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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 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 activitity for the original plants,[1] some compounds are attracting special attention related to 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** (Figure 1). Due to the diverse range of bioactivities,[1] isoflavonoids have become one of the current targets for chemical synthesis.[3]

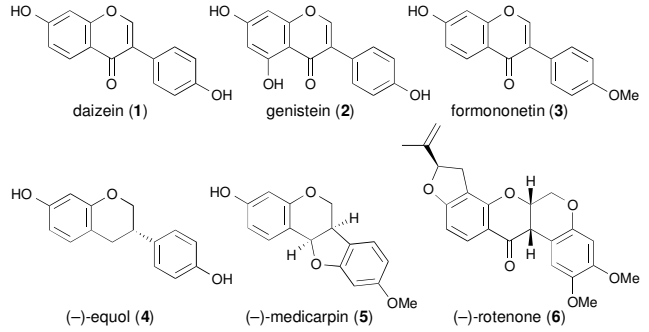
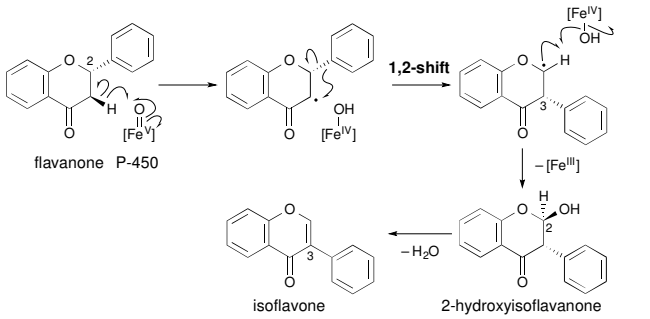


Figure 1 Natural isoflavonoids.

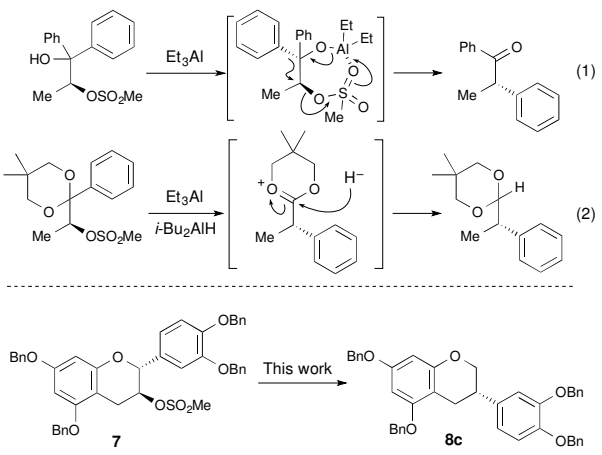
The isoflavonoid biosynthesis shares its early stage with that of the flavonoid, branching at the flavanone stage by P-450 mediated oxygenation to induce the aryl 1,2-shift within the chroman skeleton to form the 3-aryl derivatives (Scheme 1). Although the following dehydration give isoflavones,[4] stereogenic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

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



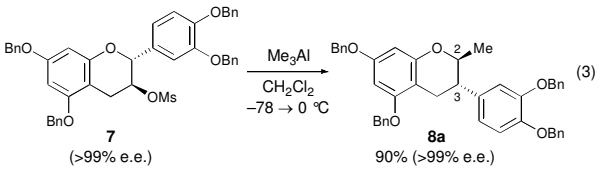
Scheme 1 Biosynthesis of isoflavonoids.

We took inspiration from our previous study (Scheme 2).[5] Eq.1 is a pinacol-type shift of a phenyl group by activating a mesylate with Et_3Al to effect stereospecific 1,2-shift.[5a] A related process involves trapping of the intermediary oxonium species by an organoaluminum ligand (eq. 2).[5b] By analogy, we asked ourself 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]



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

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 gradual warming to 0 °C, a single new product **8a** was produced in 90% yield (eq. 3). The *trans* stereochemistry of the aryl and the methyl groups was assigned by the coupling constant ($J_{2,3}$=9.2 Hz) and the ROESY experiment.[8] The stereochemical outcome could be attributed to the invertive 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 the HPLC analysis using a chiral stationary phase.[9]



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

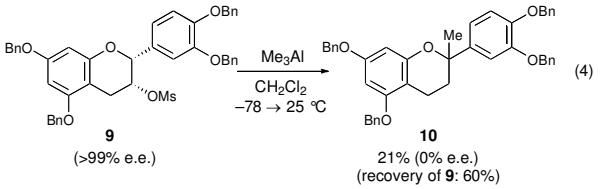
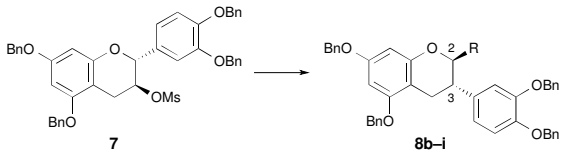


