**Note**

Isolation and Absolute Stereochemistry of Optically Active Sydonic Acid from *Glonium* sp. (Hysterailes, Ascomycota)

Shinji Kudo, Takanori Murakami, Junsuke Miyanishi, Kazuaki Tanaka, Noboru Takada, and Masaru Hashimoto

Faculty of Agriculture and Life Science, Hirosaki University, 3-Bunkyo-cho, Hirosaki 036-8561, Japan

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Optically active sydonic acid (1) was isolated for the first time from a culture broth of *Glonium* sp. The absolute stereochemistry was established to be (S) by comparing the circular dichroism (CD) spectrum with that of (+)-curcutetraol after conversion into (+)-sydonol (2).

Key words: sydonic acid; optically active form; circular dichroism (CD) spectrum

Several bisabolane-type phenolic sesquiterpenes have been isolated from such sources as herb plants,1,2 marine sponge,2,3 marine bacteria,3 and fungi.3,4,5 Some of them exhibited interesting biological activities. In the course of our studies of metabolites from fungi with unique ecologies, we disclosed a bisabolane, (+)-sydonic acid (1), from *Glonium* sp. (Hysterailes, Ascomycota) found in beech (Fagus crenata) from the Shirakami area. Although the optical rotation value of 1 has been reported to be zero, the sample obtained in the present study was found to be optically active. The absolute stereochemistry of its C7 position was established to be (S) by comparing the circular dichroism (CD) spectrum with that of (+)-curcutetraol after conversion into (+)-sydonol (2).

Reduction of 1 with LiAlH4 in THF readily provided sydonol (2) as oil in a 91% yield. The 13C-NMR spectrum in acetone-d6 was identical with the data for 2 isolated from *Aspergillus* sp.7,8) The optical rotation value for 2 thus obtained was [α]D20 = +8.6° (c 1.0, MeOH) which accorded well with that in the literature ([α]D20 = +7.2° (c 1.0, MeOH)).7)

Although the absolute configuration of 2 has not been reported, the CD spectrum of 2 prepared in the present study (Fig. 2) resembled that of (+)-curcutetraol (3), an 11-hydroxy analogue of 2, isolated from marine bacteria by Lindel et al.3,4 They established the absolute configuration of the stereogenic center of 3 to be S based on a comparison of the experimental CD spectrum with that obtained by quantum mechanics calculations. Asami’s asymmetric total synthesis has recently confirmed that.9)

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1 To whom correspondence should be addressed. Tel/Fax: +81-172-39-3782; E-mail: hmasaru@cc.hirosaki-u.ac.jp

Abbreviations: CD, circular dichroism
Since the achiral C11 hydroxy group of 3 was expected to scarcely contribute to the CD spectrum, the close CD curve of 2 suggested the same chirality as that of 3. Consequently, 1 isolated from Glonium sp. in this study was concluded to be the (S)-isomer. The similar optical rotation values for 2 and 3 might provide additional proof.

Since optically active benzyl alcohols readily racemize under mild conditions, we needed to consider the racemization of 1 during its isolation from fungi. However, no reduction of the optical rotation value was apparent when we dissolved optically active 1 in aqueous CH$_3$CN (1:1) and left at room temperature for 12 h in the presence of camphorsulfonic acid (3.0 mg/ml). Thus, racemization of 1 during its isolation hardly occurred. The electron-withdrawing carboxylic acid function at the C3 position probably destabilized benzyl cation 4, as shown in Fig. 3, which prevented the C7 hydroxyl group from elimination. Accordingly, we conclude that Aspergillus sydowi produced 1 in a racemic form, in contrast to Glonium sp.

Experimental

Isolation of (+)-sydonic acid. Glonium sp. collected from the Shirakami area of Aomori prefecture in 2007 was cultured in a potato-sucrose medium [3.0 liters, prepared from a potato extract (from 600 g potato), 60 g of sucrose, and water] at 25°C for 28 d on a rotary shaker (110 rpm). After filtration, the culture broth was extracted with ethyl acetate (2.0 liters) and concentrated in vacuo. The residue thus obtained was subjected to silica gel column chromatography (AcOEt/hexane = 20:80) to give a crude sample (35 mg). Recrystallization of the residue thus obtained was subjected to silica gel column chromatography (AcOEt/C$_6$H$_6$ = 2:3) to give a pure sydonic acid (4 mg, 38%).

The 1H-NMR spectrum in dimethylsulfoxide-$d_6$ was identical to that reported. 13C-NMR (125 MHz, CD$_3$OD) δ 22.86, 22.90, 22.98, 28.82, 28.99, 40.43, 43.57, 77.88, 118.60, 121.50, 127.77, 131.58, 138.00, 156.91, 169.86. ESIMS (rel. int.) m/z 267.1601 (18, calcd. for C$_8$H$_2$O$_3$ [MH$^+$], 167.1596), 249.1488 (100, calcd. for C$_8$H$_2$O$_3$ [M − (OH)]$^+$, 249.1485).

Reduction of 1 to produce sydonol (2). A suspension of 1 (7.5 mg, 28 μmol) and LiAlH$_4$ (1.4 mg, 38 μmol) in THF (1.0 ml) was refluxed for 2 h. After cooling to 0°C, 10% tartaric acid solution (0.2 ml) was added. The mixture was stirred at room temperature for 1 h and then filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue thus obtained was purified by silica gel column chromatography (hexane:AcOEt = 75:25) to give sydonol (2, 6.5 mg, 91%) as an oil. 1H-NMR (400 MHz, in CD$_3$OD) δ 0.82 (6H, d, J = 6.6 Hz, 1.14 (2H, m), 1.35 (2H, m), 1.49 (1H, nonatet, J = 6.6 Hz), 1.62 (3H s), 1.79, 1.91 (each 1H, ddd, J = 4.9, 11.7, 13.7 Hz), 4.02 (1H, t, J = 5.9 Hz), 4.52 (2H, d, J = 5.9 Hz), 5.24 (1H, br), 6.75 (2H, m), 7.04 (1H, d, J = 8.4 Hz), 9.70 (1H, br). ESIMS (rel. int.) m/z: 235.1709 (100, calcd. for C$_8$H$_2$O$_3$ [MH − H$_2$O]$^+$, 235.1698). The 13C NMR spectrum in acetone-$d_6$ was in good accordance with the reported data.3

References and Notes

5) Ishikawa, Y., Morimoto, K., and Hamasaki, T., Flavoglaucin, a metabolite of Eurotium chevalieri, its antioxidation and synergism with tocopherol. JAOCs, 61, 1865–1868 (1984).
6) So far, we have not found any remarkable biological activity of 1.
8) The solvent used for the 1H-NMR analysis was not described in ref. 7.