Absolute Configurations of the *cis*-Dihydroquercetin-3-*O*-β-L-Rhamnosides Isoastilbin and Neoisoastilbin

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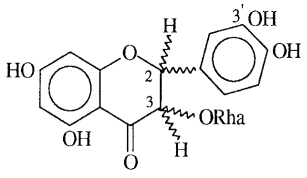
Received February 5, 1996; accepted February 28, 1996

The absolute configurations of the *cis*-dihydroquercetin-3-*O*-β-L-rhamnosides isoastilbin and neoisoastilbin are reaffirmed as 2*R*, 3*S* and 2*S*, 3*R*, respectively, despite recent reports to the contrary.

Key words absolute configuration; isoastilbin; neoisoastilbin; 3-hydroxyflavanone glycoside

Astilbin (**1**), a 3-rhamnoside of (+)-2*R*, 3*R*-*trans*-dihydroquercetin, was isolated from the bark of *Quintinnia serrata* and from the rhizomes and leaves of Asian plants in the 1950s.[1] In 1960, Tominaga reported that 2,3-*trans* **1** was isomerized upon warming in aqueous pyridine to a diastereomeric 2,3-*trans* compound **2** (neoastilbin) and a 2,3-*cis* isomer **3** that he named isoastilbin.[2] Another 2,3-*cis* isomer, **4** (neoisoastilbin), was obtained by treatment of **1** with ethanolic sodium acetate solution.[2] Because the circular dichroism (CD) of 3-hydroxyflavanones and their glycosides was known to reflect the ring chirality of the sofa conformation of the hererocyclic ring,[3,4] chiroptical measurements permitted assignment of absolute configurations to **2**, **3**, and **4** in 1975.[5] On the basis of the sign of the CD maximum at 340—345 nm, coupling constants that defined a *cis* relationship between H-2 and H-3, and a red shift of 12—13 nm of the conjugated n→π* band that indicated α-axial placement of the rhamnosyl substituent, configurations of 2*R*, 3*S* and 2*S*, 3*R* were allocated to **3** and **4**, respectively.[5] More recently, isoastilbin and neoisoastilbin have been isolated from the leaves of *Engelhardtia chrysolepis*, a Chinese folk medicine used as a sweet tea,[6] and neoisoastilbin from an Indian fern, *Sphaerostephanos arbuscula*.[7] Both of these reports[6,7] have claimed absolute configurations for **3** and **4** that are opposite to those established earlier.[5]

Investigation of the sweet herb *Tessaria dodoneifolia* has shown that (+)-2*R*, 3*R*-dihydroquercetin-3-acetate was responsible for the plant's sweetness.[8] Furthermore, 2*S*, 3*S*-**2** is claimed to be the only one of six flavanoids isolated from *E. chrysolepis* to taste sweet.[6] Due to the known dependence of a wide array of biological activities upon molecular chirality,[9] the absolute configuration of chiral compounds that potentially possess interesting properties, such as the stereoisomeric 3-glycosyloxyflavanones **3** and **4**, should be clearly defined.



	C-2	C-3
1 (2*R*,3*R*)	H, $C_6H_3(OH)_2$	ORha, H
2 (2*S*,3*S*)	$C_6H_3(OH)_2$, H	H, ORha
3 (2*R*,3*S*)	H, $C_6H_3(OH)_2$	H, ORha
4 (2*S*,3*R*)	$C_6H_3(OH)_2$, H	ORha, H

