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Stereoselective substitution of flavan skeletons: synthesis of dryopteric acid

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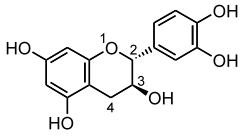
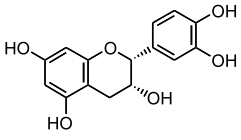
Abstract—The C(4) acetoxylated catechin and epicatechin derivatives, **4** and **5**, smoothly react with various nucleophiles under Lewis acidic conditions, giving C(4)-elaborated flavan-3-ols. Facile synthesis of dryopteric acid (**3**) was achieved. © 2002 Elsevier Science Ltd. All rights reserved.

Flavonoids or polyphenols designate a wide class of plant-derived natural products with extreme diversity. They share, explicitly or implicitly, the flavan-3-ol skeleton,[1] and the diversity arises from change in the oxidation state, skeletal modification, and oligomer formation. Although these compounds are known to possess various biological and pharmaceutical effects, the bioactivities for a single pure compound are often unclarified, as they are obtained as inseparable mixtures.



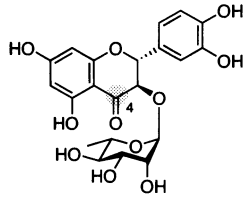
catechin (**1**)



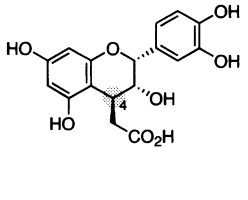
epicatechin (**2**)

During our recent synthetic study of astilbin,[2] a glycosylated flavone natural product, we became interested more generally in flavone synthesis. We reasoned that one of the key issues in this context would be the stereoselective elaboration of the C(4) position of flavanol skeletons. This would have an important relevance to the structure diversification both in the biogenetic origin of complex polyphenols, such as oligomeric catechins and arachnitannin **1**,[1c] as well as the chemical synthesis of this class of compounds.[1d,3]

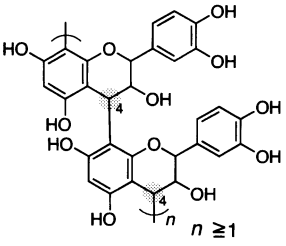
This communication describes an efficient method for introducing various groups to two prototypical flavan-3-ol skeletons, catechin (**1**) and epicatechin (**2**).



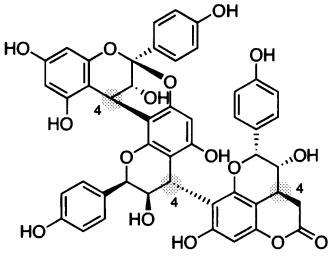
astilbin



dryopteric acid (**3**)

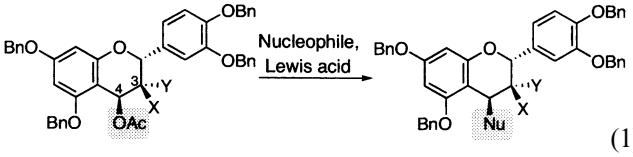


oligomeric catechins



arachnitannin 1

Eq. (1) summarizes three significant features: (1) the utility of C(4)-acetates **4** and **5** as building blocks of catechin and epicatechin series; (2) their efficient activation by Lewis acids, such as $BF_3{\cdot}OEt_2$, allowing delivery of various nucleophiles at this position, and (3) the stereochemistry of this substitution reaction.



(1)

4: X= OBn, Y = H (catechin derivative)
5: X = H, Y = OBn (epicatechin derivative)

Keywords: polyphenol; flavone; flavan; catechin; epicatechin; dryopteric acid.

