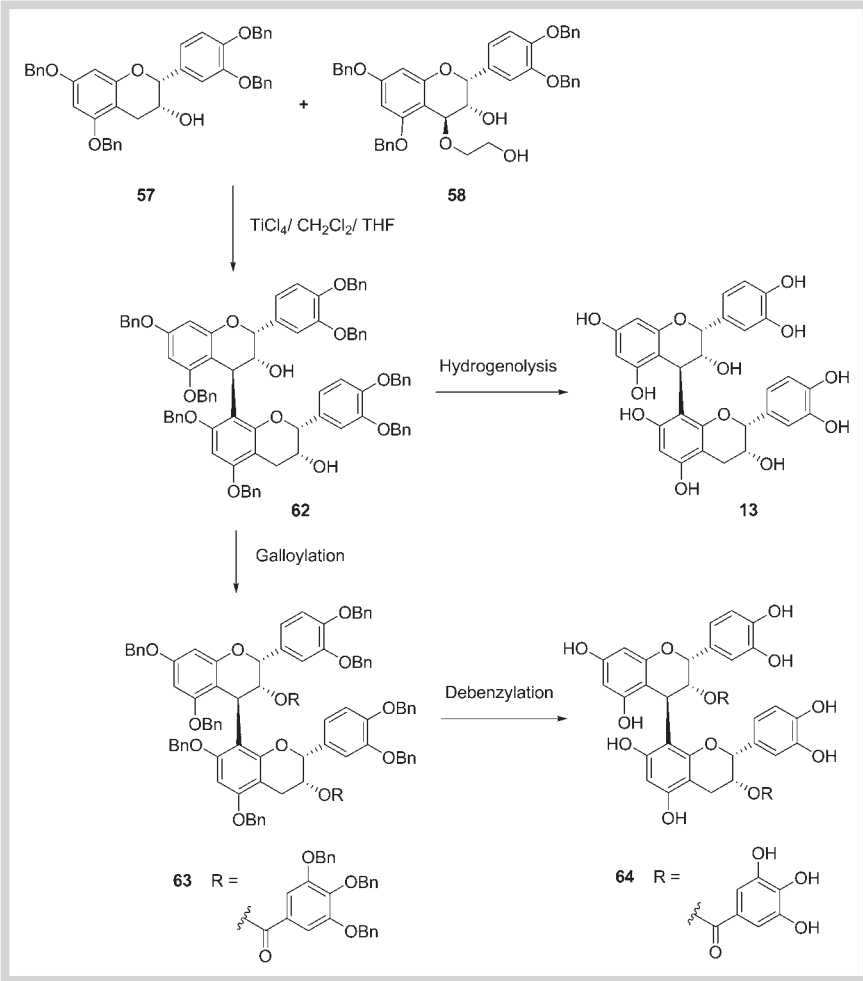

Fig. 16 Synthesis of procyanidin B-2 and its 3-*O*-bis-gallate.

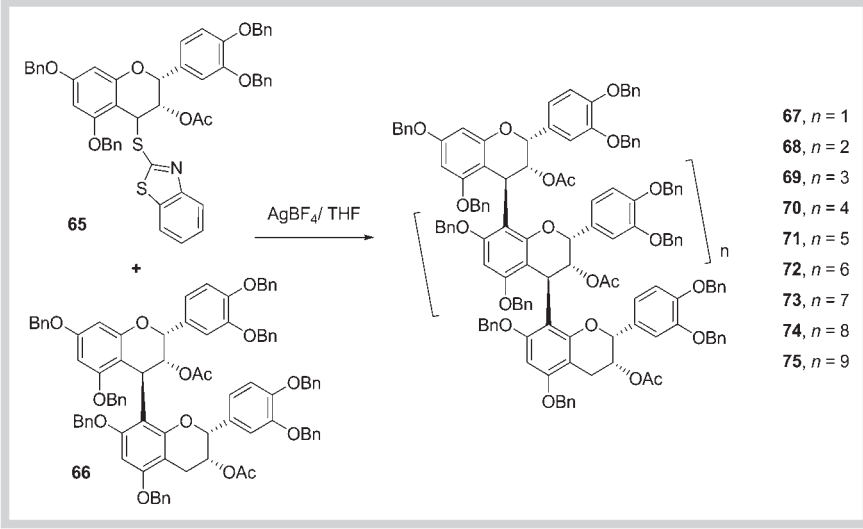

Fig. 17 Synthesis of procyanidin tri- through undecamers with epicatechin constituent units.

