

General synthesis of epi-series catechins and their 3-gallates: reverse polarity strategy†

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A general synthetic route to the epi-series catechins was developed based on the reverse polarity strategy. Aromatic nucleophilic substitution reaction followed by the sulfinyl-metal exchange and cyclization enabled stereo-controlled access to various members of epi-series catechins and their 3-gallates.

Recently, much attention has been centered on the significant bioactivities of the epi-series catechins as represented by tea catechins, *e.g.* (–)-epigallocatechin (EGC, **1**), (–)-epicatechin (EC, **2**), and (–)-epiafzelechin (EZ, **3**) (Fig. 1).¹ (–)-Epigallocatechin gallate (EGCg, **4**), one of the most abundant ingredients in green tea, exhibits remarkable suppressive effects against various human tumor cell lines, and also antimutagenic activity and antiviral effects.²

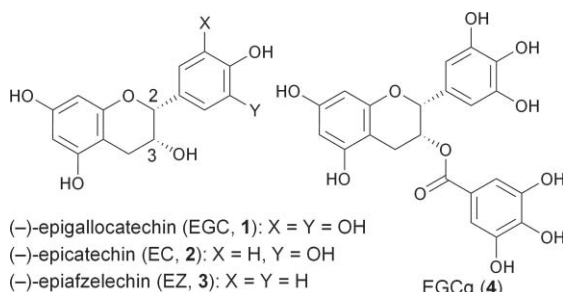
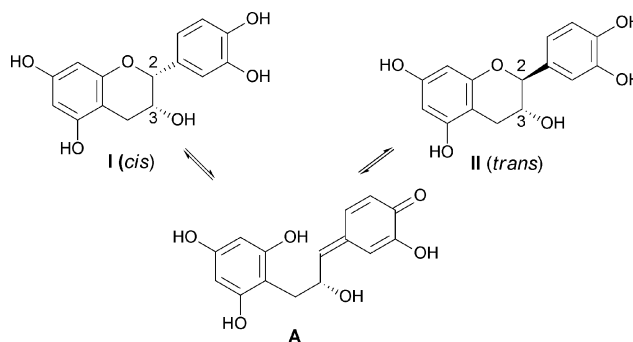


Fig. 1 Structure of epicatechin-type polyphenols.

A recent study at the molecular level revealed the specific binding of **4** to the 67 kDa laminin receptor that mediates its anticancer action at physiologically relevant concentrations.^{2c} Because of their relevance to these significant bio-functions, **4** and other epicatechin-3-gallate derivatives have attracted a great deal of scientific attention.

In spite of such promise, controlled synthesis of the epi-series catechins remains a challenge, due to chemical/stereochemical lability (Scheme 1): the C(2)-stereocenter is prone to epimerization (**I** ⇌ **A** ⇌ **II**) under basic/acidic conditions providing a variable mixture with the catechin congeners of 2,3-*trans* stereochemistry. Even racemization can take place *via*, *inter alia*, the enolization from **A**.³

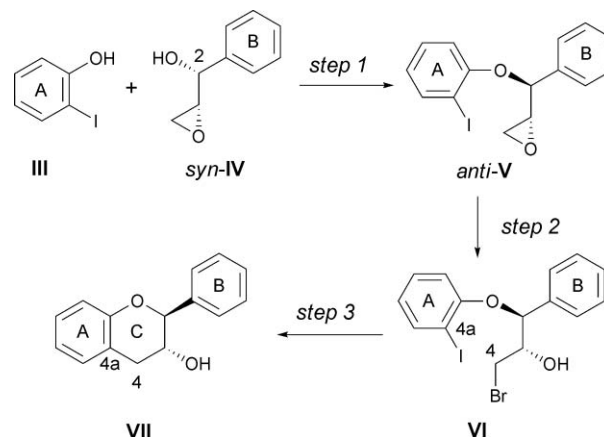
So far, preparation of the epicatechins mainly relies on the *inversion* of the C(3)-stereochemistry of the catechin derivatives *via*



