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seco-Catechin Cyclization Approach to 4→6-Linked Catechin Dimers†

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A viable route has been developed for the selective synthesis of the 4→6-linked catechin dimers, scarcely accessible from nature and/or through synthesis. An acyclic nucleophilic catechin precursor (*seco*-catechin) was used for the regioselective union with an electrophilic catechin unit, and subsequent pyran cyclization gives the desired 4→6-linked dimers, i.e., procyanidin B_6 and catechin-(4α→6)-gallocatechin.

Catechin-class polyphenols[1] constitute a large group of natural products with potential bioactivities related to human health.[2] In our synthetic study of their oligomers,[3] we focused our attention on the connectivity of flavan units as one of the origins of the extreme diversity of the "natural catechin library". Particular attention was focussed on the 4→6-linkage as a minor connectivity: in contrast to the 4→8-linkages widely found in nature as procyanidin B_3 (**1**), a rare connectivity is the 4→6-inter-flavan bonds as in procyanidins B_6 (**2**) and B_8 (**3**) (Figure 1). The scarce availability and the potential bioactivity of the latter products stimulated our synthetic interest.

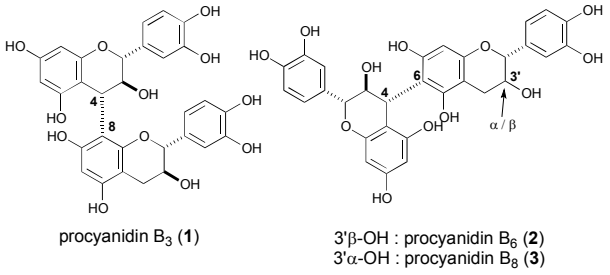


Figure 1 Procyanidin B_3, B_6 and B_8.

The synthetic challenge in accessing 4→6-linked oligomers[4,5] comes from a strong inherent tendency in the nucleophilic flavan units to react at C8 rather than C6 (**A** in Figure 2).[6] This trend is presumably related to the natural abundance of the 4→8-inter-flavan linkages (vide supra), but what is the origin?

A rough analysis suggests that the lone pairs of the adjacent three oxygens pose electron-donating effect equally on C6 and C8 (see **B**). As such, the electronic effect would be a minor factor,[7] and the major difference is steric in nature (see **C**): the pyran oxygen, O1, is included within a ring, and consequently, its substituent is held away from the C8 position. By contrast, the C6 position suffers from severe steric congestion due to freely rotating substituents.
This led us to the idea of blocking the C8 center, and indeed, a chlorine atom (but not bromine or iodine)[8] worked nicely (see **D**). The projected reaction was achieved at C6 en route to the 4→6-linked catechin dimers, allowing the first synthesis of **2**.[5a] However, a drawback of this chloro-capping strategy was extra steps needed for the chlorination/dechlorination.

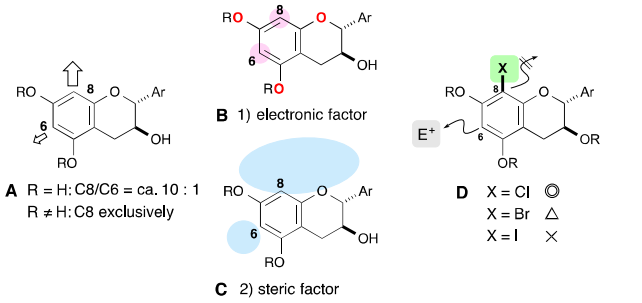


Figure 2 Ground State Consideration and Chloro-capping Strategy.

We recently noticed that this C8/C6 selectivity is better understood by comparing the Wheland intermediates of these reaction paths, i.e., σ-complexes **E** and **F** (Figure 3). As the reacting electrophile is very bulky C4-cation of a catechin unit, **E** is obviously preferred over **F**; space being available in **E** by the presence of a pyran ring (vide supra). An inevitable conclusion was that the selective reaction at C6 is unlikely so long as the pyran ring is present. However, this notion led us to an alternative idea: "Why not open the pyran ring?"