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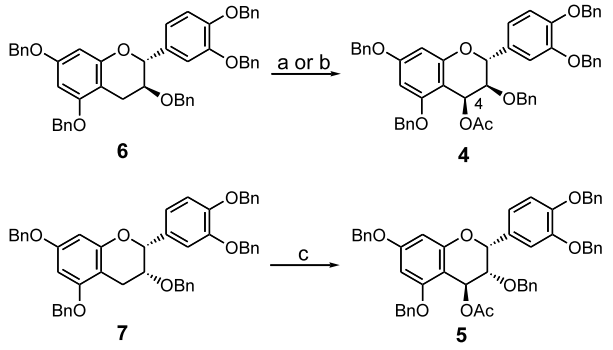
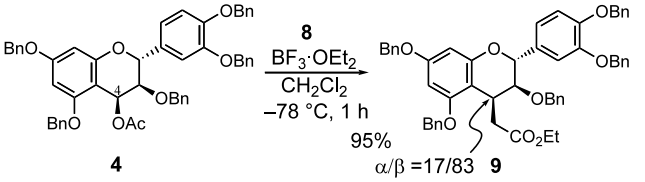
Scheme 1 shows the preparation of C(4)-acetoxy derivatives, **4** and **5**, from the penta-benzylated catechin **6** and epicatechin **7**,[4] respectively. Introduction of an acetoxy group at C(4) in **6** was achieved by oxidation with DDQ in wet CH_2Cl_2 followed by acetylation of the resulting alcohol, giving the β-isomer **4** as the sole product in 41% yield. Direct acetoxylation of **6** was also attempted with DDQ and acetic acid, which gave a 7/3 mixture of **4** and its C(4)-epimer (54% combined yield).[5] On the other hand, the corresponding epicatechin derivative **5** was obtained as the single isomer in 51% yield by applying the direct acetoxylation protocol to epicatechin derivative **7**.

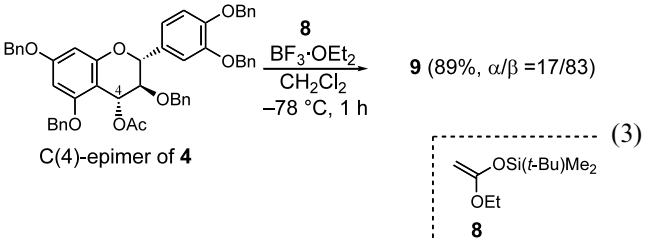


Scheme 1. *Reagents and conditions*: (a) (i) DDQ (1.5 mol equiv.), 2% aq. CH_2Cl_2, (ii) Ac_2O, pyridine (41%); (b) DDQ (1.5 mol equiv.), AcOH (5 mol equiv.), CH_2Cl_2 (54%, **4**/C(4)-epimer of **4** = 7/3); (c) DDQ (1.5 mol equiv.), AcOH (5 mol equiv.), CH_2Cl_2 (51%).

Catechin series: For the initial feasibility study, we attempted the reactions of acetate **4** with ketene silyl acetal (KSA) **8** in the presence of a Lewis acid. Upon exposure of **4** and KSA **8** (3 mol equiv.) with $BF_3{\cdot}OEt_2$ (1 mol equiv., CH_2Cl_2, −78°C, 1 h), departure of the acetate and trapping with **8** smoothly occurred, giving the corresponding ester **9** in 95% yield in good β-selectivity (α/β = 17/83, Eq. (2)).[6] The S_N1 nature of the reaction was clearly shown by a comparison experiment with the C(4)-epimer of **4**, which gave exactly the same stereoselectivity (Eq. (3)).



(2)



(3)

The stereochemical outcomes were determined by NMR studies (Fig. 1). Although α- and β-isomers of **9** were inseparable, the spectrum was resolved enough to assess the selectivity, and both compounds showed diagnostic NOE for the structure assignment.

Under the same Lewis acidic conditions, we attempted the reactions of **4** with various carbon- as well as hetero-nucleophiles (**10**–**15**; Table 1). It was found the chemical yields of these reactions depended on the nucleophilicity of the reagents.[7] Silyl enolates **10** and **11** were reactive enough, giving the substitution products in high yields, respectively (runs 1 and 2). However, allyltrimethylsilane (**12**) gave only poor yield, and the primary side reaction was the self-condensation of **4**.[8] Thus, if the nucleophile is not reactive enough, competitive attack of the aromatic π-system of other molecule of **4** becomes predominant, leading to the oligomer formation (run 3). Allyltriphenylstannane (**13**), 10 times more nucleophilic than **12**,[7] also failed to react efficiently, giving polymeric products (run 4). On the other hand, hetero nucleophiles, such as PhSH and Me_3SiN_3, cleanly took part in the reaction (runs 5 and 6).

