

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

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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 heterocyclic 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 $n \rightarrow \pi^*$ 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.

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 assignments⁵⁾ to the *cis*-isomers **3** and **4**. Thus Tominaga's levorotatory (pyridine) sample²⁾ 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) sample²⁾ 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 ¹H-NMR spectrum of **3** is identical within experimental error to the 500 MHz ¹H-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 earlier⁵⁾ from the 100 MHz ¹H-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 later⁵⁾; this difference was noted in footnote 16 of our joint publication.⁵⁾ However, Tominaga's hydrolysis¹⁰⁾ of **3** and

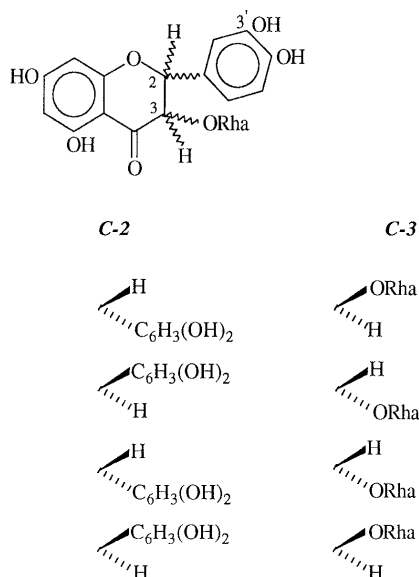


Table 1. Chiroptical Properties of **3** and **4**

Compound	$[\alpha]_D$ (C ₅ H ₅ N)	$[\alpha]_D$ (MeOH)	$[\theta]_{296}$ (MeOH)	$[\theta]_{342}$ (MeOH)
3	−217	−155	−41,700	+18,600
4	+114	+82	+53,600	−20,400

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 results⁵⁾ 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 $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ 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 isolated¹¹⁾ from the needles of *Pinus sylvestris* and assigned¹¹⁾ 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 published⁵⁾ for isoastilbin. Four isomers of dihydroquercetin that contain xylose as a 3-substituent were isolated from the leaves of *Thujopsis dolabrata*.¹²⁾ The configurations of these isomers were established¹²⁾ by CD comparison of the 3-hydroxyflavanones obtained upon enzymatic hydrolysis of the xylosides. Finally, (+)-*cis*-3-hydroxyflavanone that was isolated¹³⁾ 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 (C₅H₅N)],²⁾ 2*R*,3*S*; neoisoastilbin [mp 168–169 °C, $[\alpha]_D^{11}$ +121 °C (C₅H₅N)],²⁾ 2*S*,3*R*.

Experimental

General Experimental Procedures Samples of isoastilbin and neoisoastilbin were provided by Tominaga²⁾ 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 ¹H-NMR spectra were obtained on a Bruker ARX-400 spectrometer in DMSO-*d*₆.

References

- 1) Cambie R. C., *J. Chem. Soc.*, **1959**, 848–849.
- 2) Tominaga T., *J. Pharm. Soc. Jpn.*, **80**, 1202–1206 (1960).
- 3) Gaffield W., *Tetrahedron*, **26**, 4093–4108 (1970).
- 4) Markham K. R., Mabry T. J., *Tetrahedron*, **24**, 823–827 (1968).
- 5) Gaffield W., Waiss A. C., Jr., Tominaga T., *J. Org. Chem.*, **40**, 1057–1061 (1975).
- 6) Kasai R., Hirono S., Chou W.-H., Tanaka O., Chen F.-H., *Chem. Pharm. Bull.*, **36**, 4167–4170 (1988).
- 7) De Britto J., Manickam V. S., Gopalakrishnan S., Ushioda T., Tanaka N., *Chem. Pharm. Bull.*, **43**, 338–339 (1995).
- 8) Kinghorn A. D., Kim J., "Bioactive Natural Products: Detection, Isolation and Structural Determination," ed. by Colegate S. M., Molyneux R. J., CRC Press, Boca Raton, FL, 1993, pp. 173–193.
- 9) Gaffield W., "Studies in Natural Products Chemistry," Vol. 7, ed. by Atta-ur-Rahman, Elsevier, Amsterdam, 1990, pp. 3–28.
- 10) Tominaga T., *J. Pharm. Soc. Jpn.*, **80**, 1206–1212 (1960).
- 11) Lundgren L. N., Theander O., *Phytochemistry*, **27**, 829–832 (1988).
- 12) Nonaka G., Goto Y., Kinjo J., Nohara T., Nishioka I., *Chem. Pharm. Bull.*, **35**, 1105–1108 (1987).
- 13) Kiehlmann E., Li E. P. M., *J. Nat. Prod.*, **58**, 450–455 (1995).