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The flavan–isoflavan rearrangement: bioinspired synthetic access to isoflavonoids *via* 1,2-shift–alkylation sequence†

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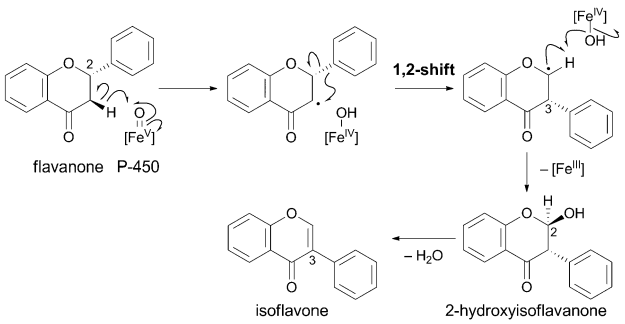
An approach to 2-substituted isoflavonoids is reported based on the 1,2-shift of the aryl group in the catechin skeleton followed by the *in situ* alkylation. Synthesis of (−)-equol, a natural isoflavan with estrogenic activities, was achieved.

Isoflavonoids constitute a class of natural products widely found in leguminous plants. In addition to the phytoalexin activity in the original plants,[1] some compounds have been attracting special attention in the field of human health care, *e.g.*, the estrogen activities identified in the soybean-derived compounds **1**–**3**.[2] Furthermore, several elaborated compounds with stereogenicity are found in nature, including isoflavans, pterocarpans, and rotenonoids, such as **4**–**6** (Fig. 1). Due to the diverse range of bioactivities,[1] isoflavonoids have become one of the current targets for chemical synthesis.[3]

The isoflavonoid biosynthesis shares its early stage with that of the flavonoid, branching at the flavanone stage by P-450 mediated oxygenation to induce the aryl 1,2-shift within the chroman skeleton to form the 3-aryl derivatives (Scheme 1). Although the following dehydration gives isoflavones,[4] stereogenic compounds, *e.g.*, **4**–**6** are generated by further biosynthetic elaborations. This biogenetic 1,2-shift and the presence of the intriguing natural products **4**–**6** prompted us to devise a synthesis route for obtaining isoflavonoids.



Scheme 1 Biosynthesis of isoflavonoids.

In this communication, we describe a synthetic access to isoflavonoids *via* a 1,2-shift and alkylation sequence within the flavonoid scaffolds.

We took inspiration from our previous study (Scheme 2).[5] Eqn (1) is a pinacol-type shift of a phenyl group by the activation

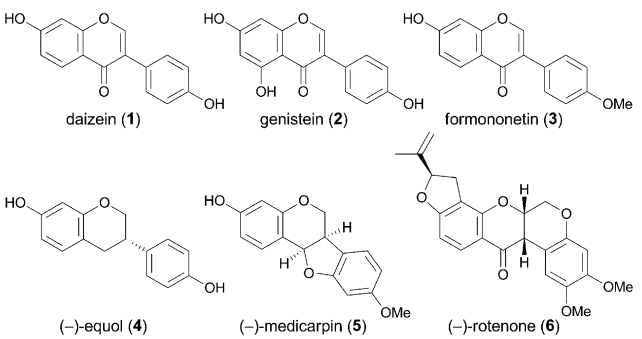
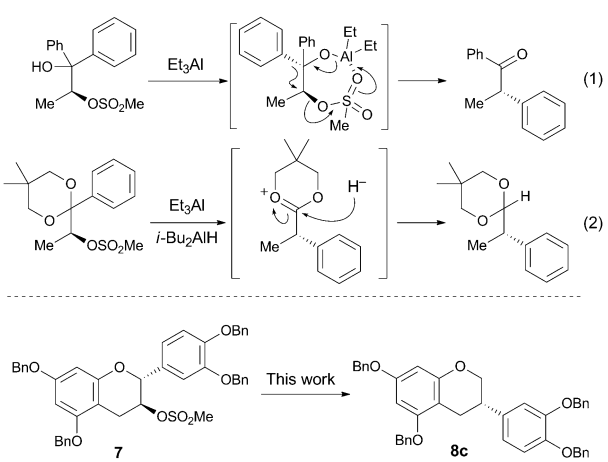


Fig. 1 Natural isoflavonoids.



