



Pergamon

Tetrahedron Letters 41 (2000) 5537–5541

TETRAHEDRON
LETTERS

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

Ken Ohmori, Hiroki Ohruai and Keisuke Suzuki*

*Department of Chemistry, Tokyo Institute of Technology, and CREST, Japan Science and Technology (JST),
O-okayama, Meguro-ku, Tokyo 152-8551, Japan*

Received 27 April 2000; accepted 11 May 2000

Abstract

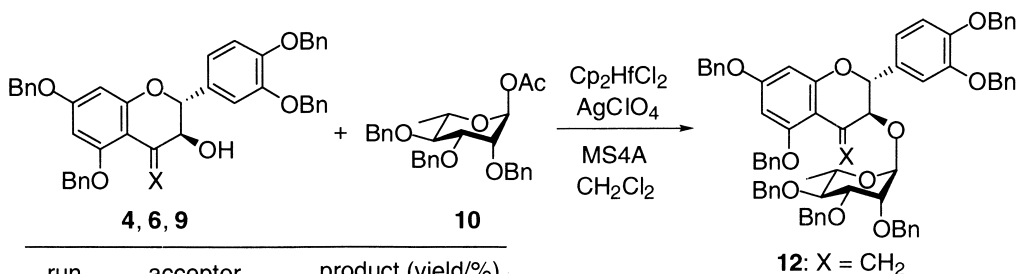
A synthetic route to a biologically active glycosyl flavonoid, astilbin (**1**), was developed. The tetra-benzyl ether **4**, derived from (+)-catechin, was glycosylated with the L-rhamnosyl donor **10** by using Cp_2HfCl_2 – AgClO_4 , and subsequent oxidation of the C(4) position of the flavan skeleton followed by deprotection gave **1**. © 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 (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*-BuMe₂SiCl (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 TPAP⁶ (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.

* Corresponding author.

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

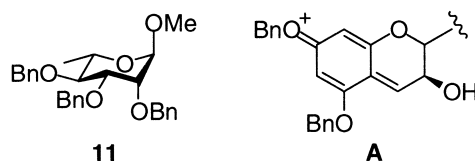
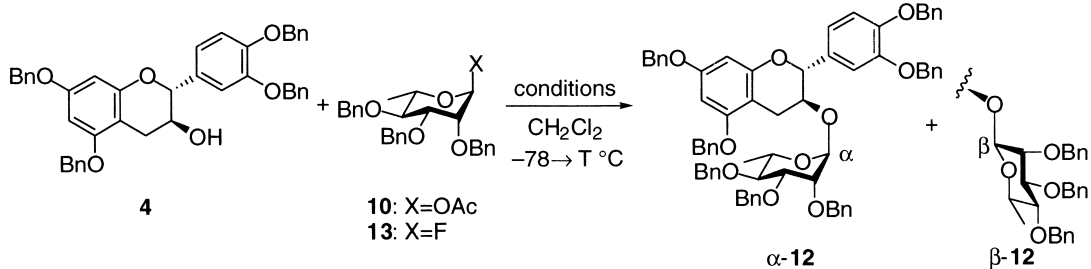


Table 2

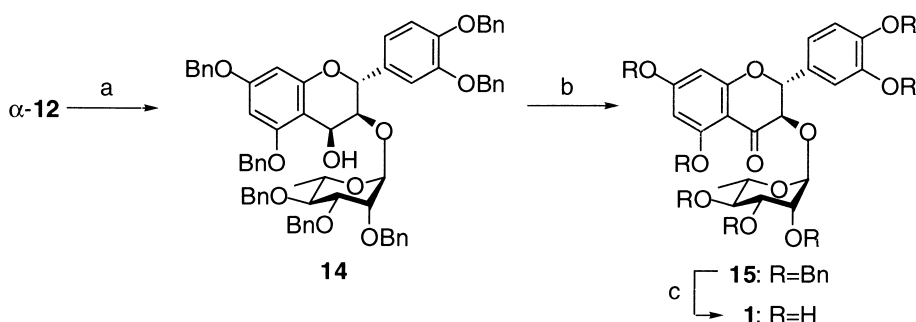


run	donor	promoter	T/°C	12 (yield/%)	recovery of 4 /%
1	10	Cp ₂ HfCl ₂ , AgClO ₄	-35	α (82)	7
2	10	Cp ₂ ZrCl ₂ , AgClO ₄	-35	α (74)	8
3	10	BF ₃ ·OEt ₂	25	α (38)	16
4	10	TMSOTf	-30	α (55), β (16)	16
5	10	SnCl ₄	-30	α (10), β (20)	18
6	13	Cp ₂ HfCl ₂ , AgClO ₄	-55	α (57), β (31)	10
7	13	Cp ₂ HfCl ₂ , AgOTf	-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 (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, $[\alpha]_{\text{D}}$, mp) were fully identical with those of the authentic specimen¹⁰ by direct comparison, $[\alpha]_{\text{D}}^{18} -11$ (*c* 0.52, EtOH) [lit. $[\alpha]_{\text{D}}^{25} -13.6$ (*c* 0.52, EtOH)],^{1d} mp $179\text{--}182^\circ\text{C}$ [lit. mp $179\text{--}180^\circ\text{C}$].^{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%)

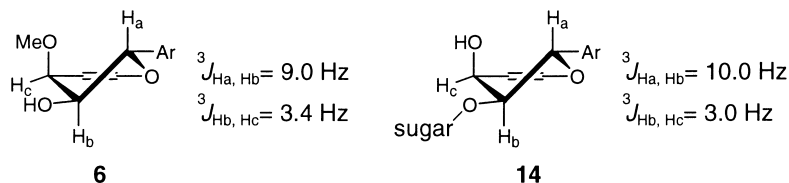
Acknowledgements

We thank Suntory for bringing this topic to our attention and providing partial financial support.

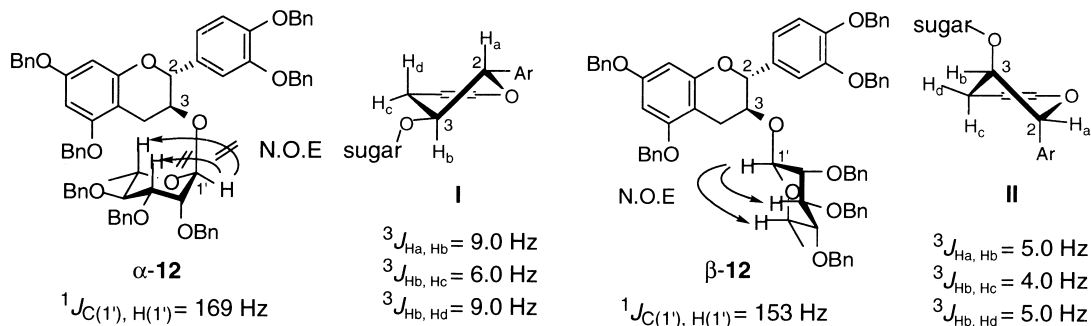
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5. The stereostructures of **6** and **14** were assigned from the ^1H NMR (CDCl_3 , 500 MHz) as shown below.



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 $\text{C}(1')$ and $\text{H}(1')$.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 $\text{C}(2)$ and $\text{C}(3)$ 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.
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.