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First synthesis of astilbin, biologically active glycosyl flavonoid isolated from Chinese folk medicine

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Abstract

A synthetic route to a biologically active glycosyl flavonoid, astilbin (**1**), was developed. The tetra-benzyl ether **4**, derived from (+)-catechin, was glycosylated with the L-rhamnosyl donor **10** by using Cp_2HfCl_2–$AgClO_4$, and subsequent oxidation of the C(4) position of the flavan skeleton followed by deprotection gave **1**.

Astilbin (**1**) is a glycosyl flavonoid isolated from the root of *Astilbe odontophylla* Miquel,[1] which has recently been proven to exhibit some important bioactivities including antioxidant and aldose reductase inhibitory effects.[2] Such bioactivities, as well as the lack of synthetic routes, attracted our interest in this compound. Herein, we describe the first synthetic route to **1** starting from readily available (+)-catechin (**2**) and L-rhamnose (**3**). Scheme 1 shows our retrosynthetic analysis with three issues to be considered: (1) choice of the protecting group (*R*) that could be detached under mild conditions to cope with the acid- and base-labile nature of **1**; (2) oxidation of the C(4) position of the flavan skeleton, i.e. the viability and the timing; and (3) introduction of the sugar moiety.

Our initial attention was focused on the oxidation of the C(4) position of the flavan skeleton. As a model reaction to address this issue, the tetra-benzyl catechin **4**[3] was treated with DDQ and MeOH ($CHCl_3$, 4 h)[4] to give the methyl ether **6** in 79% yield as a single diastereomer.[5] Under the similar conditions, the silyl ether **5**, derived from **4** [*t*-$BuMe_2SiCl$ (TBSCl), imidazole, CH_2Cl_2, 90% yield], was treated with DDQ in CH_2Cl_2–H_2O, thereby giving the alcohol **7** in 76% yield again as a single diastereomer. Oxidation of the alcohol **7** with TPAP[6] (NMO, CH_2Cl_2, 16 h) afforded the ketone **8** in 32% yield. Attempts to improve the yield of this step, unfortunately, were unfruitful. Desilylation with PPTS in EtOH (25°C, 66 h) gave the ketol **9** in 60% yield.

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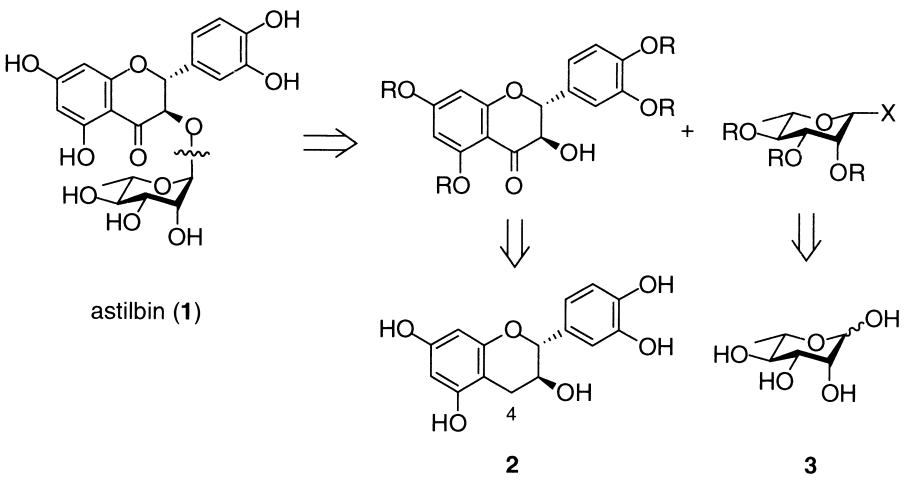
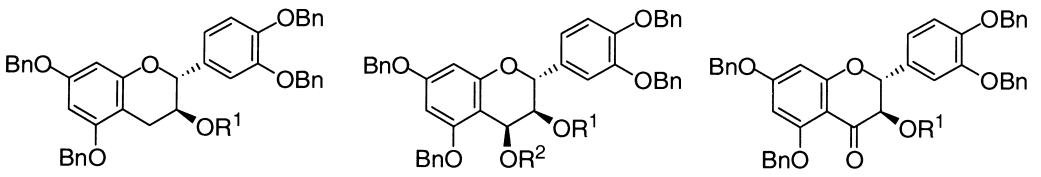


Scheme 1.