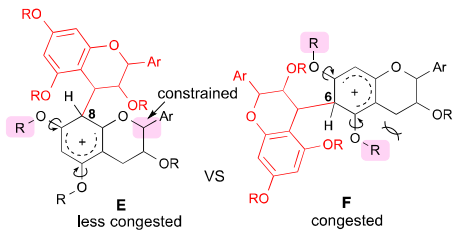
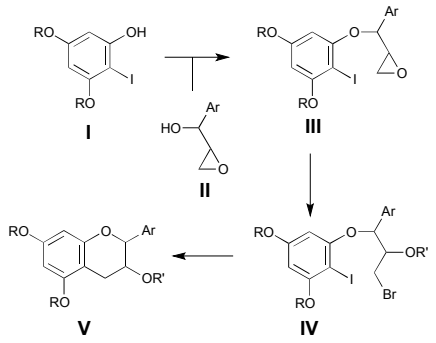


Figure 3 Wheland intermediates.

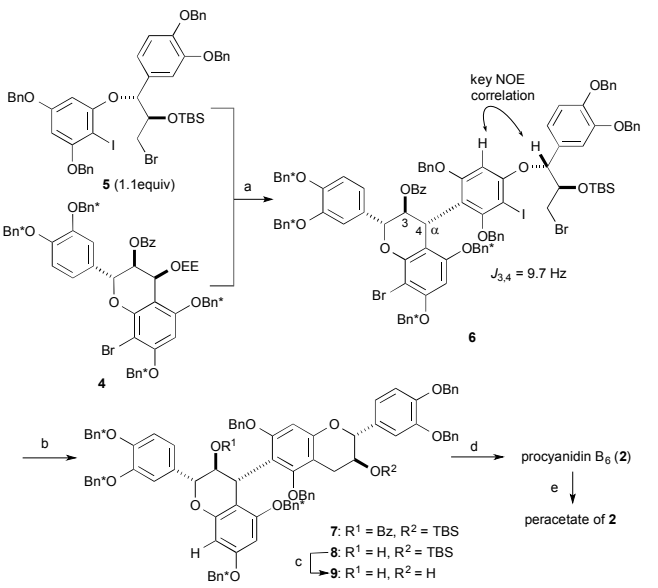
If one assumed the retrosynthetic opening of the pyran ring, one is presented with non-pyran precursor(s) that may undergo regio-selective union with an electrophilic catechin unit. Indeed, our previously reported, *de novo* synthesis of catechin monomers provided us with a strategic basis (Scheme 1).[9]

The three-step synthesis proceeds as follows: 1) union of iodophloroglucinol **I** and epoxy alcohol **II** by Mitsunobu reaction; 2) opening and protection of epoxy ether **III** to give bromide **IV**, and 3) pyran cyclization by halogen–metal exchange of **IV**, constructing the catechin skeleton **V**. "Could any precursors **I**, **III**, or **IV**, be combined with the upper flavan unit at the pro-C6'-position?" Pleasingly, stage **IV** turned out to be ideally suited for this purpose, allowing access to the 4→6-linked structure.



Scheme 1 *De novo* synthesis of catechin monomers.

Protected alcohol **5**, prepared previously in our laboratory,[9] was employed as a nucleophile for the union with bromo-capped catechin unit **4**[8, 10] (Scheme 2). Pleasingly, upon reaction of **4** with **5** in the presence of $BF_3{\cdot}OEt_2$, a single adduct **6** was cleanly produced in 95% yield. Structure of **6** was assigned by extensive 1D- and 2D-NMR study, and the ROESY correlation was diagnostic for assigning the 4→6' connectivity. The stereochemical assignment at the C4 position of the upper unit relied on the coupling constant between H3 and H4 ($J_{3,4}$ = 9.7 Hz) as shown in Scheme 2.