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

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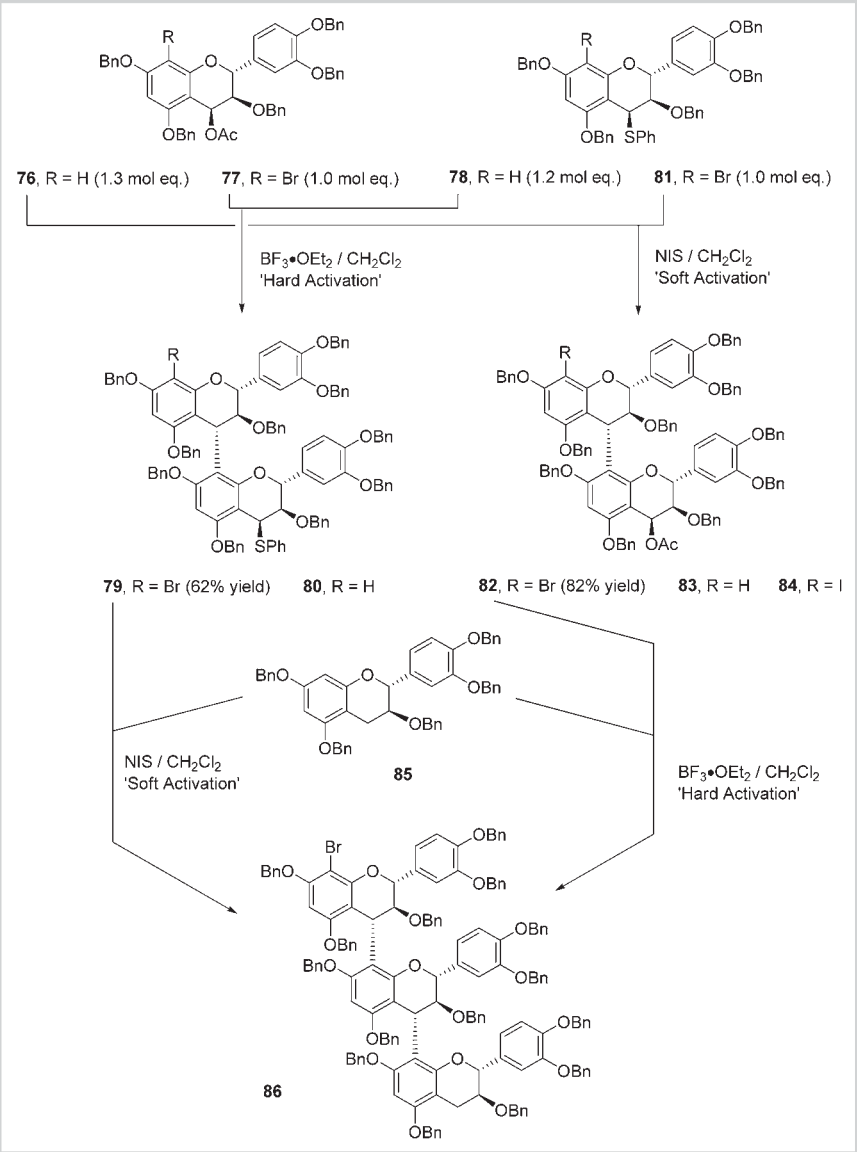

Fig. 18 Synthesis of procyanidin B-3 analogues and trimeric procyanidins via application of the principle of "soft" and "hard" activation of C-4 electrophiles.