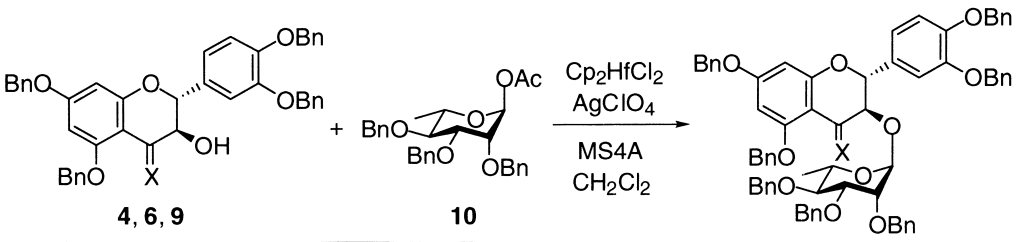


With these data in hand, we next examined the introduction of the rhamnoside moiety. The rhamnosyl acetate **10** was used as the glycosyl donor, and three compounds, **4**, **6** and **9** were tested as the glycosyl acceptor. Attempts were made by using Cp_2HfCl_2 and $AgClO_4$ as the promoter[7,8] in CH_2Cl_2 with the reaction temperature starting from –78°C followed by warming up to –20 or 0°C. The results are summarized in Table 1.

It turned out that the glycosyl acceptors with a C(4)-oxygen function, **9** and **6**, gave only poor results. In the case of **9**, none of the glycosylated product was obtained, although the donor **10** was completely consumed (run 1). Partial recovery of the glycosyl acceptor **9** suggests the low reactivity of its C(3)-hydroxyl group due to the internal hydrogen bonding to the C(4) carbonyl. In the case of **6**, decomposition of the glycosyl acceptor **6** was the main event observed, which could be rationalized by the Lewis acid-induced departure of the C(4)-methoxy group to generate a *p*-quinonemethide **A**, which might undergo various side reactions (run 2, Table 1). Formation of the methyl glycoside **11**, albeit in 12% yield, is consistent with this rationalization. On the other hand, we were pleased to find that the alcohol **4**, *without an oxygen function at C(4)*, underwent the glycosylation under these conditions, thereby giving the corresponding α-rhamnoside (α-**12**) in 68% yield (run 3, Table 1). Further optimization of the glycosylation of the acceptor **4** is summarized in Table 2.

Notable features are the following: (1) the yield was improved by carrying out the reaction at a lower temperature (run 1, Table 2); (2) the use of Cp_2ZrCl_2 and $AgClO_4$ also gave a good yield for α-**12** (run 2), whereas other promoters gave poor yields (runs 3–5); and (3) substantial

Table 1



run	acceptor	product (yield/%)
1	**9**: X = O	–[a, b]
2	**6**: X = H, OMe	**11** (12)[a, c]
3	**4**: X = CH_2	**12** (68)[d]

a) –78 to 0 °C; b) recovery of **9** (43%);
c) recovery of **10** (73%); d) –78 to –20 °C

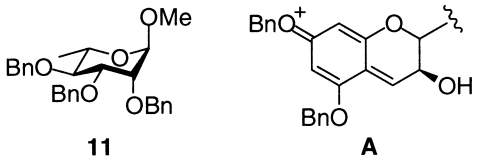
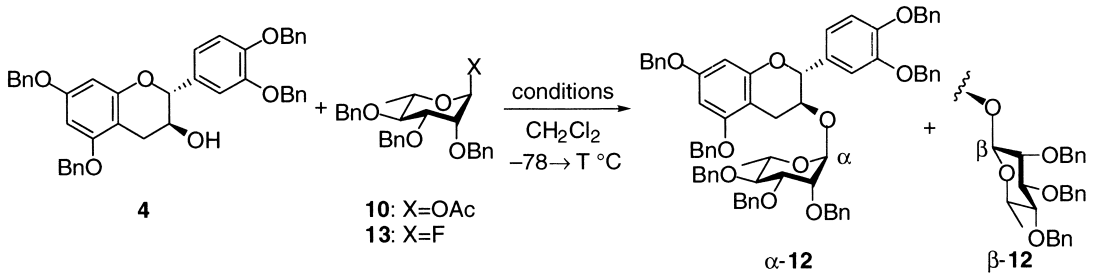


