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COMMUNICATION

A new synthetic strategy for catechin-class polyphenols: concise synthesis of (−)-epicatechin and its 3-*O*-gallate†

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Concise synthesis of (−)-epicatechin and its 3-*O*-gallate is described, illustrating efficacy of the new strategy for catechin-class polyphenols based on assembly of lithiated fluorobenzene and epoxy alcohol followed by a pyran cyclization. 1,3,5-Trifluorobenzene serves as the A-ring equivalent for functionalization and the pyran annulation.

Increasing interests are currently focussed on the catechin-class polyphenols,[1] such as (−)-epicatechin (EC, **1**) and (−)-epicatechin 3-*O*-gallate (ECg, **2**) (Fig. 1). Besides these major ingredients in green tea, the Nature produces a huge "catechin library" consisting of enormous numbers of related polyphenols, differing in oxygenation, stereochemistry, and degree of oligomerization.[4] Despite a potentially rich source of compounds of biological or pharmaceutical relevance, such a natural library has been hardly explored due to difficulty in obtaining pure samples of individual compounds: natural sources such as plant extracts are highly complex mixtures of closely related compounds (*vide supra*), hardly separable even by modern separation techniques.

Although chemical synthesis has the potential for supplying the requisite samples, reported methods have certain limitations in the relative/absolute stereocontrol.[2] In addition, the real issues emerge after deprotection: handling of free polyphenols is difficult due to their high sensitivity to oxidants, acid, base, light, and metallic species. Scheme 1 exemplifies the vulnerability to basic conditions: facile deterioration of C(2)–C(3) stereogenic centers or skeletal rearrangements.[3]

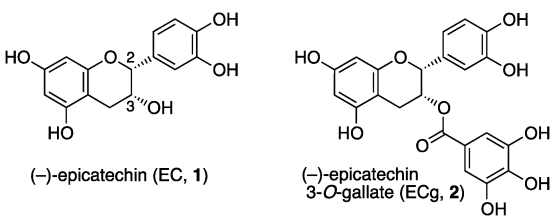

Fig. 1 Two representative green tea catechins.

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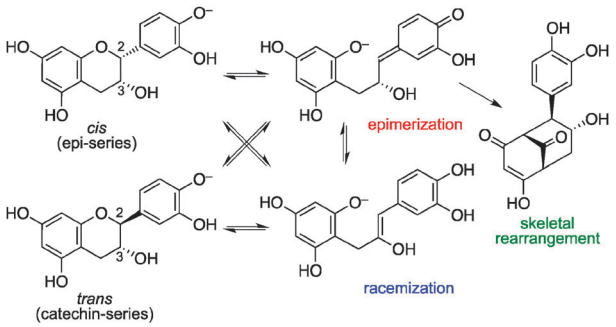


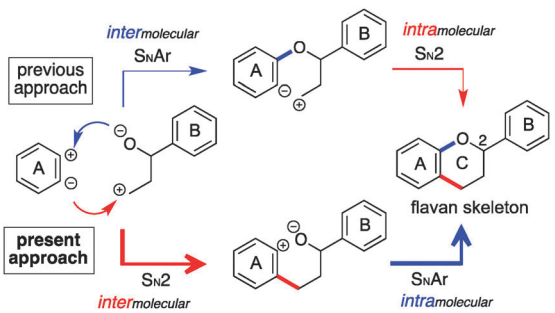
Scheme 1 Instability of free flavans.