Because of the close identity of the CD spectra of **3** and **4** to the related pair of isomeric 3-rhamnosyloxyflavanones isoengeletin and neoisoengeletin,[5] the possibility of interchanged samples in our research appeared unlikely. Nonetheless, we have remeasured the CD spectra and optical rotations (not reported in our previous paper)[5] and have reaffirmed the correctness of the earlier configurational assignments[5] to the *cis*-isomers **3** and **4**. Thus Tominaga's levorotatory (pyridine) sample[2] of isoastilbin was levorotatory both in methanol and pyridine and gave positive and negative CD maxima at 342 and 296 nm, respectively (Table 1). Similarly, Tominaga's dextrorotatory (pyridine) sample[2] of neoisoastilbin was dextrorotatory both in methanol and pyridine and gave negative and positive CD maxima at 342 and 296 nm, respectively (Table 1). Furthermore, the 400 MHz ^{1}H-NMR spectrum of **3** is identical within experimental error to the 500 MHz ^{1}H-NMR spectrum of the 2*R*, 3*S*-isomer reported by DeBritto *et al.*[7] (mistakenly called neoisoastilbin) and both spectra display shielding and deshielding of certain rhamnosyl protons that reflect a conformation predominantly preferred by this isomer. Similar conclusions had been derived earlier[5] from the 100 MHz ^{1}H-NMR spectrum of **3**. A potential source of confusion regarding the configurational assignments of **3** and **4** arises from tentative assignments offered by Tominaga in 1960.[10] In the structural diagrams of this paper,[10] the configurational assignments of **3** and **4** were opposite to those determined later[5]; this difference was noted in footnote 16 of our joint publication.[5] However, Tominaga's hydrolysis[10] of **3** and

Table 1. Chiroptical Properties of **3** and **4**

Compound	$[\alpha]_D$ (C_5H_5N)	$[\alpha]_D$ (MeOH)	$[\Theta]_{296}$ (MeOH)	$[\Theta]_{342}$ (MeOH)
3	−217	−155	−41,700	+18,600
4	+114	+82	+53,600	−20,400

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4 to (−)- and (+)-*cis*-dihydroquercetin (albeit with some racemization), respectively, is now known to be consistent with the 2*R*,3*S* and 2*S*,3*R* configurations, respectively (see below). An inexplicable discrepancy remains between our results[5] and those of the two Japanese groups[6,7]; for a given sign of optical rotation (589 nm), opposite patterns of CD signs are observed for the conjugated n→π* and π→π* bands (see below).

Our configurational assignments for **3** and **4** are consistent with those allocated to other *cis*-3-glycosylflavanones and to the enantiomeric *cis*-3-hydroxyflavanones. For example, *cis*-3′-*O*-β-D-glucopyranosyl-2,3-dihydroquercetin was isolated[11] from the needles of *Pinus sylvestris* and assigned[11] the 2*R*,3*S*-configuration based upon the similar CD spectra shown by the (−)-*cis*-3-hydroxyflavanone derived from the glucoside and that previously published[5] for isoastilbin. Four isomers of dihydroquercetin that contain xylose as a 3-substituent were isolated from the leaves of *Thujopsis dolobrata*.[12] The configurations of these isomers were established[12] by CD comparison of the 3-hydroxyflavanones obtained upon enzymatic hydrolysis of the xylosides. Finally, (+)-*cis*-3-hydroxyflavanone that was isolated[13] from the hot water-soluble fraction of Douglas fir bark has been shown to be formed by C-2 epimerization of *trans* 2*R*,3*R*-dihydroquercetin during the extraction and therefore is of 2*S*,3*R*-configuration. Each of these examples has shown that levorotatory *cis*-3-hydroxyflavanones and their glycosides possess a positive CD maximum near 340 nm and a negative maximum near 295 nm and are of 2*R*,3*S*-configuration. Conversely, *cis*-3-hydroxyflavanones and their glycosides possessing oppositely signed chiroptical properties are of 2*S*,3*R*-configuration. Because of the preponderance of evidence, it is clearly prudent to retain the absolute configurations assigned to **3** and **4** some years ago,[5] as follows: Isoastilbin [mp 278—280 °C dec., $[\alpha]_D^{20}$ −276 °C (C_5H_5N)],[2] 2*R*,3*S*; neoisoastilbin [mp 168—169 °C, $[\alpha]_D^{11}$ +121° (C_5H_5N)],[2] 2*S*,3*R*.

Experimental

General Experimental Procedures Samples of isoastilbin and neoisoastilbin were provided by Tominaga[2] in 1970 and have been stored at 5 °C. Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter at 27 °C, CD spectra were measured on a Jasco J-600 Spectropolarimeter in MeOH at 25 °C and ^{1}H-NMR spectra were obtained on a Bruker ARX-400 spectrometer in DMSO-d_6.

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