Scheme 2 Organoaluminum-mediated stereospecific 1,2-shift.

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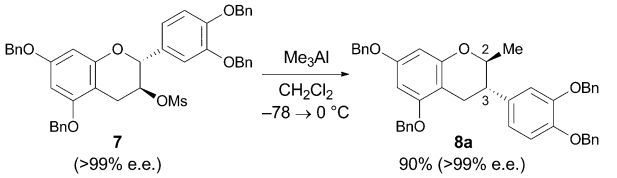
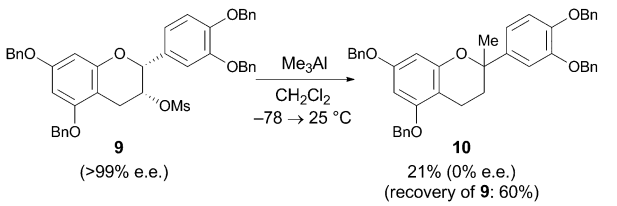
of a mesylate with Et_3Al to effect a stereospecific 1,2-shift.[5a] A related process involves trapping of the intermediary oxonium species by an organoaluminum ligand (eqn (2)).[5b] By analogy, we asked ourselves whether such a 1,2-shift was viable within a catechin framework, and the model study started with a catechin-derived substrate, *i.e.* mesylate **7**.[6]

Mesylate **7** was prepared from tetra-*O*-benzyl catechin[7] (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 96% yield). Upon treatment of **7** with Me_3Al (2 equiv.) in CH_2Cl_2 at −78 °C followed by gradually warming to 0 °C, a single new product **8a** was produced in 90% yield (eqn (3)). The *trans* stereochemistry of the aryl and the methyl groups was assigned using the coupling constant ($J_{2,3}$ = 9.2 Hz) and the ROESY experiment.[8] The stereochemical outcome could be attributed to the inversive 1,2-shift followed by trapping by a methyl nucleophile from the opposite side. Furthermore, the enantiomeric purity of **8a** (>99% e.e.) was verified by HPLC analysis using a chiral stationary phase.[9]



(3)

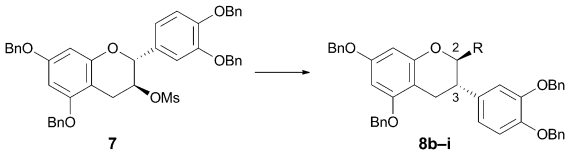
A control experiment showed the well-known importance of the anti-relationship of the leaving group and the migrating group (eqn (4)). Epicatechin derivative **9**, upon reaction with Me_3Al, led only to a slow 1,2-shift of the hydride to give **10** in 21% yield, and mesylate **9** was largely recovered. The ee of **10** was 0%, not surprisingly, suggesting that the reactive species that underwent trapping by a methyl nucleophile was the oxonium species after the hydride shift was fully completed.



(4)

Table 1 shows the generality of the process, giving various 2-substituted isoflavans. Reaction of **7** with Et_3Al proceeded smoothly to give the ethylated product **8b** in excellent yield (run 1). AlH_3, *in situ* prepared from $LiAlH_4$ and $AlCl_3$,[10] induced the 1,2-shift of **7** followed by hydride trapping, giving isoflavan **8c** in 73% yield (run 2). Reaction of **7** with i-Bu_3Al gave the expected product **8d** with an i-butyl group. A small amount of **8c** was obtained, arising from the β-hydride delivery from i-Bu_3Al (run 3). Furthermore, reactions of other organoaluminum reagents gave various isoflavans **8e–8i** in moderate to high yields and rigorous *trans* selectivities. In runs 4–6, triorganoaluminum reagents were generated *in situ* from the respective organolithium and $AlCl_3$.[11] In runs 7 and 8, $EtAlCl_2$ was used for this purpose, where the alkynyl ligands were exclusively transferred.[12]

