Revised Structure of Gonioheptolide A

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(±)-Gonioheptolide A (3) was unambiguously synthesized from (±)-goniofupyrone (4) and thereby its structure was revised as (1′*R,2*S**,3*S**,4*S**,5*R**)-3,4-dihydroxy-2-[(1′-hydroxy-2′-methoxycarbonyl)ethyl]-5-phenyltetrahydrofuran. Methanolysis of (±)-goniofupyrone (4) with conc.H_2SO_4 at room temperature provided (±)-gonioheptolide A (3) in 48% yield. The synthetic (±)-gonioheptolide A and its triacetate were comparable to natural gonioheptolide A and its triacetate, respectively.**

Key words gonioheptolide A; goniofupyrone; eight-membered lactone; first synthesis

In 1993, two novel eight-membered lactone natural products, named gonioheptolides[1] A (**1**) and B (**2**) were newly isolated from the bark extract of *Goniothalamus giganteus* HOOK, f. and THOMAS (Annonaceae). Many related antitumor styryllactones have also been isolated from the same bark.[2] The novel eight-membered structures of **1** and **2** were proposed on the basis of spectral evidence.[1] In addition, the relative stereochemistries of **1** and **2** were based on NMR spectral considerations including the correlation spectroscopy (COSY), nuclear Overhauser enhancement spectroscopy (NOESY), and heteronuclear multiple bond connectivity (HMBC) spectra. More careful reexamination of these NMR spectra, however, raised questions about the structure of these eight-membered natural products. Namely, during our studies[3] on total syntheses of the antitumor styryllactones, we prepared several compounds having a benzylic proton with the ether functionality as a common structural feature. These benzylic protons tend to appear in the range of δ 5.0 to 4.7 in the ^{1}H-NMR spectra. However, the benzylic proton of **1**, which attaches the lactone moiety, resonates at δ 4.59 similar to those of benzylic protons with an ether functionality. We assumed that if the benzylic carbon is attached to an electron withdrawing group like the lactone functionality, the benzylic proton would occur at a lower value than δ 5.0. On the other hand, the methyl signal of the methoxy group of **1** appeared at δ 3.70 in the ^{1}H-NMR spectrum, while its ^{13}C-NMR spectrum showed a methoxy peak at δ 52.1. These chemical shifts would be more reasonably explained as an aromatic methoxy group or methyl ester rather than as an aliphatic methoxy group. In addition, we recently revised the proposed structure of (−)-gonifupyrone (**4**) *via* its total synthesis. The ^{1}H-NMR spectral data of **4** exhibits similar chemical shifts and coupling constants except for the lower field shifted H-1 (δ 4.96 compared to δ 4.34 of gonioheptolide A) and the absence of a methoxy signal. It was at this stage, according to these NMR considerations, that we tentatively reached the conclusion that (±)-gonioheptolide A must have structure **3**, which might be easily derived from goniofupyrone (**4**). Therefore, we tried to elucidate the structure of gonioheptolide A by transformation from goniofupyrone (**4**). We describe herein the first synthesis of (±)-gonioheptolide A, whereby its structure was unambiguously established as **3**.

The conversion of (±)-**4** into (±)-**3** was realized as follows (Chart 2). The treatment of **4** with conc.H_2SO_4 in a mixture of solvents, tetrahydrofuran (THF) and MeOH, at room temperature gave the corresponding methyl ester derivative **3** in 48% yield along with recovery of starting **4** in 30% yield. Recyclization of **3** to **4** on exposure to diazabicyclo[5.4.0]-undec-7-ene (DBU) in THF at refluxing temperature demonstrated that **3** has the same relative stereochemistry as that of (±)-goniofupyrone (**4**). Acetylation of **3** under conventional conditions afforded the triacetate **5** in 93% yield. The obtained spectral data of **3** and **5** were in good agreement with those of gonioheptolide A and its triacetate, respectively.

Thus (±)-gonioheptolide A is now unambiguously shown to possess the structure depicted as **3** based on its synthesis, although its absolute stereochemistry has not been established yet. We did not prepare (±)-gonioheptolide B, but it is reasonable to conclude that gonioheptolide B should be the ethyl ester congener of gonioheptolide A because of the similarity of both NMR spectra.