Scheme 1 Stereochemical lability of catechin/epicatechin derivatives.

oxidation and reduction,⁴ which, however, inevitably depends on the availability of the catechin starting materials. Other approaches have started to appear, which, however, are still limited in scope in terms of the versatility or the accessibility of the single enantiomer.⁵

Recently, we reported a stereo-controlled synthetic approach to the catechin derivatives *via* three key steps (Scheme 2);⁶ the Mitsunobu-type C–O bond formation⁷ of iodophenol **III** and epoxy alcohol *syn*-**IV** (step 1), cleavage of the oxirane ring to give the corresponding bromohydrin **VI** (step 2), and the pyran-ring closure *via* the selective iodine–metal exchange, constructing the catechin skeleton **VII** (step 3). Ready availability of *syn*-**IV**⁸ *via* Sharpless asymmetric dihydroxylation⁹ makes this protocol a general route to various catechin derivatives.

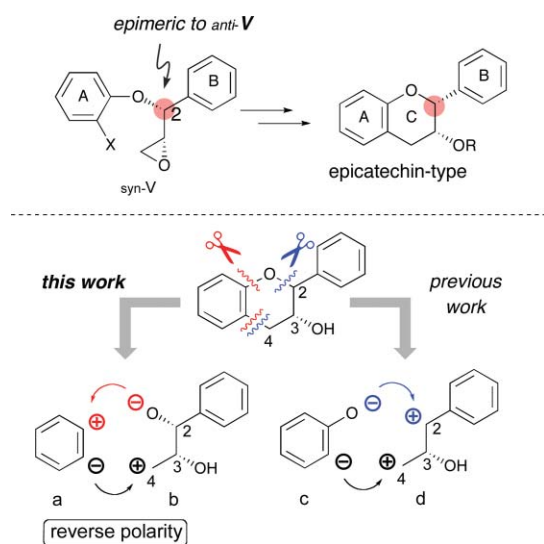


Scheme 2 Stereo-controlled approach to catechin derivatives.

We envisioned that such an approach could provide access to the epicatechins as well, given that the epimeric precursor *syn*-**V** was accessible (Scheme 3). Among several options for the preparation of the requisite structure *syn*-**V**,¹⁰ we focused on a change in the

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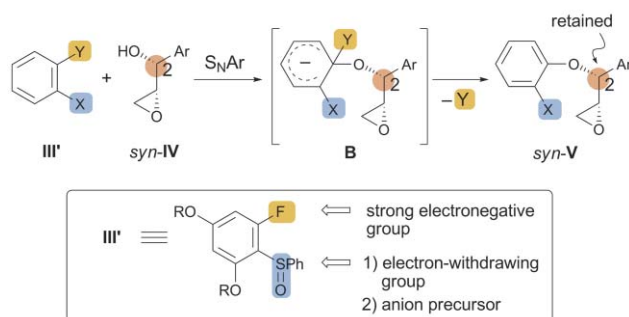
† Electronic supplementary information (ESI) available: Experimental procedures for the preparation and spectral data of all compounds. See DOI: 10.1039/c003464a



Scheme 3 Change of the connectivity for reverse polarity strategy.

connectivity of the A/B-ring fragments: Instead of dissecting the C ring into fragments **c** and **d** (blue lines), disconnection at the Ar–O and Ar–C bonds (red lines) provides a new fragment pair, **a** and **b**, which could be combined in a reversed polarity (*umpolung*) fashion without affecting the C(2)-stereochemistry in **b**.

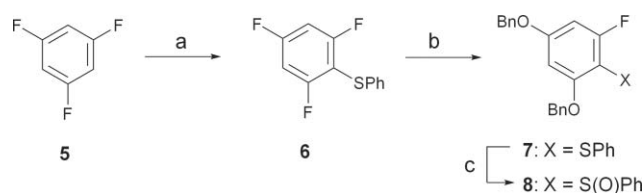
To realise this scenario, we planned the aromatic nucleophilic substitution (S_NAr)¹¹ by employing electrophilic unit **III'** and the alkoxide derived from *syn*-**IV** (Scheme 4).



