Stereocontolled Synthesis of (−)-Afzelechin: General Route to Catechin-class Polyphenols by Solving an S_N2 vs. S_N1 Problem

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Stereocontrolled synthesis of (−)-afzelechin was achieved via the Mitsunobu reaction, where complete stereospecificity was observed when an electron-withdrawing group was introduced to the para-position of the B-ring fragment.

In spite of increasing interest in the catechin-class polyphenols,[1] progress of biochemical studies are limited by the poor availability of pure samples, because natural materials are obtained as a hardly separable mixture of closely related compounds. At this juncture, organic synthesis of catechins and related compounds has been gaining increasing importance (Figure 1).[2]

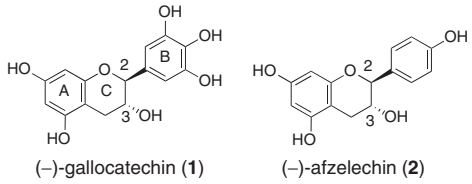
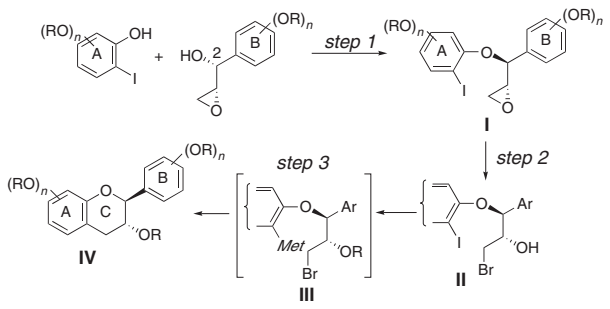


Figure 1. Structures of (−)-gallocatechin and (−)-afzelechin.

This communication reports problems and solutions found in the general application of our recent synthetic approach to various *catechin* congeners.[3]

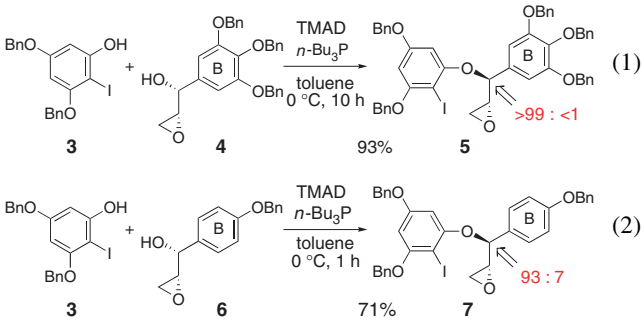
Scheme 1 outlines the synthetic route, which we hoped to be generally applicable to various catechins sharing the 2,3-trans stereochemistry, but differing in the oxygenation pattern of the A/B rings. We reasoned that a narrow window would be the *stereospecificity* of step 1, i.e. the Mitsunobu etherification.[4] Given an electron-rich B-ring, the stereochemical integrity may be lost due to S_N1 ionization at the benzylic 2-position.[5] This issue is relevant to the well-known tendency of catechins to epimerize at the 2-positions,[6] as well as being a fundamental problem in organic chemistry, S_N2 vs. S_N1 mechanism.

Fortunately, substrate **4** with a trioxygenated B-ring, *seemingly* highly susceptible to S_N1 reaction, underwent the Mitsunobu reaction with clean inversion by using *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) and *n*-Bu_3P (eq 1).[4b] Results of this test case, allowing the stereoselective synthesis of (−)-gallocatechin (**1**), made us believe that *less* oxygenated substrates would be more easily subject to stereochemical control.



Scheme 1. Synthetic route to catechin-class flavans.

However, this naïve perception proved wrong, as the stereospecificity became disrupted for less oxidized substrates. When the Mitsunobu reaction of epoxy alcohol **6** and phenol **3** was attempted (eq 2), the reaction proceeded much faster, within 1 h, to give ether **7** in 71% yield, but as a mixture of diastereomers (93:7 ratio).[7]



This unexpected result prompted us to study the dependence of the stereospecificity on the oxidation state of the B-ring. It turned out that the ratio was *not linearly* related to the number of the oxy-functions (Table 1): A single diastereomer is produced when the B-ring is a simple phenyl, while the dioxy congener results in a 97:3 ratio.[7] Thus, the extent of the competing S_N1 pathway relative to the number of oxy-group(s) is in the order of $1 > 2 > 3 \simeq 0$.

Table 1. Stereospecificity of the Mitsunobu reaction

	B	B(OBn)	B(OBn)(OBn)	B(OBn)(OBn)(OBn)
n(*p*-oxy)[a]	0	1	1	1
n(*m*-oxy)[b]	0	0	1	2
ratio	>99:<1	93:7	97:3	>99:<1

a) Number of *p*-oxy substituents. b) Number of *m*-oxy substituents.

Apparently, one is required to separate the *inductive* and the *mesomeric* effects (Figure 2). While the *p*-oxygen works to stabilize the benzylic cation, the *m*-oxy group(s), out of conjugation, leads to destabilization (−I effect). This accounts for the recovery of the S_N2 pathway with increment in the *m*-oxygen(s).