Table 1 shows generality of the process, giving various 2-substituted isoflavans. Reaction of **7** with Et_3Al proceeded smoothly to give the ethylated product **8b** in excellent yield (run 1). AlH_3, in-situ prepared from $LiAlH_4$ and $AlCl_3$,[10] induced the 1,2-shift of **7** followed by the hydride 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 ammount 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]

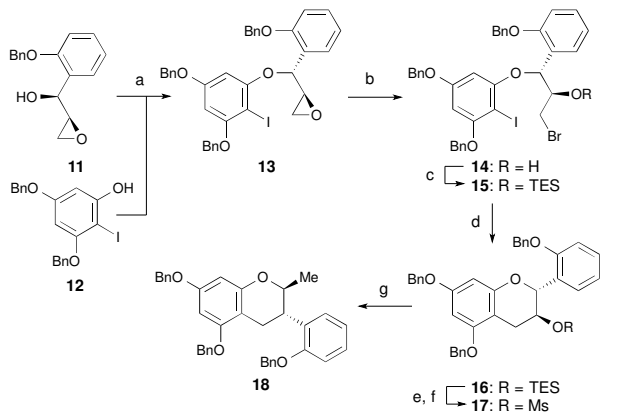
Table 1. Conversion of catechin mesylate **7** to various isoflavans.



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
		H	**8c**	11
4	$Al(CH_2SiMe_3)_3$[a]	CH_2SiMe_3	**8e**	83
5	Ph_3Al[a]	Ph	**8f**	95
6	$Al(t\text{-Bu})_3$[a]	*t*-Bu	**8g**	54
7	$EtAl(C{\equiv}CPh)_2$[b]	C≡CPh	**8h**	73
8	$EtAl(C{\equiv}CSiMe_3)_2$[b]	C≡CSiMe$_3$	**8i**	96

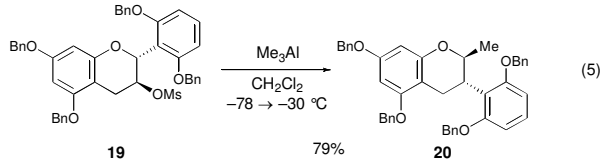
[a] Prepared from the corresponding organolithium and $AlCl_3$.; [b] Prepared from the corresponding alkynyllithium and $EtAlCl_2$

As 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] 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 removal of 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]



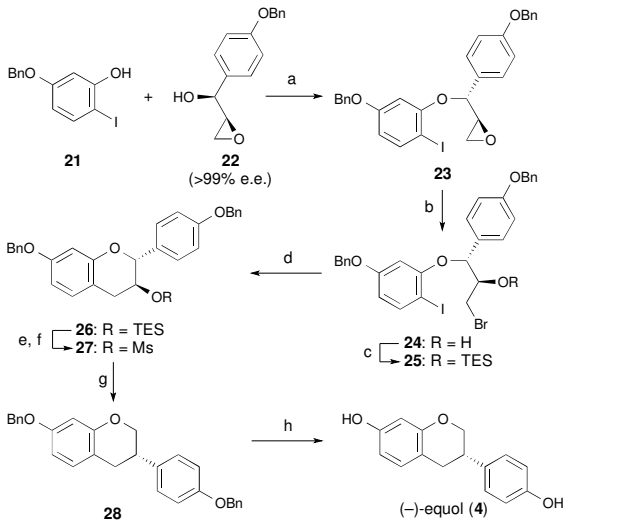
Scheme 3 Keys: (a) TMAD, *n*-Bu_3P, toluene, 0 °C, 2 h (83%, single diastereomer) (b) Li_2NiBr_4, THF, 0 °C → RT, 80 h (91%) (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 20 min (95%) (d) PhMgBr, PhLi, HMPA, THF, –78 → 0 °C, 30 min (62%) (e) *n*-Bu_4NF, THF, 0 °C, 20 min (quant.) (f) MsCl, Et_3N, CH_2Cl_2, 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.

Previously, we noted that *o,o'*-disubstituted phenyl groups are often sluggish to undergo 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** (eq. 5). This is a promising result in view of the synthesis of many natural isoflavonoids with an aryl group possessing *ortho*-hydroxy group(s).



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

Scheme 4 outlines the synthesis of **4**. The key intermediate **27** was prepared from the resorcinol derivative **21**. Union of **21** with epoxide **22** (>99% e.e.)[7] by 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 by 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 an 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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Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