oxidation of per-*O*-benzylcatechin (**61**), substituting $TiCl_4$ 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-4*β*-*O*-acetylcatechin **76**, penta-*O*-benzyl-4*β*-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-(4$\alpha \rightarrow$8)]-catechin derivative **86** (**Fig. 18**). Utilization of the 8-bromo-4*β*-acetoxycatechin **77** or the 4*β*-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 $AgBF_4$ or N-iodosuccinimide (NIS), and "hard activation" of the C-4 acetoxy nucleofuge in **77** by $BF_3 \cdot OEt_2$ 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 $AgBF_4$ 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 $BF_3 \cdot OEt_2$ 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

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(**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 ^{13}C- and ^{14}C-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-^{14}C]phenylalanine or [1-^{14}C]acetate was fed to willow tree shoots [43]. Similar incorporation of [1-^{13}C]phenylalanine into cell suspension cultures of *Vitis vinifera* [44] afforded the ^{13}C-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-[^{13}C]catechin [45], enantiopure 4-[^{13}C]catechin, and 4-[^{13}C]epicatechin [46,47], and gram quantities of 4-[^{13}C]procyanidin B-3 [48,49].

Saito and his coworkers [50] began their synthetic studies of procyanidins by refining the conditions involving the $TiCl_4$-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.

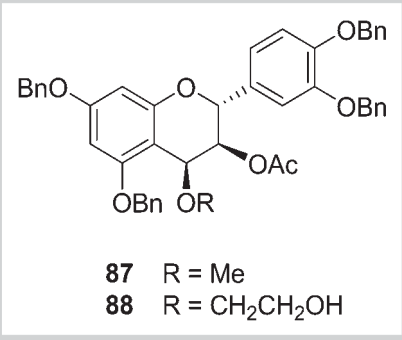

Fig. 19 C-4 Oxygenated catechin analogues as electrophiles in procyanidin synthesis.