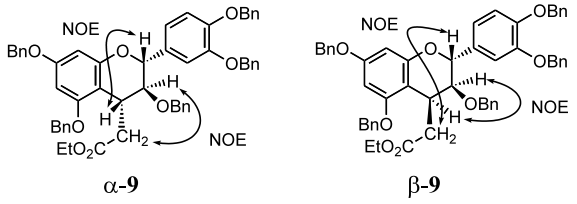
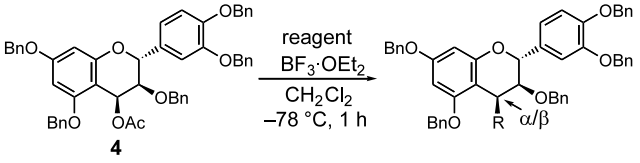


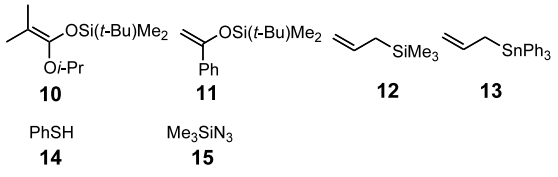
Figure 1.

Table 1.



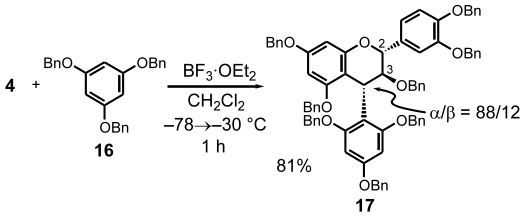
run	reagent	R	yield/%	α/β
1	**10**	-C(Me)$_2$CO$_2$*i*-Pr	87	β
2	**11**	-CH$_2$C(O)Ph	88	12/88
3	**12**	-CH$_2$CH=CH$_2$	7	8/92
4	**13**	-CH$_2$CH=CH$_2$	22	β
5	**14**	-SPh	92	β
6	**15**	-N$_3$	81	β

a. reagent (3 mol equiv.), $BF_3{\cdot}OEt_2$ (1 mol equiv.).



The reactions were generally β-selective, and the respective β-product was obtained as the sole isomer, except for runs 2 and 3. These β-selectivities could be rationalized by considering the torsional strain associated with the quinonemethide intermediate **A**, generated from **4**, as shown in Fig. 2. The α-attack would give the *pseudo*-twist-boat product **I** as the initial product, which undergoes conformational change afterwards. On the other hand, the β-attack directly gives the *pseudo*-chair product **III**, and the latter path would be the lower energy process.

Interestingly, a remarkable change of the stereoselectivity was noted with aromatic nucleophiles, such as tribenzyl phloroglucinol **16** (Eq. (4)). Thus, the reaction of acetate **4** with **16** (3 mol equiv.) in the presence of $BF_3{\cdot}OEt_2$ (1 mol equiv., CH_2Cl_2, −78°C, 1 h) gave α-**17** as a major product. Although the origin of this stereochemical reversal is not yet clear, we have some results suggesting the reversibility of the C–C bond formation. More detailed studies on this particular process are underway and have an important implication for the stereoselective synthesis of oligomeric catechins.



(4)

This finding also drew our attention to the 'directed' α-selective reaction, which may be applicable in general to non-aromatic nucleophiles. By simple analogy with carbohydrate chemistry, we expected that neighboring-group participation would work for this purpose. Although acetyl, benzoyl, or methoxycarbonyl groups were tested as the C(3) protecting group, the resulting α-selectivities were lower than expected.[9] However, an excellent α-selectivity was attained by using carbonate derivative **18**, previously prepared by Yoneda,[10] giving a 92/8 selectivity in favor of α-**19** (Eq. (5)).

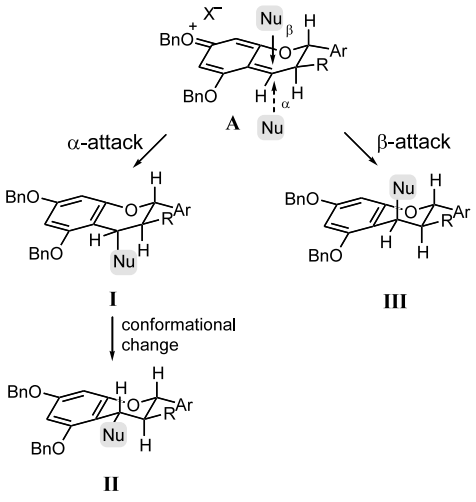
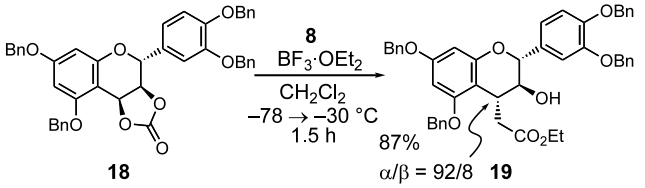


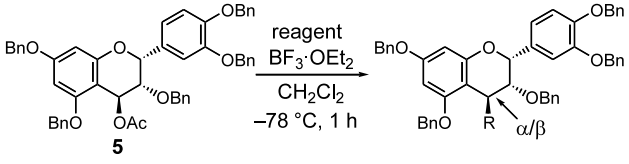
Figure 2.