Table 2

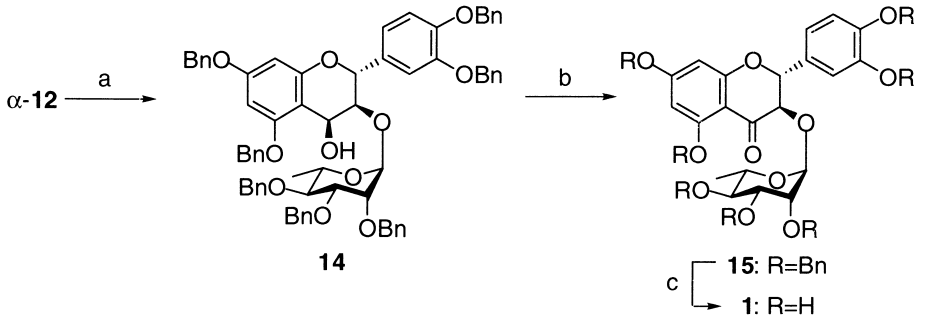


run	donor	promoter	T/°C	**12** (yield/%)	recovery of **4**/%
1	**10**	Cp_2HfCl_2, $AgClO_4$	–35	α (82)	7
2	**10**	Cp_2ZrCl_2, $AgClO_4$	–35	α (74)	8
3	**10**	$BF_3{\cdot}OEt_2$	25	α (38)	16
4	**10**	TMSOTf	–30	α (55), β (16)	16
5	**10**	$SnCl_4$	–30	α (10), β (20)	18
6	**13**	Cp_2HfCl_2, $AgClO_4$	–55	α (57), β (31)	10
7	**13**	Cp_2HfCl_2, AgOTf	–72	α (47), β (36)	10

amounts of the anomeric product β-**12** were produced by the reaction with TMSOTf or $SnCl_4$ (runs 4 and 5),[9] which were even prominent when the fluoride **13** was used as the glycosyl donor under the hafnocene-promoted conditions (runs 6 and 7).

With the requisite glycoside α-**12** in hand, we focused on the final stages of the synthesis. Thus, we attempted at oxidation of the C(4) position of the flavan skeleton of α-**12**, which was nicely

effected in the following two steps. Upon treatment with DDQ (H_2O, CH_2Cl_2, 25°C, 5 h), the alcohol **14** was obtained in 68% yield as a single diastereomer,[5] which was then treated with PDC (CH_2Cl_2, 25°C, 19 h) to give the ketone **15** in 85% yield (Scheme 2). It was pleasing for us that the latter step (**14**→**15**) proceeded far more cleanly than the reaction of the non-glycosidic counterpart (cf. **7**→**8**; vide supra). Final removal of the seven benzyl-protecting groups in **15** required some experimentation, which eventually went nicely. Initial attempts, when using Pd–C as the catalyst, resulted in a slow reaction and a very low yield of the desired product. The poor material balance suggested that the deprotected products were strongly absorbed to the charcoal. Addition of an acid (0.01 M HCl aq.) accelerated the deprotection process, which, however, produced an unidentified side product. Eventually, the best result was attained by employing Pd-black as the catalyst, and the target **1** was obtained in 91% yield. All the physical data of **1** (^1H and ^{13}C NMR, IR, $[\alpha]_D$, mp) were fully identical with those of the authentic specimen[10] by direct comparison, $[\alpha]_D^{18}$ −11 (*c* 0.52, EtOH) [lit. $[\alpha]_D^{25}$ −13.6 (*c* 0.52, EtOH)],[1d] mp 179–182°C [lit. mp 179–180°C].[1b]



Scheme 2. Reagents and conditions: (a) DDQ, H_2O, CH_2Cl_2 (66%); (b) PDC, CH_2Cl_2 (85%); (c) H_2, Pd-black, MeOH (91%)

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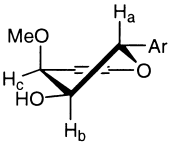
References