An additional factor to be considered, particularly for the trioxy substrate, is the *steric inhibition of the resonance*,[5b] as supported by the following experiment (eq 3). Mono-oxy substrate **8** with two *m*-methyl groups underwent the reaction in an S_N2 fashion.

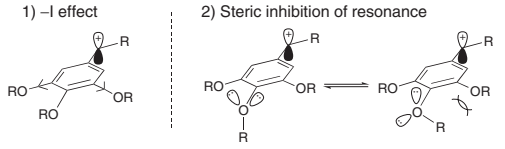
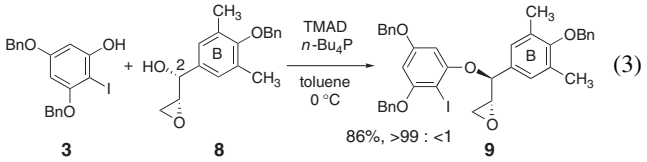


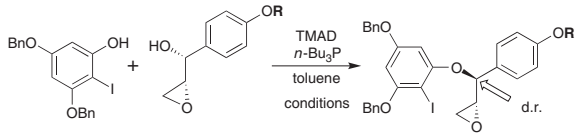
Figure 2. Two possible rationales.



(3)

To suppress the S_N1 reaction in the most challenging monooxy substrates, the choice of protecting group proved to be effective (Table 2). While the use of bulky protective groups, aiming at the steric inhibition of resonance, proved ineffective (Runs 1–4), use of an electron-withdrawing protective group, for decreasing the n-electron donation, gave promising results (Runs 5–8). Among others, *t*-butoxycarbonyl (Boc) gave the best result (Run 8).

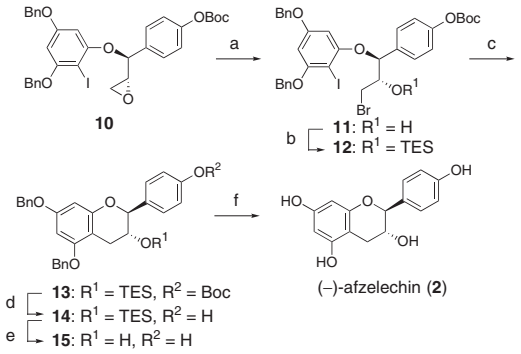
Table 2. Effect of protecting group



Run	R	Conditions	Yield/%	d.r.
1	$C(CH_3)_2Ph$	0 °C, 1.5 h	74	93:7
2	$CH(CH_3)Ph$	0 °C, 1.5 h	66	93:7
3	$SiPh_2(t\text{-Bu})$	0 °C, 1.8 h	61	96:4
4	$Si(i\text{-Pr})_3$	0 °C, 3 h	83	91:9
5	$CH_2C_6F_5$	0 °C, 0.5 h	44	>99:<1
6	Bz	0 °C, 1.5 h then rt, 1.3 h	68	>99:<1
7	Ms	0 °C, 1.5 h then rt, 5 h	65	>99:<1
8	Boc	0 °C, 0.5 h then rt, 2 h	77	>99:<1

Having fixed the problem, we carried out the stereocontrolled synthesis of (−)-afzelechin (**2**), the less abundant enantiomer of this natural product (Scheme 2).[8,9] Boc-ether **10** (Run 8, Table 2) was converted to the corresponding bromohydrin **11** by using Li_2NiBr_4. After protection of alcohol **11** to give triethylsilyl (TES) ether **12**, the pyran ring formation was carried out by treatment with Ph_3MgLi (2.5 equiv) and HMPA (10 equiv) in THF to afford the desired product **13** in 88% yield. The Boc group was removed with DIBAL (2.9 equiv, THF, −78 °C, 1 h) to give phenol **14**, and subsequent treatment with *n*-Bu_4NF gave alcohol **15** in 84% yield. Finally, the benzyl groups were detached by catalytic hydrogenolysis to afford (−)-afzelechin (**2**) {$[\alpha]_D^{31}$ −18 (*c* 0.28, acetone); lit. $[\alpha]_D^{25}$ −20 (*c* 0.63, acetone)[9]} as snow-white amorphous solid in high yield.[10,11]

In conclusion, an efficient synthetic approach to *catechin* derivatives is described that allows access to various congeners sharing the 2,3-trans stereochemistry. The efficiency is demonstrated by the stereoselective synthesis of (−)-afzelechin (**2**), scarcely obtained from nature.



Scheme 2. Synthesis of (−)-afzelechin (**2**). Conditions: (a) Li_2NiBr_4, THF, 0 °C, 87%; (b) TESCl, imidazole, DMF, 0 °C, 97%; (c) Ph_3MgLi, HMPA, THF, 0 °C, 88%; (d) DIBAL, CH_2Cl_2, −78 °C, 96%; (e) TBAF, THF, 0 °C, 84%; (f) H_2, $Pd(OH)_2$, THF, MeOH (1:1), rt, 76%.

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7 The relative stereochemistry of C(2) and C(3) stereogenic centers was assigned by NMR analysis after conversion to the corresponding cyclized product ($J_{2,3} = 8.4$ Hz).
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10 All spectroscopic means (^1H, ^{13}C NMR, IR, MS) and combination analysis was identical to those of natural product.
11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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