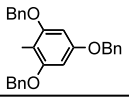


(5)

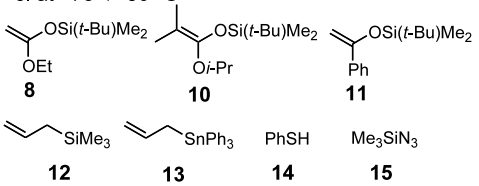
Epicatechin series: These reactions were also applied to epicatechin derivative **5** (Table 2). Characteristic features follow: (1) although **5** was activated by $BF_3{\cdot}OEt_2$ at −78°C, chemical yields were generally lower than the corresponding catechin series (cf. Table 1); polymeric byproducts were consistently observed. (2) Reactions uniformly proceeded in rigorous β-selectivity, including the case with aromatic nucleophile **16** (run 8, cf. Eq. (4)). This is not surprising, as the α-face in **5** is blocked by the C(2)- and C(3)-substituents. (3) KSA **8** and silyl enolate **11** worked well to give the products in high yields (runs 1 and 3), while dimethylated KSA **10** gave substantially lower yield (run 2). (4) Allylations were again not productive, giving a complex mixture of unidentified byproducts (runs 4 and 5).[11] (5) Sulfur and nitrogen nucleophiles were smoothly delivered (runs 6 and 7).

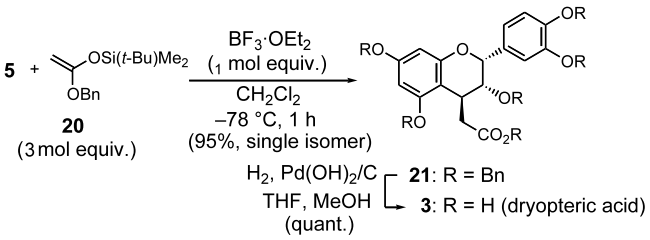
Table 2.



run	reagent	R	yield/%	α/β
1	**8**	$-CH_2CO_2Et$	89	β
2	**10**	$-C(Me)_2CO_2i$-Pr	34	β
3	**11**	$-CH_2C(O)Ph$	80	β
4	**12**	$-CH_2CH{=}CH_2$	–[b]	–
5	**13**	$-CH_2CH{=}CH_2$	2	β
6	**14**	-SPh	88	β
7	**15**	$-N_3$	59	β
8[c]	**16**		72	β

a. reagent (3 mol equiv.), $BF_3{\cdot}OEt_2$ (1 mol equiv.).
b. the reaction gave only a mixture of unidentified side products.
c. at –78→–30 °C





Scheme 2.

Finally, these findings were applied to the synthesis of dryopteric acid (**3**), a unique natural product possessing a flavan acetic acid.[12] Upon reaction of epicatechin acetate **5** with KSA **20** in the presence of $BF_3{\cdot}OEt_2$, ester **21** was obtained as the sole product in 95% yield. All six benzyl protecting groups in **21** were removed by hydrogenolysis over 20% $Pd(OH)_2/C$ in THF–MeOH (6:1) at 25°C for 21 h to give dryopteric acid (**3**) as an amorphous solid in quantitative yield. All the physical data of **3** (^1H and ^{13}C NMR, IR, $[\alpha]_D$) coincided with those of the natural product, $[\alpha]_D^{28}$ –44 (*c* 0.69, acetone), [lit. $[\alpha]_D^{24}$ –46 (*c* 0.7, acetone)] (Scheme 2).[12b]

In conclusion, an effective method has been developed for introducing various substituents to the C(4) position of flavan skeletons, and was applied to the synthesis of dryopteric acid. Currently, we are examining the synthesis of more complex natural polyphenols.