Table 1 Conversion of catechin mesylate **7** to various isoflavans

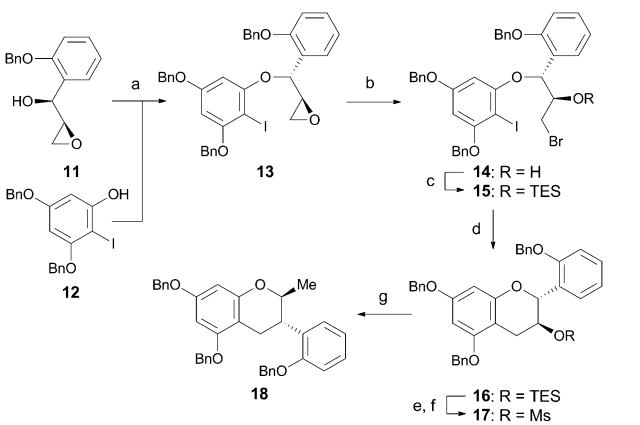


Run	Reagent	R	Product	Yield [%]
1	Et_3Al	Et	**8b**	86
2	AlH_3	H	**8c**	73
3	i-Bu_3Al	i-Bu	**8d**	74
4	$Al(CH_2SiMe_3)_3$[a]	CH_2SiMe_3	**8e**	83
5	$PhAl$[a]	Ph	**8f**	95
6			**8g**	54
7	$EtAl(C{\equiv}CPh)_2$[b]	$C{\equiv}CPh$	**8h**	76
8	$EtAl(C{\equiv}CSiMe_3)_2$[b]	$C{\equiv}CSiMe_3$	**8i**	96

[a] Prepared from the corresponding organolithium and $AlCl_3$. [b] Prepared from the corresponding alkynyllithium and $EtAlCl_2$.

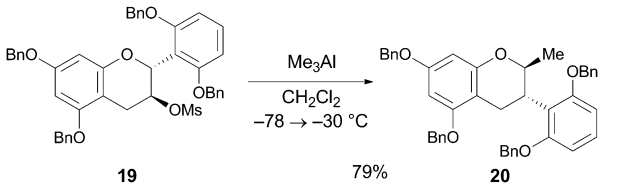
As a variation of the migrating group, an *ortho*-substituted phenyl group was tested (Scheme 3). Mesylate **17** was prepared *via* our method for the flavan synthesis.[13] The Mitsunobu reaction of epoxy alcohol **11**[8] and iodophenol **12** gave ether **13** as a single product, and the subsequent cyclization gave flavan **16**. After the removal of the TES group in **16**, mesylation of the resulting alcohol gave mesylate **17**. Treatment of **17** with Me_3Al (−78 → −10 °C) induced a smooth 1,2-shift, giving isoflavan **18** in 84% yield as a single product.[8]

Previously, we noted that *o*,*o*′-disubstituted phenyl groups are often sluggish to undergo the 1,2-shift, particularly when the substrate has steric hindrance.[5c] To address this point, we prepared mesylate **19** with an *o*,*o*′-dibenzyloxyphenyl group in a similar manner. To our delight, the reaction of **19**[8] with Me_3Al (−78 → −30 °C) gave 79% yield of the rearranged product **20**



Scheme 3 Keys: (a) TMAD, *n*-Bu_3P, toluene, 0 °C, 2 h (83%, single diastereomer), (b) Li_2NiBr_4, THF, 0 °C → RT, 80 h (91%), (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 20 min (95%), (d) PhMgBr, PhLi, HMPA, THF, −78 → 0 °C, 30 min (62%), (e) *n*-Bu_4NF, THF, 0 °C, 20 min (quant.), (f) MsCl, Et_3N, CH_2Cl_2, 0 °C, 40 min (94%), (g) Me_3Al, CH_2Cl_2, −78 → −10 °C, 1.5 h (84%). TMAD = *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide. HMPA = hexamethylphosphoric triamide.