Scheme 4 S_NAr strategy for retentive assembly of **III'** and *syn*-**IV**.

The choice of the two substituents X and Y was critical. The Y group has to be a strongly electronegative group such as fluorine, being capable of attracting the incoming nucleophile to form the Meisenheimer complex **B**. On the other hand, the X group must play two roles, (1) a π -electron acceptor to facilitate the conjugate attack, and (2) an anion precursor at the stage of the pyran-ring closure later in the synthetic scheme. We chose a *sulfinyl* group as X,¹² expecting that the sulfinyl–metal exchange¹³ would serve for the latter purpose.

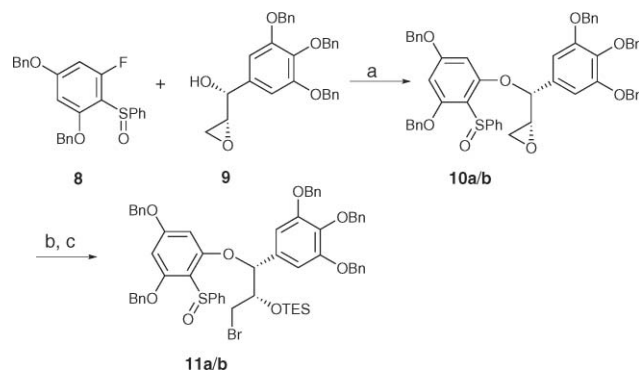
Scheme 5 shows the preparation of fluoro-sulfoxide **8**. Lithiation of 1,3,5-trifluorobenzene (**5**)¹⁴ with *n*-BuLi¹⁵ followed by trapping of the resulting anion with $PhSSO_2Ph$ ¹⁶ gave sulfide **6** in 87% yield. Upon careful treatment of **6** with sodium benzyloxide (2.5 mol equiv., 0 °C, DMF, 1 h), two fluorine atoms were displaced with high regioselectivity, giving the 2,4-bis-benzyl ether **7**. A small amount of the 2,6-regioisomer was also produced which was inseparable at this stage. However, oxidation to the corresponding



Scheme 5 Conditions: (a) *n*-BuLi, $PhSSO_2Ph$, Et_2O , $-78\text{ }^\circ\text{C}$, 87%. (b) BnOH, NaH, DMF, 0 °C. (c) *m*CPBA, CH_2Cl_2 , 0 °C, 2 steps 85%.

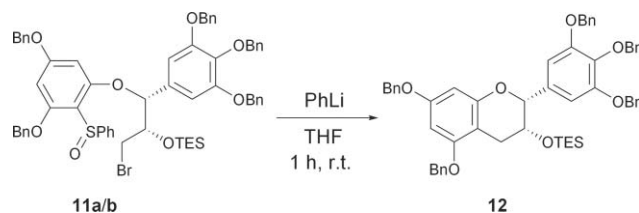
sulfoxides allowed isolation of **8** in 85% yield by silica-gel column chromatography (hexane–EtOAc = 4 : 1). The corresponding 2,6-regioisomer was separated in 8% yield.

With the requisite acceptor **8** in hand, the projected S_NAr reaction was attempted (Scheme 6). Upon treatment of **8** with the sodium alkoxide of **9**,⁶ the reaction proceeded smoothly in a mixed solvent (toluene–DMPU = 4 : 1) at 0 °C. Notably, the Payne rearrangement¹⁷ was not observed under these conditions, thereby giving the desired S_NAr -product **10** in 76% yield as a mixture of diastereomers. Separation by silica-gel column chromatography gave diastereomeric epoxy ethers **10a** (39%) and **10b** (37%), albeit the sulfoxide stereochemistry was unspecified. Oxirane cleavage with Li_2NiBr_4 ¹⁸ followed by silylation with triethylsilyl (TES) triflate afforded the diastereomeric bromides **11a/b** (97%: **11a** from **10a**, 91%: **11b** from **10b**), respectively.