Scheme 2 Synthesis of procyanidin B_6 (**2**). Reagents and conditions: (a) $BF_3{\cdot}OEt_2$ (1.2 equiv), CH_2Cl_2, –78→–10 ºC, 2 h (95%); (b) Ph_3MgLi, HMPA, THF, –78→0 ºC, 3 h then EtMgBr, 60 ºC, 2 h (92%); (c) *n*-Bu_4NF, THF, RT, 5 h (95%); (d) H_2, ASCA-2® [5% $Pd(OH)_2$/C], THF, MeOH, H_2O, RT, 2 h; (e) Ac_2O, pyridine, 0 ºC, 24 h (84%, 2 steps). Bn* = [D_7]-benzyl, OEE = 2-ethoxyethoxy, HMPA = hexamethylphosphoric triamide.

The regio- and stereoselectivities are rationalized below (Figure 4). In terms of regioselectivity, the buttressing effect of the iodine atom equally poses steric hindrance around both nucleophilic centers C6 and C8. However, the steric congestion around the C8 site would become more severe by the larger side chain. The α-stereoselectivity is rationalized by the neighboring-group participation of the C3-*O*-benzoyl group.[11]

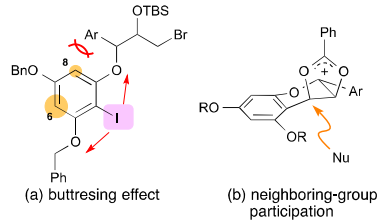


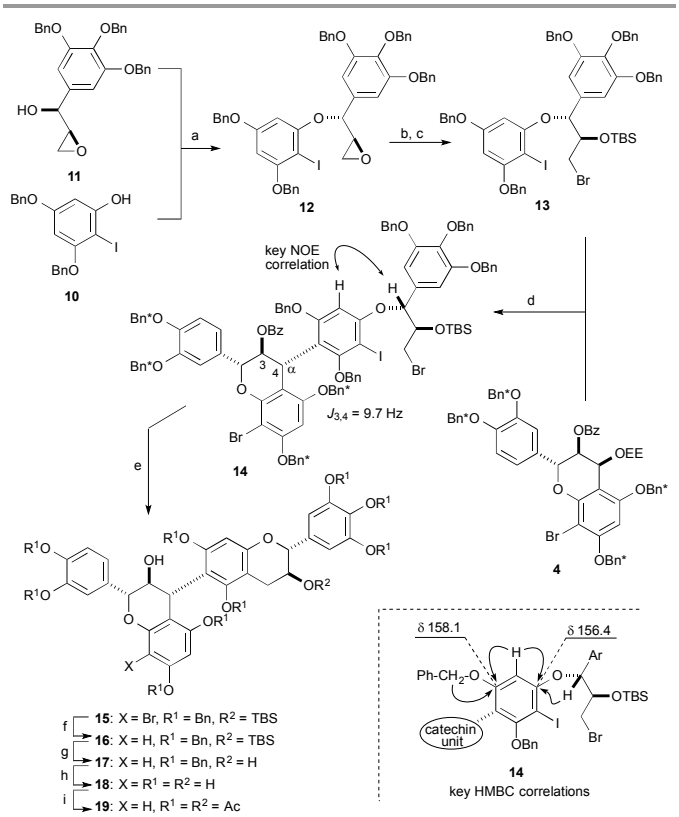
Figure 4 Rationale for regio- and stereoselectivities.

The *seco*-catechin adduct **6**, thus obtained, was subjected to the key cyclization to construct the catechin skeleton. Upon treatment of **6** with Ph_3MgLi[12] (2.0 equiv, THF, 0 ºC) in the presence of HMPA (2.5 equiv), the halogen–metal exchange induced the pyran cyclization. Concomitantly, debromination and partial debenzoylation proceeded, giving **7** (with benzoyl, 67%) and **8** (de-benzoylated, 22%).

