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

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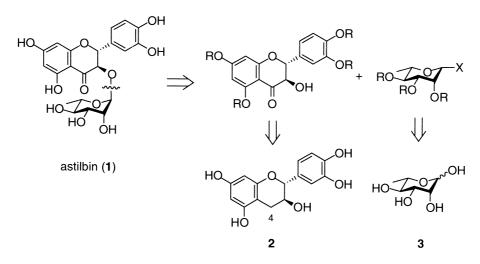
Abstract

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 -AgClO₄, and subsequent oxidation of the C(4) position of the flavan skeleton followed by deprotection gave 1. © 2000 Elsevier Science Ltd. All rights reserved.

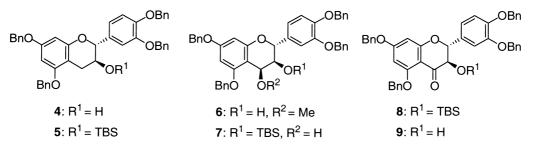
Astilbin (1) is a glycosyl flavonoid isolated from the root of Astilbe odontophylla Miquel,¹ which has recently been proven to exhibit some important bioactivities including antioxidant and aldose reductase inhibitory effects.² Such bioactivities, as well as the lack of synthetic routes, attracted our 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 (CHCl₃, 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*-BuMe₂SiCl (TBSCl), imidazole, CH₂Cl₂, 90% yield], was treated with DDQ in CH₂Cl₂–H₂O, thereby giving the alcohol **7** in 76% yield again as a single diastereomer. Oxidation of the alcohol **7** with TPAP⁶ (NMO, CH₂Cl₂, 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 Cp₂HfCl₂ and AgClO₄ as the promoter^{7,8} in CH₂Cl₂ 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

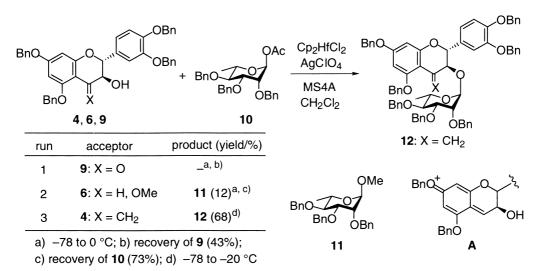


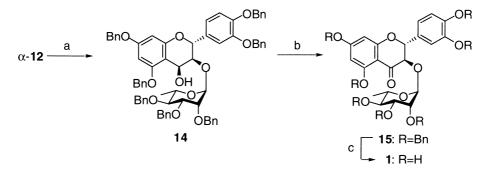
Table 2

Bn	BnO	4	OBn + BnO BnO OE 10: X=OAc 13: X=F	$ \begin{array}{c} $	BnO OBn BnO OBn α-12	OBn OBn + β OBn OBn OBn OBn OBn OBn
_	run	donor	promoter	T/°C	12 (yield/%)	recovery of 4/%
_	1	10	Cp ₂ HfCl ₂ , AgClO ₄	-35	α (82)	7
	2	10	Cp ₂ ZrCl ₂ , AgClO ₄	-35	α (74)	8
	3	10	BF ₃ ·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 ₂ HfCl ₂ , AgClO ₄	-55	α (57), β (31)	10
	7	13	Cp ₂ HfCl ₂ , AgOTf	-72	α (47), β (36)	10

amounts of the anomeric product β -12 were produced by the reaction with TMSOTf or SnCl₄ (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 (H₂O, CH₂Cl₂, 25°C, 5 h), the alcohol **14** was obtained in 68% yield as a single diastereomer,⁵ which was then treated with PDC (CH₂Cl₂, 25°C, 19 h) to give the ketone **15** in 85% yield (Scheme 2). It was pleasing for us that the latter step (**14** \rightarrow **15**) proceeded far more cleanly than the reaction of the non-glycosidic counterpart (cf. 7 \rightarrow **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 ¹³C NMR, IR, [α]_D, mp) were fully identical with those of the authentic specimen¹⁰ by direct comparison, [α]_D¹⁸ –11 (*c* 0.52, EtOH) [lit. [α]_D²⁵ –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%)

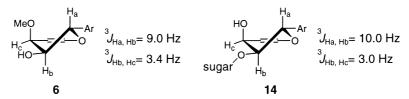
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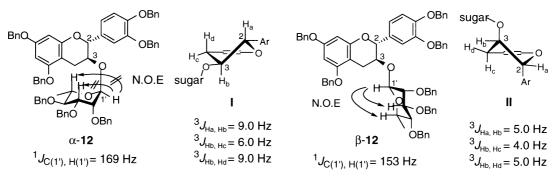
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5. The stereostructures of 6 and 14 were assigned from the 1 H NMR (CDCl₃, 500 MHz) as shown below.



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- 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.



- 10. The natural sample was kindly provided by Dr. Takashi Nakatsuka, Suntory.
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