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Absolute Configuration of Scyphostatin

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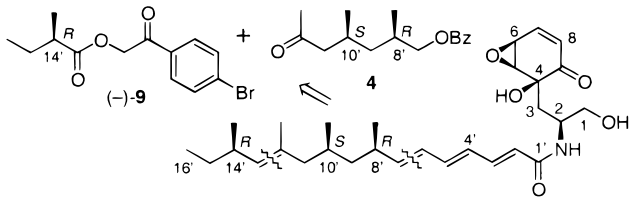
ABSTRACT



The absolute configuration of the side chain of scyphostatin (1) has been established. The chemical degradation of 1 gave 4 and 9, which correspond to the C7′–C12′ and C13′–C16′ fragments of the natural products, respectively. The spectroscopic data and $[\alpha]_D$ values of both compounds were compared to those of authentic samples. The results show that the absolute configuration of 1 is 8′*R*,10′*S*,14′*R*.

Scyphostatin (**1**) was isolated as a potent inhibitor of neutral sphingomyerinase by Ogita et al. in 1997.[1] This compound is the first low-molecular-weight inhibitor of the enzyme, either from natural sources or of synthetic origin. These factors combine with interesting biological activity and unique structure to make **1** a synthetic target of enormous interest (Figure 1).

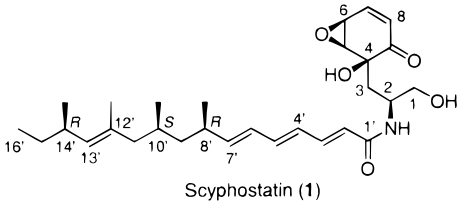


Figure 1.

A previous structure elucidation of **1** only determined the absolute stereochemistry of the epoxy cyclohexenone moiety.[1a] The stereochemistry of the side chain, containing three asymmetric centers, still remains unelucidated. In this communication, we describe the entire stereochemical structure of **1**, including the absolute stereochemistry, by degradation of the side chain followed by correlation to known chiral compounds.

Natural scyphostatin (**1**) was treated with potassium hydroxide in methanol under reflux conditions, and subsequent reaction with (trimethylsilyl)diazomethane gave methyl ester **2** ($[\alpha]_D = -2.5$ (*c* 0.50, $CHCl_3$)) in 61% yield (two steps). Oxidative cleavage of the ester **2** was accomplished by ozonolysis followed by reductive workup to yield diol **3**, corresponding to the C7′−C12′ fragment. It contains both the C8′ and C10′ asymmetric centers as a mixture of inseparable diastereoisomers. Treatment of the diol **3** with benzoyl chloride and triethylamine followed by the Dess−Martin reagent[2] provided keto ester **4** ($[\alpha]_D = -7.0$ (*c* 0.53, $CHCl_3$)) in 80% yield (two steps) as a single isomer. To determine the absolute stereochemistry of **4**, the optically active carboxylic acid **6**, a chiral starting material which has a known absolute configuration,[3] was readily derived from lactone (±)-**5**.[3,4] Reduction of **6** ($[\alpha]_D = -5.7$ (*c* 4.60,

(1) (a) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871. (b) Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525. (c) Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamamoto, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531.

(2) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(3) Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5539.

(4) (a) Ungnade, H. E.; Nightingale, D. V. *J. Am. Chem. Soc.* **1944**, *66*, 1218. (b) Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5545.

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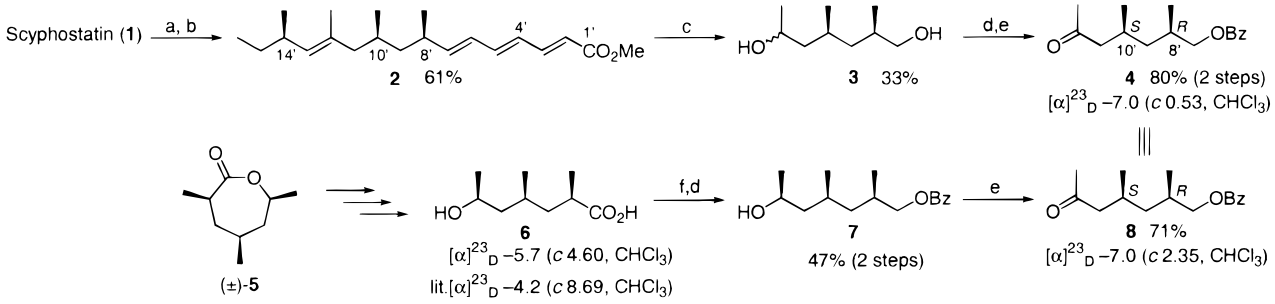
Scheme 1