In our current study on catechin oligomers,[5] scarce availability of various catechin monomers is retarding the progress. Except for (+)-catechin, other congeners are expensive or not commercially available, and thus we started trying to establish a facile and flexible synthetic method of monomers.[6]

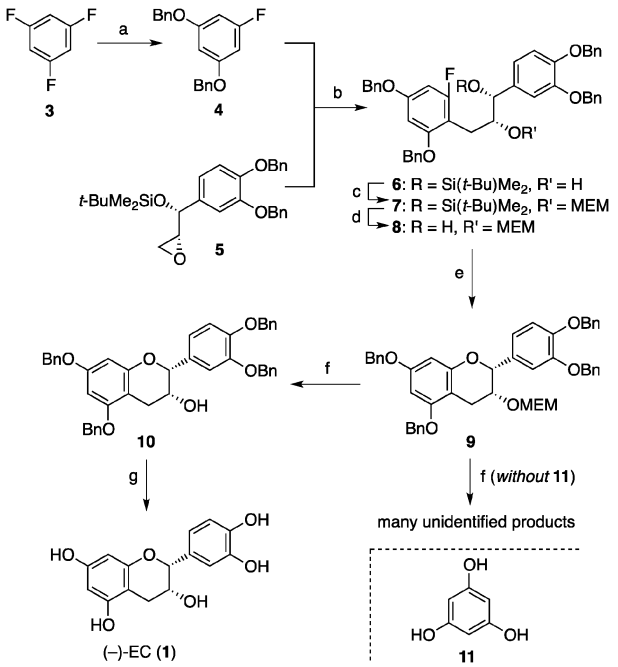
Scheme 2 (the upper sequence) is the *polarity analysis* of our previous approach[6c] based on an *intermolecular* S_NAr reaction[7] to form the C–O bond followed by *intramolecular* C–C bond formation *via* aryl anion species to close the central pyran ring.

Seeking for other possibilities, we were interested in the *optional* sequence of two-bond formations, *i.e.*, the C–C bond first followed by the C–O bond (the lower sequence in Scheme 2). Pleasingly, this simple reversal allowed us to develop a new efficient synthetic route discussed in this communication. Promising potentials as facile and rapid access to catechin-class polyphenols will be featured by concise syntheses of (−)-epicatechin (EC, **1**) and its 3-*O*-gallate (ECg, **2**).

Scheme 3 outlines the access to (−)-EC (**1**) starting from 1,3,5-trifluorobenzene (**3**), which was treated with sodium



Scheme 2 Polarity analysis.



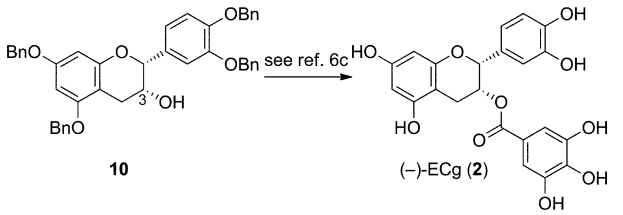
Scheme 3 Reaction conditions: (a) BnOH, NaH, NMP, 100 °C, 2 h (79%). (b) *n*-BuLi, THF, −78 °C, 1 h; then **5**, $BF_3{\cdot}OEt_2$, −78 °C, 15 min (88%). (c) MEMCl, *i*-Pr_2NEt, *n*-Bu_4NI, CH_2Cl_2, room temp., 15 h (92%). (d) *n*-Bu_4NF, THF, room temp., 14 h (99%). (e) KH, DMF, 0 °C, 5 h (91%). (f) *p*-TsOH·H_2O, **11**, CH_2Cl_2, room temp., 6 d (87%). (g) H_2, $Pd(OH)_2$/C, MeOH, THF, H_2O, room temp., 2.5 h (quant.). NMP = *N*-methylpyrrolidone, MEM = methoxyethoxymethyl.

benzyl oxide (2.5 mol equiv.) at 100 °C to give 79% yield of 3,5-dibenzyloxy-1-fluorobenzene (**4**) as the A-ring surrogate. Fluorobenzene **4** was regioselectively lithiated (*n*-BuLi, −78 °C),[8,9] and then treated with enantiomerically enriched epoxide **5** (>99% ee)[10] in the presence of $BF_3{\cdot}OEt_2$ to give adduct **6** in 88% yield. After protection as MEM ether **7**, removal of the silyl group (*n*-Bu_4NF) gave alcohol **8** in 91% yield from **6**, ready for pyran cyclization.