More conveniently, a sequential one-pot protocol was devised to access product **8**. After completion of the cyclization and debromination, a large excess (30 equiv) of EtMgBr was added, and the resulting mixture was heated (60 ºC, 2 h), allowing complete detachment of the remaining benzoyl groups to give alcohol **8** in 92% yield. Finally, all protecting groups were removed: the silyl group was cleaved (*n*-Bu_4NF, THF, room temp., 5 h), giving diol **9** in 89% yield, and all benzyl groups were removed by hydrogenolysis over ASCA-2®[13] (5% $Pd(OH)_2$/C) [THF, MeOH, H_2O (2/2/1), room

temp., 2 h].[14] Due to the high air sensitivity of **2**, careful non-aerobic filtration, partial evaporation, and lyophilization were adopted, giving **2** as white powders. After acetylation (84% yield, 2 steps), all physical properties were consistent with the reported data (^{1}H, ^{13}C, IR).[5]

The utility of this approach was further proven by the synthesis of a natural hetero-dimer with a 4→6-linkage, catechin-(4α→6)-gallocatechin[15] (**18**) (Scheme 3). Mitsunobu reaction[16] of epoxy alcohol **11** with phenol **10** gave ether **12** as a single diastereomer (93% yield). The oxirane ring in **12** was cleaved with Li_2NiBr_4[17], and the resulting alcohol was protected with TBS group, giving *seco*-gallocatechin **13**. Union of **13** with electrophilic unit **4** in the presence of $BF_3{\cdot}OEt_2$ proceeded smoothly, giving 90% yield of the desired product **14** in excellent regio- and stereoselectivity. Structure of **14** was assigned by extensive NMR studies, such as HSQC, HMBC, and ROESY, confirming the 4→6' connectivity. The stereochemical assignment at the C4 position of the upper unit relied on the coupling constant between H3 and H4 ($J_{3,4}$ = 9.7 Hz). The pyran cyclization was carried out by treatment of **14** with Ph_3MgLi and HMPA (THF, –78→0 ºC, 2 h), which was treated in situ with EtMgBr and heated (60 ºC, 6 h). This sequential operation allowed complete detachment of the benzolyl group and partial removal of the bromo substituent, affording a mixture of bromide **15** and the debrominated product **16**, which were inseparable. Treatment of this mixture with $LiAlH_4$ gave **16** in 58% overall yield from **14** (3 steps). The TBS group in **16** was removed with *n*-Bu_4NF, giving alcohol **17** in 78% yield. Finally, all benzyl groups were removed by hydrogenolysis over ASCA-2® (5% $Pd(OH)_2$/C) [THF, MeOH, H_2O (2/2/1), room temp., 2 h] to afford catechin-(4α→6)-gallocatechin (**18**). The workup employed previously (see Scheme 2) gave the pure compound **18** as white powders, which was fully acetylated to give the corresponding peracetate **19** in 41% yield (2 steps) as white solid.[18]



Scheme 3 Synthesis of hetero-dimer **18**. Reagents and conditions: (a) TMAD, *n*-Bu_3P, toluene, RT, 22 h (93%, >99% d.r.); (b) Li_2NiBr_4, THF, 0 ºC→RT, 19 h (98%); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC, 6 h (96%); (d) $BF_3{\cdot}OEt_2$ (1.2 equiv), CH_2Cl_2, –78→–25 ºC, 1.5 h (90%); (e) Ph_3MgLi, HMPA, THF, –78→0 ºC, 2 h, then EtMgBr, 60 ºC, 6 h; (f) $LiAlH_4$, THF, 0 ºC, 6 h (58%, 2 steps); (g) *n*-Bu_4NF, THF, RT, 4 h (78%); (h) H_2, ASCA-2® [5% $Pd(OH)_2$/C], THF, MeOH, H_2O, RT, 2 h; (i) Ac_2O, pyridine, RT, 48 h (41%, 2 steps). TMAD = *N,N,N′,N′*-tetramethylazodicarboxamide, HMPA = hexamethylphosphoric triamide.

In conclusion, selective synthesis of the 4→6-linked catechin dimers has been made possible through the use of an acyclic nucleophilic catechin precursor (*seco*-catechin), allowing regioselective union with an electrophilic catechin unit followed by pyran cyclization. The efficacy of this strategy has been demonstrated by the syntheses of homo- and hetero-catechin-(4α→6)-dimers.

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