Acknowledgements

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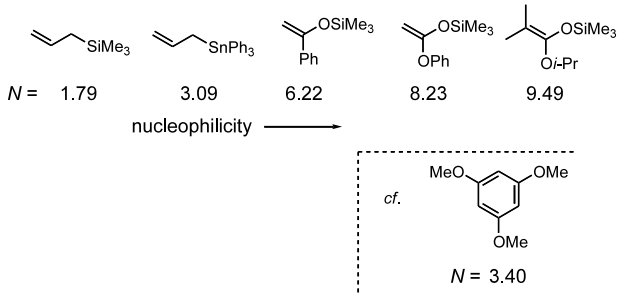
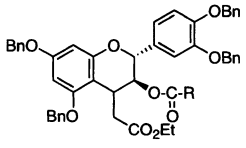
References

1. (a) Bohm, B. A. *Introduction to Flavonoids*; Harwood Academic Publishers: Amsterdam, 1998; (b) The Flavonoids; Harborne, J. B.; Mabry, H., Eds.; Chapman & Hall: New York, 1988; (c) Tanaka, N.; Orii, R.; Ogasa, K.; Wada, H.; Murakami, T.; Saiki, Y.; Chen, C.-M. *Chem. Pharm. Bull.* **1991**, *39*, 55; (d) Li, X.-C.; Ferreira, D. *Nat. Prod. Rep.* **2000**, *17*, 193.
2. Ohmori, K.; Ohrui, H.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 5537.
3. (a) Tückmantel, W.; Kozikowski, A. P.; Romanczyk, L. J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12073; (b) Kozikowski, A. P.; Tückmantel, W.; George, C. *J. Org. Chem.* **2000**, *65*, 5371; (c) Steynberg, P. J.; Nel, R. J. J.; Rensburg, H.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1998**, *54*, 8153; (d) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1991**, *37*, 488 and references cited therein.
4. The pentabenzylated catechin **6** was prepared by a modified procedure of Kawamoto [Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Synth. Commun.* **1996**, *26*, 531.]. Thus, (+)-catechin (**1**) was acetylated, and subsequent benzylation with benzyl chloride (5.5 mol equiv.) and NaH (12 mol equiv.) in moist DMF (25°C, 72 h) gave **6** in 78% yield. Epicatechin derivative **7** was prepared by benzylation of 5,7,3′,4′-tetra-*O*-benzylepicatechin[3a] (BnBr, NaH, DMF, 25°C, 4 h, 91% yield).
5. The diastereomers of acetate **4** and its C(4)-epimer were inseparable, while the separation was possible for the corresponding alcohol. Thus, C(4)-epimer of **4** was obtained by applying the procedure to 7/3 mixture of **4** and C(4)-epimer of **4**: (1) 1 M NaOH, H_2O, MeOH, THF (24% for α-isomer, 58% for β-isomer); (2) diastereomer separation by silica gel column chromatography (hexanes/EtOAc = 4/1); (3) re-acetylation (78%).
6. Activation of the 4-methoxy derivative of **6** under the same conditions was much less effective than that of **4**. Product **9** was obtained only in 16% yield, and considerable amounts of oligomeric byproducts were observed. On the other hand, using $TiCl_4$ for the reaction of **4** gave almost the same result (94% yield, α/β = 16/84).
7. Nucleophilic index (*N*) of various π-compounds were defined by Mayr: Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938 and references cited therein. See also: Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500.



8. When a large excess of **12** (100 mol equiv.) was employed for this reaction, the chemical yield was improved to 54%.
9. The chemical yields and stereoselectivities of the reactions of acyl protected substrates with **8** are shown below.



R	yield/%	α/β
CH_3	95	23/77
Ph	95	35/65
OMe	74(25)[a]	29/71

a. recovery of the starting material.

10. Yoneda, S.; Kawamoto, H.; Nakatsubo, F. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1025.
11. Even by employing a large excess of **12** (100 mol equiv.), the reaction gave only 6% yield for the corresponding allylated product.
12. (a) *The Handbook of Natural Flavonoids*, Harborne, J. B.; Baxter, H., Eds.; Wiley: Chichester, 1999; Vol. 2; p. 499; (b) Hwang, T.-H.; Kashiwada, Y.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1990**, *29*, 279. For isolation of related compounds, see: (c) Karl, C.; Pedersen, A. P.; Müller, G. *Naturforsch.* **1981**, *36C*, 607; (d) Tanaka, N.; Orii, R.; Ogasa, K.; Wada, H.; Murakami, T.; Saiki, Y.; Chen, C.-M. *Chem. Pharm. Bull.* **1991**, *39*, 55; (e) Baek, N.-I.; Kennelly, E. J.; Kardono, L. B. S.; Tsauri, S.; Padmawinata, K.; Soejarto, D. D.; Kinghorn, A. D. *Phytochemistry* **1994**, *36*, 513.