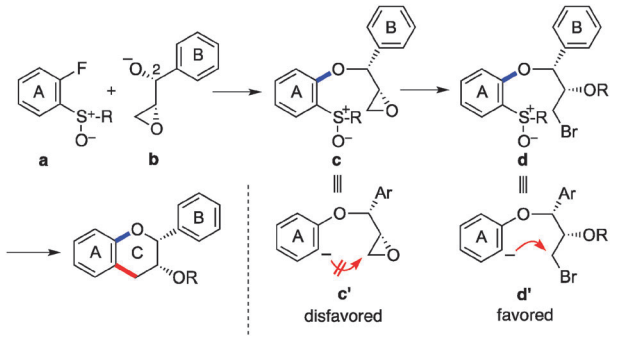
Screening of basic conditions[11] revealed that KH (DMF, 0 °C, 5 h) allowed clean cyclization of pyran **9** in excellent yield. The C(2)–C(3) *cis* relationship in **9** was verified by ^{1}H NMR analysis ($J_{2,3}$ = <0.5 Hz). Notably, the *intramolecular* S_NAr reaction nicely proceeded without help by an electron-withdrawing group (*vide infra*).

The next stage was to detach the MEM group in **9** under acidic conditions, which was troublesome. Exposure of **9** to acids gave uniformly many unidentified products. We assumed that the issues came from the formaldehyde[12] that is liberated during deprotection. Among additives tested for scavenging formaldehyde, phloroglucinol (**11**) proved to be most effective: Treatment of ether **9** with *p*-toluenesulfonic acid in the presence of **11** realized slow, but clean deprotection, giving alcohol **10** in 87% yield.

Finally, four benzyl groups in **10** were removed by hydrogenolysis [5% $Pd(OH)_2$/C, MeOH–THF–H_2O (v/v/v = 1 : 1 : 1), 2.5 h]. After careful anaerobic filtration through a Celite® pad (argon), concentration and lyophilization quantitatively gave (−)-EC (**1**) as a snow-white solid, which was identical to an authentic specimen.[13]



Scheme 4 Access to (−)-ECg (**2**).



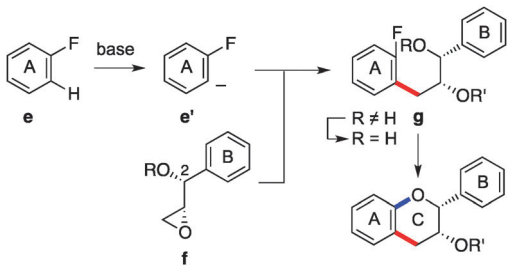
Scheme 5 Previous approach.

It should be noted that alcohol **10** is readily convertible to (−)-ECg (**2**)[14] as reported previously[6c] (Scheme 4).

What makes the present approach so concise and effective? Scheme 5 shows key aspects of the previous approach,[6c] featured by the dual roles of a sulfinyl group: (1) to ease the S_NAr attack of alkoxide **b** to the electrophilic unit **a** at the fluorine-bearing carbon center, and (2) to serve as a carbanion precursor *via* sulfinyl–lithium exchange[15] for the S_N2 pyran cyclization. The sulfinyl group also caused cumbersome handling of diastereomeric intermediates. In addition, there was a *trajectory issue* at the pyran cyclization (**c**′),[16,17] requiring extra steps for converting epoxide **c** into bromo ether **d** as a viable *seco*-precursor.

The present approach is free from these complications simply by reversing the order of C–O and C–C bond formations (Scheme 6). A primary difference is that the sulfinyl group is not required because of the following reasons: (1) the aryl anion formation uses the high C–H acidity of fluorobenzene **e**,[7] (2) the intramolecular nature of the S_NAr reaction allows smooth replacement of aryl fluoride by an internal alkoxide derived from **g**. Furthermore, epoxide **f** could be used, as the reaction with aryllithium **e** is intermolecular (no trajectory issue).

In conclusion, an effective approach has been developed that would enable the synthesis of a wide range of catechin-class polyphenols and their unnatural congeners. Work is now in progress along these lines.



Scheme 6 Present approach.

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