Scheme 6 Conditions: (a) NaH, toluene, DMPU room temp., 39% for **10a**, 37% for **10b**. (b) Li_2NiBr_4 , THF, 0 °C. (c) TESOTf, 2,6-lutidine, CH_2Cl_2 , 0 °C, 2 steps, 97% for **11a**, 91% for **11b**. DMPU = *N,N'*-dimethylpropyleneurea, TES = triethylsilyl.

The next stage was to construct the flavan skeleton. We planned the cyclization of **11a/b** via the sulfinyl–metal exchange followed by intramolecular nucleophilic substitution (Scheme 7). Thus, upon treatment of diastereomeric sulfoxides **11a** and **11b** with PhLi (2.0 equiv in THF, room temp., 1 h),¹⁹ smooth cyclization of the pyran ring occurred, giving a single cyclized product **12**, respectively (81% from **11a** and 62% from **11b**). The C(2) and C(3)

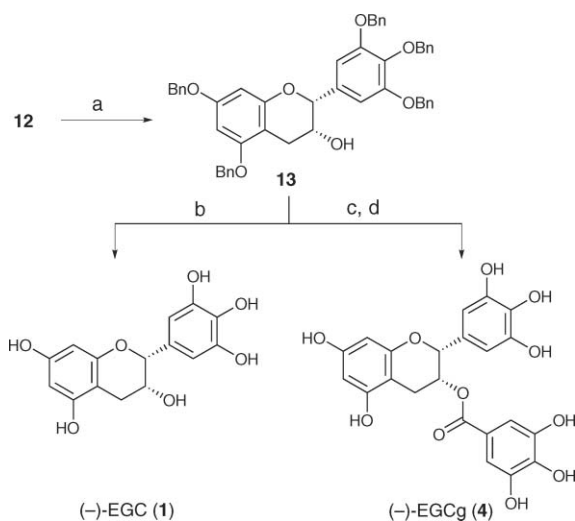


Scheme 7 Construction of flavan skeleton by sulfur–metal exchange and intramolecular nucleophilic substitution.

relative stereochemistry was unambiguously assigned by ^1H NMR analysis ($J_{2,3} = <0.5$ Hz).

It is noteworthy that the aryl lithium species generated by the sulfinyl–metal exchange could be exploited for such an efficient C–C bond formation, which has sizable potential for application for other purposes.

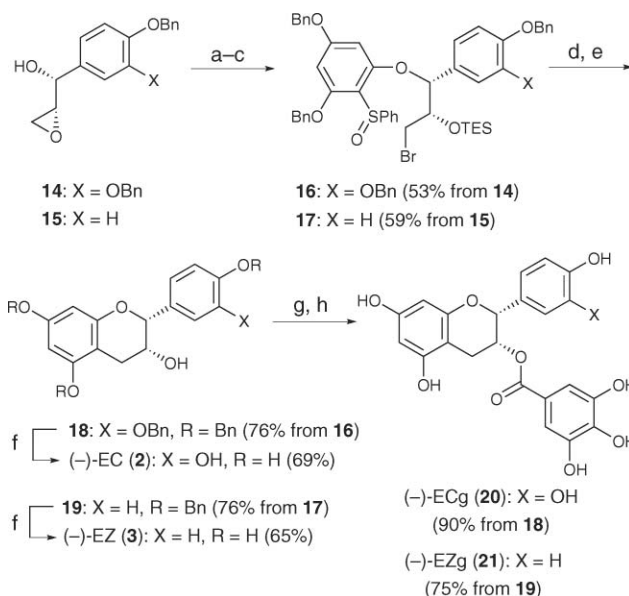
Conversion of **12** into EGC (**1**) was carried out as follows (Scheme 8). After removal of the TES group by $n\text{-Bu}_4\text{NF}$ to give alcohol **13**, all the benzyl protecting groups were removed by hydrogenolysis over 20% $\text{Pd}(\text{OH})_2/\text{C}$ in a mixed solvent (THF–MeOH– $\text{H}_2\text{O} = 4:4:1$, 12 h). Careful non-aerobic filtration through a Celite pad (washed with MeOH) followed by purification by Sephadex LH-20 column chromatography (MeOH) afforded (–)-EGC (**1**) as a snow-white amorphous solid (64% yield from **12**), which was indistinguishable from the authentic specimen in all respects $\{[\alpha]_D^{21} -56.0$ (c 1.02, acetone– $\text{H}_2\text{O} = 1:1$), *lit.* $[\alpha]_D^{24} -57.1$ (c 1, acetone– $\text{H}_2\text{O} = 1:1$).^{3c}