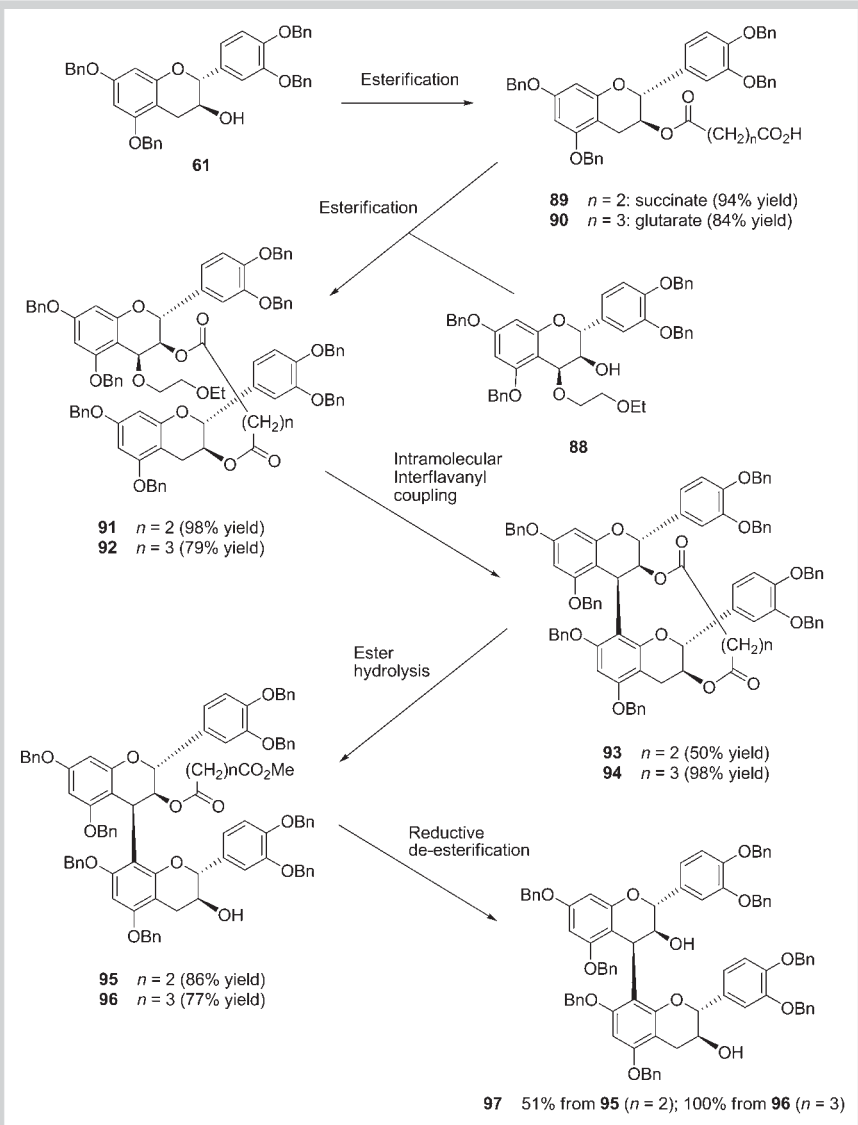

Fig. 20 Synthesis of octa-*O*-benzylcatechin-(4β → 8)-catechin **87**.

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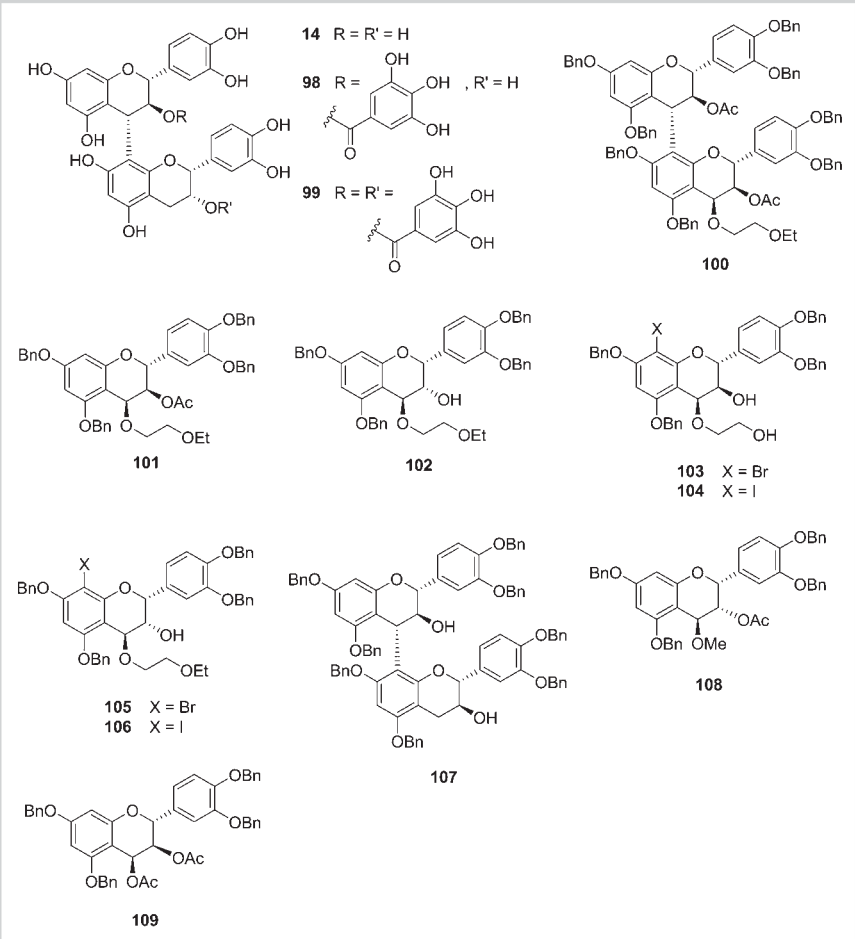

Fig. 21 Various C-4 oxygenated catechin and epicatechin analogues used in procyanidin syntheses, and related dimeric compounds.