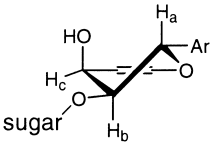
1. (a) Hayashi, K.; Ohuti, K. *Shigenkagaku Kenkyusyo Iho* **1950**, *17/18*, 19–24. (b) Shimada, H.; Sawada, T.; Fukuda, S. *Yakugaku Zasshi* **1952**, *72*, 578–580. (c) Kasai, R.; Hirono, S.; Chou, W.-H.; Tanaka, O.; Chen, F.-H. *Chem. Pharm. Bull.* **1988**, *36*, 4167–4170. (d) Britto, J. D.; Manichckam, V. S.; Gopalakrishinam, S.; Ushioda, T.; Tanaka, N. *Chem. Pharm. Bull.* **1995**, *43*, 338–339.
2. (a) Han, L.-K.; Ninomiya, H.; Taniguchi, M.; Baba, K.; Kimura, Y.; Okuda, H. *J. Nat. Prod.* **1998**, *61*, 1006–1011. (b) Hiraguchi, H.; Mochida, Y.; Sakai, S.; Masuda, H.; Tamura, Y.; Mizutani, K.; Tanaka, O.; Chou, W.-H. *Biosci. Biotech. Biochem.* **1996**, *60*, 945–948. (c) Hiraguchi, H.; Ohmi, I.; Fukuda, A.; Tamura, Y.; Mizutani, K.; Tanaka, O.; Chou, W.-H. *Biosci. Biotech. Biochem.* **1997**, *61*, 651–654.
3. (a) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1991**, *37*, 488–493. (b) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Synth. Commun.* **1996**, *26*, 531–534.
4. Steenkamp, J. A.; Mouton, C. H. L.; Ferreira, D. *Tetrahedron* **1991**, *47*, 6705–6716.

5. The stereostructures of **6** and **14** were assigned from the ^{1}H NMR ($CDCl_3$, 500 MHz) as shown below.



$^3J_{Ha, Hb}$= 9.0 Hz
$^3J_{Hb, Hc}$= 3.4 Hz

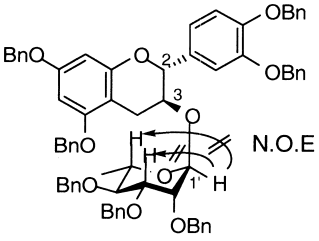
6



$^3J_{Ha, Hb}$= 10.0 Hz
$^3J_{Hb, Hc}$= 3.0 Hz

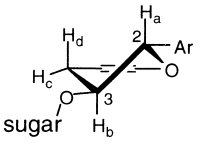
14

6. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
7. (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett*. **1988**, *29*, 3567–3570. (b) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett*. **1988**, *29*, 3571–3574.
8. For activation of glycosyl acetate with Cp_2HfCl_2 and $AgClO_4$, see: Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett*. **1990**, *31*, 4629–4632.
9. The anomeric stereochemistries of α-**12** and β-**12** were determined by the NOE experiments and the coupling constant between C(1′) and H(1′).[11] The conformations of the flavan skeleton in these compounds were deduced from the coupling constants. As for α-**12**, the conformation **I** was suggested, where two substituents at C(2) and C(3) were both equatorial. In contrast, surprisingly, the anomer β-**12** adopts the conformation **II**, disposing the two substituents at axial positions.



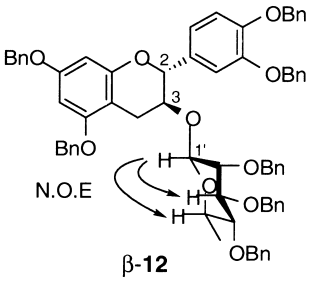
α-**12**

$^1J_{C(1'), H(1')}$= 169 Hz



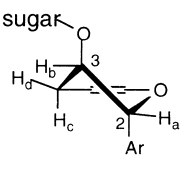
I

$^3J_{Ha, Hb}$= 9.0 Hz
$^3J_{Hb, Hc}$= 6.0 Hz
$^3J_{Hb, Hd}$= 9.0 Hz



β-**12**

$^1J_{C(1'), H(1')}$= 153 Hz



II

$^3J_{Ha, Hb}$= 5.0 Hz
$^3J_{Hb, Hc}$= 4.0 Hz
$^3J_{Hb, Hd}$= 5.0 Hz

10. The natural sample was kindly provided by Dr. Takashi Nakatsuka, Suntory.
11. For assignment of the anomeric structure of carbohydrates by ^{13}C–^1H coupling constants, see: Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.