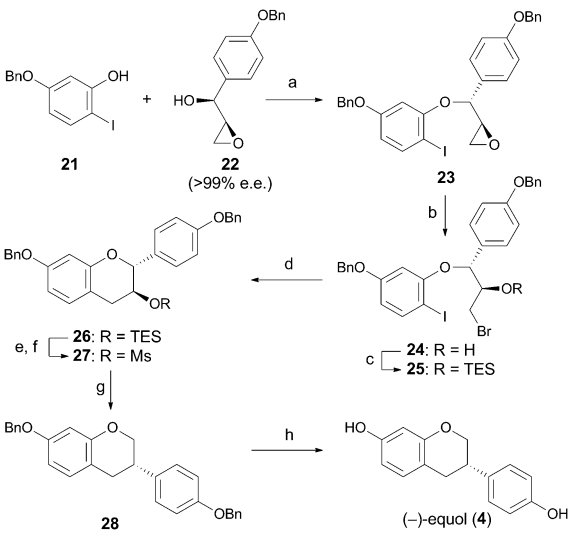
(eqn (5)). This is a promising result in view of the synthesis of many natural isoflavonoids with an aryl group possessing *ortho*-hydroxy group(s).



(5)

Finally the enantiospecific synthesis of (−)-equol (**4**), a soy-derived isoflavonoid known since 1932 is described.[14] Recently, sizable phytoestrogenic activity has been found in **4**,[15] making it the current target of chemical synthesis.[16]

Scheme 4 outlines the synthesis of **4**. The key intermediate **27** was prepared from the resorcinol derivative **21**. The union of **21** with epoxide **22** (>99% e.e.)[7] *via* the Mitsunobu reaction gave ether **23** in 78% yield as an inseparable mixture of diastereomers (93 : 7 ratio),[13b] which was used for the next step. Regioselective cleavage of oxirane **23** gave bromohydrin **24** (87% yield) and its epimer **24′** (4% yield), which were separated using flash column chromatography (hexane/toluene/EtOAc = 5/5/1). After protection of **24** as a TES ether, the cyclization precursor **25**, thus obtained, was treated with Ph_3MgLi to give flavan **26** in 88% yield.[13] After two-step conversion of **26** into mesylate **27**, treatment with AlH_3 (CH_2Cl_2, 0 °C → room temp., 2.5 h) cleanly afforded the desired isoflavan **28** in 85% yield. Finally, two benzyl groups were removed by hydrogenolysis [H_2, $Pd(OH)_2$/C, THF, MeOH, H_2O (2/2/1), room temp., 45 min], giving (−)-equol (**4**) as a white solid (99% e.e.).[17] All the physical data of the synthetic sample of **4** (^1H and ^{13}C NMR, IR, $[\alpha]_D$) coincided with the reported data.[16]



Scheme 4 Keys: (a) TMAD, *n*-Bu_3P, toluene, 0 °C, 1 h (78%, dr = 93/7), (b) Li_2NiBr_4, THF, 0 °C, 24 h (87%), (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 20 min (97%), (d) PhMgBr, PhLi, HMPA, THF, −78 → 0 °C, 45 min (88%), (e) *n*-Bu_4NF, THF, 0 °C → RT, 15 min (95%), (f) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min (99%), (g) $LiAlH_4$, $AlCl_3$, CH_2Cl_2, 0 °C → RT, 2.5 h (85%), (h) H_2, ASCA-2 [5% $Pd(OH)_2$/C], THF, MeOH, H_2O, RT, 45 min (quant.).

In conclusion, an approach to the stereoselective synthesis of isoflavans has been established based on the 1,2-shift of aryl groups in flavan-3-ol derivatives and *in situ* alkylation by organoaluminum reagents. The method was applied in the synthesis of (−)-equol (**4**).

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17 An authentic sample of (±)-**4** was purchased from Tokyo Chemical Industry Co., Ltd. (TCI) and the enantiomeric purity of synthetic **4** was assessed by HPLC analysis. See the ESI†.