1 D. A. Smith and S. W. Banks, *Phytochem.* 1986, **25**, 979.
2 G. G. J. M. Kuiper, J. G. Lemmen, B. Carlsson, J. C. Corton, S. H. Safe, P. T. Saag, B. Burg and J.-A. Gustafsson, *Endocrinology* 1998, **139**, 4252.
3 (a) A. Lévai, *J. Heterocyclic Chem.* 2004, **41**, 449; (b) A. Goel, A. Kumar and A. Raghuvanshi,.*Chem. Rev.* 2013, **113**, 1614; (c) M. A. Selepe and F. R. V. Heerden, *Molecules*, 2013, **18**, 4739; (d) R. L. Farmer and K. A. Scheidt, *Chem. Sci.* 2013, **4**, 3304; (e) Z.-G. Feng, W.-J. Bai and T. R. R. Pettus, *Angew.Chem. Int. Ed.* 2015, **54**, 1864, and references therein.
4 M. F. Hashim, T. Hakamatsuka, Y. Ebizuka and U. Sankawa, *FEBS Lett.* 1990, **271**, 219.
5 (a) K. Suzuki, E. Katayama and G. Tsuchihashi, *Tetrahedron Lett.*, 1983, **24**, 4997; (b) Y. Honda, E. Morita and G. Tsuchihashi, *Chem. Lett.* 1985, 1153; (c) T. Saito, T. Suzuki, M. Morimoto, C. Akiyama, T. Ochiai, K. Takeuchi, T. Matsumoto and K. Suzuki, *J. Am. Chem. Soc.* 1998, **120**, 11633.
6 For early examples for the use of 1,2-shift to construct 3-aryl isoflavones, see (a) A. C. Jain, P. D. Sarpal and T. R. Seshadri, *Indian*

J. Chem. 1965, **3**, 369; (b) W. D. Ollis, K. L. Ormand and I. O. Sutherland, *Chem. Commun.* 1968, 1237; (c) O. Prakash, S. Pahuja, S. Goyal, S. N. Sawhney and M. Moriarty, *Synlett* 1990, 337; (d) O. V. Singh, C. P. Garg and R. P. Kapoor, *Tetrahedron Lett*. 1990, **31**, 2747; (e) T. Kinoshita, K. Ichinose and U. Sankawa, *Tetrahedron Lett.* 1990, **31**, 7355; (f) C. D. Gabbutt, J. D. Hepworth, B. M. Heron and J. -L. Thomas, *Tetrahedron Lett*, 1998, **39**, 881.

7 H. Kawamoto, F. Nakatsubo and K. Murakami, *Synth. Commun.* 1996, **26**, 531.

8 See the ESI†.

9 An authentic sample of ent-**7** was prepared by the C2-epimerization of (–)-epicatechin (EC) (pH 8 phosphate buffer, 80 °C, 2 h), giving a mixture of (–)-catechin and (–)-EC. Peracetylation followed by the Kawamoto protcol, separation and mesylation gave ent-**7**. See the ESI†.

10 (a) A. E. Finholt, A. C. Bond and H. I. Schlesinger, *J. Am. Chem. Soc.* 1947, **69**, 1199; (b) S. Raghavan, S. R. Reddy, K. A. Tony, C. N. Kumar, A. K. Varma and A. Nangia, *J. Org. Chem.* 2002, **67**, 5838.

11 In the run 6, the isoflavene (3-aryl-4H-chromene) derivative was obtained as a byproduct (16% yield). See the ESI†.

12 (a) J. Fried, C.-H. Lin and S. H. Ford, *Tetrahedron Lett.* 1969, 1379. (b) R. T. Hansen, D. B. Carr and J. Schwartz, *J. Am. Chem. Soc.* 1978, **100**, 2244. (c) K. Taya, T. Nagasawa and K. Suzuki, *Synlett* 1997, 304.

13 (a) T. Higuchi, K. Ohmori and K. Suzuki, *Chem. Lett.* 2006, **35**, 1006. (b) K. Ohmori, M. Takeda, T. Higuchi, T. Shono and K. Suzuki, *Chem. Lett.* 2009, **38**, 934.

14 G. F. Marrian and G. A. D. Haslewood, *Biochem. J.* 1932, 1227.

15 (a) J.-P. Yuan, J.-H. Wang and X. Liu, *Mol. Nutr. Food Res.* 2007, **51**, 765; (b) P. J. Magee, *Proc. Nutr. Soc.* 2011, **70**, 10; (c) R. L. Jackson, J. S. Greiwe and R. J. Schwen, *Nutr. Rev.* 2011, **69**, 432; (d) D. Shor, T. Sathyapalan, S. L. Atkin and N. J. Thaycher, *Eur. J. Nutr.*, 2012, **51**, 389.

16 (a) J. M. Heemstra, S. A. Kerrigan, D. R. Doerge, W. G. Helferich and W. A. Boulanger, *Org. Lett.* 2006, **8**, 5441; (b) Y. Takashima and Y. Kobayashi, *Tetrahedron Lett.* 2008, **49**, 5156; (c) Y. Takashima, Y. Kaneko and Y. Kobayashi, *Tetrahedron* 2010, **66**, 197; (d) J.-W. Lee and B. List, *J. Am. Chem. Soc.* 2012, **134**, 1824; (e) S. Yang, S.-F. Zhu, C.-M. Zhang, S. Song, Y.-B. Yu, S. Li and Q.-L. Zhou, *Tetrahedron* 2012, **68**, 5172.

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†.