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 anyhdrides 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 (K_2CO_3 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) diastereoisomer **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-$(CH_2)_7$-COOH] unit gave highly stereoselective access to procyanidin B-3 (**14**) [54].

The Saito group [55] also used TMSOTf-induced intermolecular coupling of tetra-*O*-benzyl-4*β*-*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-(4*β*→8)]-epicatechin}, procyanidin C-2{bis-[catechin-(4*α*→8)]-catechin}, bis-[epicatechin-(4*β*→8)]-catechin, and epicatechin-(4*β*→8)-catechin-(4*α*→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 4*β*-*O*-(2-hydroxyethyl)catechin or epicatechin as their 8-bromo [**103** or **105**] or iodo [**104** or **106**] derivatives (**Fig. 21**), and $TiCl_4$-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

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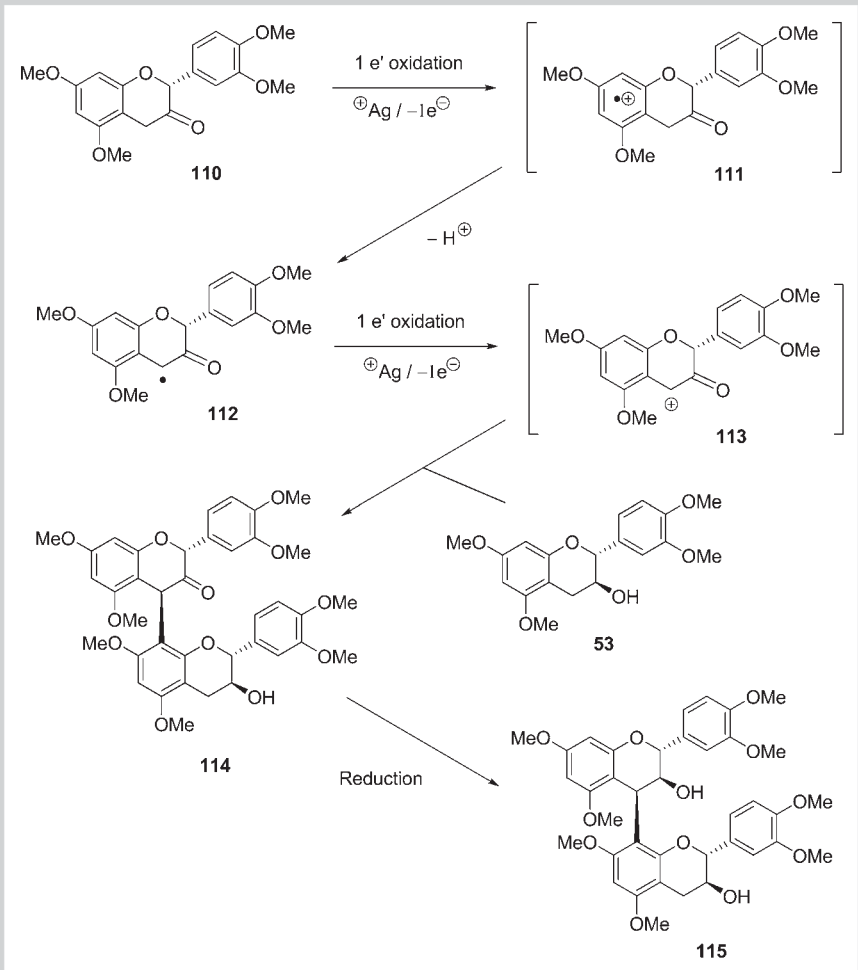

Fig. 22 Formation of the interflavanyl bond of procyanidins under oxidative conditions.

derivative **107** (**Fig. 21**) using $Pd(OH)_2/Et_3N$ [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 4*β*-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 4*β*-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-(4*β* → 8)-catechin **114** and traces of the (4*α* → 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 (4*β* → 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 interflavanyl bond formation of proanthocyanidin constituent units. This review should not only excite the proanthocyani-

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din expert, but should also be an invaluable reference for young scientists with regards to this complex but fascinating area of research.

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