Scheme 8 Conditions: (a) $n\text{-Bu}_4\text{NF}$, THF, 0°C , 99%. (b) H_2 , $\text{Pd}(\text{OH})_2$, THF, MeOH, H_2O (4:4:1), room temp., 71%. (c) 3,4,5-tri-*O*-benzylgallic acid, EDCI–HCl, DMAP, Et_3N , CH_2Cl_2 room temp. (d) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, THF, MeOH, H_2O (4:4:1), room temp., 68% (2 steps).

Furthermore, the protection pattern of alcohol **13** is ideally suited for straightforward access to EGCg (**4**): Esterification of **13** with 3,4,5-tri-*O*-benzylgallic acid followed by hydrogenolysis of all benzyl groups gave **4** $\{[\alpha]_D^{21} -218$ (c 0.660, acetone– $\text{H}_2\text{O} = 1:1$), *lit.*^{3c} $[\alpha]_D^{24} -216.4$ (c 1, acetone– $\text{H}_2\text{O} = 1:1$) as a snow-white amorphous solid in good yield.

Starting from epoxy alcohols **14** and **15**, applicability of these protocols was further demonstrated by the syntheses of (–)-EC (**2**) and (–)-EZ (**3**), and its 3-gallates, respectively (Scheme 9). After the same three-step sequence as before, the resulting bromides **16** and **17** were subjected to the cyclization followed by desilylation as before, giving the corresponding pyrans, **18** and **19** in good yield, respectively. Detachment of all the benzyl groups in **18** and **19** gave (–)-EC (**2**)²¹ and (–)-EZ (**3**)²² as a snow-white amorphous solid, respectively. Furthermore, esterification of **18** and **19** with 3,4,5-tri-*O*-benzylgallic acid followed by hydrogenolysis of all the benzyl groups gave the 3-gallate of (–)-epicatechin [(–)-ECg (**20**)],²³ and that of (–)-epiafzelechin [(–)-EZg (**21**)],²⁴ in good yields, respectively.



Scheme 9 Synthesis of (–)-epicatechin [EC (**2**)] and (–)-epiafzelechin [EZ (**3**)] and their 3-gallates, (–)-ECg (**20**) and (–)-EZg (**21**). Conditions: (a) NaH , toluene, DMPU, room temp. (b) Li_2NiBr_4 , THF, 0°C . (c) TESOtf , 2,6-lutidine, CH_2Cl_2 , 0°C . (d) PhLi , THF, 0°C . (e) $n\text{-Bu}_4\text{NF}$, THF, 0°C , 99%. (f) H_2 , $\text{Pd}(\text{OH})_2$, THF, MeOH, H_2O (4:4:1), room temp.; (g) 3,4,5-tri-*O*-benzylgallic acid, EDCI–HCl, DMAP, Et_3N , CH_2Cl_2 room temp.; (h) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, THF, MeOH, H_2O (4:4:1), room temp. DMPU = *N,N'*-dimethylpropyleneurea, TES = triethylsilyl.

In summary, the work described above entails a number of noteworthy developments, including 1) the general and stereoselective access to the epi-series catechins and their 3-gallates, 2) the retentive assembly of the cyclization precursors *via* the nucleophilic aromatic substitution of aryl fluoride bearing a sulfinyl group at the *ortho* position, 3) the sulfinyl–metal exchange and following nucleophilic substitution to form the corresponding cyclized product. The efficient C–C bond formation in this process was especially striking, which should be useful for other purposes.

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