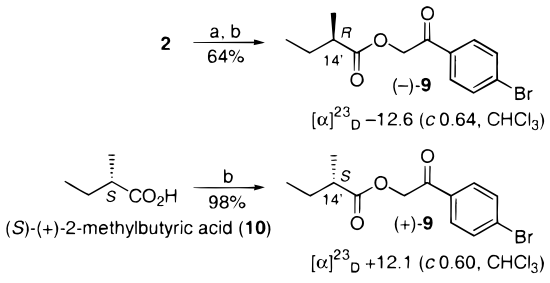


(a) KOH, MeOH, reflux; (b) Me_3SiCHN_2, MeOH, benzene, rt; (c) O_3, MeOH, –40 to –10 °C; (d) PhCOCl, cat. DMAP, Et_3N, CH_2Cl_2, rt; (e) Dess—Martin reagent, CH_2Cl_2, rt; (f) BH_3-Me_2S, THF, 0 °C.

$CHCl_3$), lit.[3] $[\alpha]_D = -4.2$ (*c* 8.69, $CHCl_3$)) with borane−methyl sulfide complex followed by treatment with benzoyl chloride and triethylamine provided the monobenzoyl ester **7** in 47% yield (two steps). Dess−Martin oxidation of the secondary hydroxyl group of **7** afforded the keto ester **8** ($[\alpha]_D = -7.0$ (*c* 2.35, $CHCl_3$)) in 71% yield (Scheme 1). Its spectral data and physical properties (^1H and ^{13}C, IR, and $[\alpha]_D$) were identical with those of the degradation product **4**. This result shows that the absolute configuration of **4** is 8′*R*,10′*S*. During these operations the compound corresponding to the C13′−C16′ moiety could not be isolated.

To determine the stereochemistry of chiral center C14′, we attempted the isolation of the C13′−C16′ fragment as its 2-methylbutyric acid derivative (Scheme 2). The ester **2**

Scheme 2



(a) $RuCl_3$, $NaIO_4$, MeCN-CCl_4-H_2O (2 : 2 : 3), rt; (b) KF, *p*-bromophenacyl bromide, DMF, rt.

was treated with $RuCl_3/NaIO_4$[5] and esterified with *p*-bromophenacyl bromide and KF in DMF,[6] furnishing the *p*-bromophenacyl ester (−)-**9** ($[\alpha]_D = -12.6$ (*c* 0.64, $CHCl_3$); mp 52.5−53.5 °C) in 64% yield (two steps).[7] An authentic sample was prepared from commercially available (*S*)-(+)-2-methylbutyric acid (**10**)[8] under the same esterification conditions in 98% yield. The physical and spectroscopic data of the authentic *p*-bromophenacyl ester (+)-**9** ($[\alpha]_D = +12.1$ (*c* 0.60, $CHCl_3$); mp 53−54 °C) were identical with those of the degradation product (−)-**9** (^1H NMR, ^{13}C NMR, IR, and HRMS), with the exception of the sign of the optical rotation ($[\alpha]_D = -12.6$). This result means that the absolute configuration of C14′ is *R*. These results in total offered the complete stereochemical structure of scyphostatin (**1**) as 8′*R*,10′*S*,14′*R*, as shown in Figure 1.

Acknowledgment. We thank Drs. Takeshi Ogita and Masahiro Tanaka in our laboratories for providing us with natural scyphostatin.

Supporting Information Available: Spectral data for compounds **2**, **4**, **8**, **9,** and **11** and representative ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991351P

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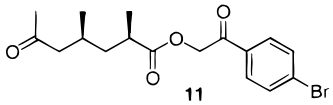
(7) Another *p*-bromophenacyl ester, **11**, was also obtained in 70% yield without epimerization. The compound was identical with an authentic sample, which was derived from **6** in two steps ((a) *p*-bromophenacyl bromide, KF, DMF (90%); (b) Dess−Martin oxidation (93%)).



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(8) (*S*)-(+)-2-Methylbutyric acid was purchased from Aldrich Chemical Co.