Experimental

Infrared spectra were measured using a Shimadzu FTIR-8700 spectrometer, mass spectra with a Hitachi M-80 mass spectrometer, and ^{1}H-NMR and ^{13}C-NMR spectra with JNM-GSX 500 spectrometers in $CDCl_3$ using tetramethylsilane and $CDCl_3$ (77.00 ppm) as the internal standards, respectively. CH_2Cl_2 was freshly distilled from P_2O_5, and THF from sodium diphenylketyl prior to use. Silica gel (silica gel 60, 230—400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

(1′*R,2*S**,3*S**,4*S**,5*R**)-3,4-Dihydroxy-2-[(1′-hydroxy-2′-methoxylcarbonyl)ethyl]-5-phenyltetrahydrofuran [(±)-3]** One drop of conc. H_2SO_4 was added to a solution of (±)-goniofupyrone (**4**) (9.3 mg, 0.04

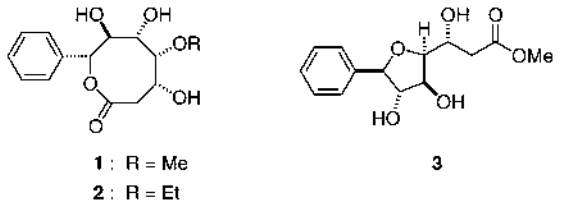

Chart 1

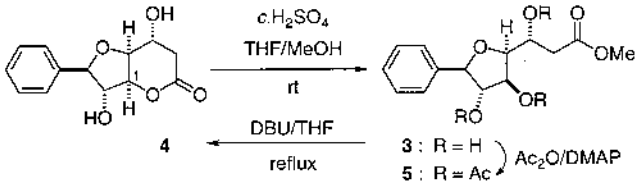

Chart 2

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mmol) in THF (0.3 ml) and MeOH (0.3 ml) . The reaction mixture was allowed to stand for 30 min, then diluted with saturated $CaCO_3$ solution, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (1 : 1) gave (±)-**3** (5.0 mg, 48%) along with (±)-**4** (2.8 mg, 30%). The methyl ester **3** was a colorless oil: MS (EI) *m/z*: 282 (M^+, 2.1), 264 (7.7), 251 (5.4), 246 (1.7), 133 (44), 120 (55), 107 (93), 105 (45), 97 (22), 91 (100), 79 (42), 77(41). IR (neat): 3417, 1727 cm^{-1}. ^{1}H-NMR δ: 7.48—7.26 (5H, m, aromatic H), 4.59 (1H, d, J=6.4 Hz, C_5-H), 4.43 (1H, m, $C_{1'}$-H), 4.34 (1H, dd, J=6.4, 4.8 Hz, C_3-H), 4.11—4.09 (2H, m, C_2-H, C_4-H), 3.72 (3H, s, OMe), 2.88 (1H, dd, J=16.6, 8.8 Hz, $C_{2'}$-H), 2.65 (1H, dd, J=16.6, 3.9 Hz, $C_{2'}$-H). ^{13}C-NMR: 173.30, 139.41, 128.52, 128.10, 126.40, 84.53, 83.88, 79.84, 67.82, 52.04, 37.56. HRMS Calcd for $C_{14}H_{18}O_6$: 282.1104. Found: 282.1107.

(1′*R,2*S**,3*S**,4*S**,5*R**)-3,4-Diacetoxy-2-[(1′-acetoxy-2′-methoxylcarbonyl)ethyl]-5-phenyltetrahydrofuran [(±)-5]** To a solution of (±)-**3** (3.9 mg, 0.01 mmol) in CH_2Cl_2 (0.5 ml) was successively added dimethylaminopyridine, (DMAP, 5.1 mg, 0.04 mmol) and Ac_2O (one drop). The reaction mixture was stirred at room temperature for 30 min, diluted with water, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (1 : 1) gave (±)-**5** (5.2 mg, 93%) as a colorless oil. MS (CI) *m/z*: 409 (M^++1, 100), 377 (4.8), 349 (55), 289 (7.2), 229 (18), 215 (5.2). IR ($CHCl_3$): 1745 cm^{-1}. ^{1}H-NMR δ: 7.48—7.26 (5H, m, aromatic H), 5.57 (1H, dt, J=7.3, 5.4 Hz, $C_{1'}$-H), 5.39 (1H, dd, J=5.4, 3.9 Hz C_3-H), 5.21 (1H, dd, J=4.9, 3.9 Hz, C_4-H), 4.90 (1H, d, J=4.9 Hz, C_5-H), 4.53 (1H, t, J=5.4 Hz, C_2-H), 3.69 (3H, s, OMe), 2.77 (1H, dd, J=15.6, 5.4 Hz, $C_{2'}$-H), 2.67 (1H, dd, J=15.6, 7.3 Hz, $C_{2'}$-H). ^{13}C-NMR 170.19, 169.99, 169.85, 169.66, 138.38, 128.37, 128.10, 126.07, 83.31, 81.67, 79.03, 76.08, 68.27, 52.01, 35.92, 21.10, 20.86, 20.61. HRMS (FAB) Calcd for $C_{20}H_{25}O_9$: 409.1499. Found: 409.1506.

Conversion of (±)-3 into (±)-4 A solution of (±)-**3** (4.2 mg, 0.01 mmol) and DBU (1.5 mg, 0.01 mmol) in THF (2.5 ml) was refluxed for 2 h. After cooling, the reaction mixture was diluted with saturated NH_4Cl, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (1 : 1) afforded (±)-**4** (2.7 mg, 72%). (±)-Goniofupyrone (**4**) was identified by spectral comparison with an authentic specimen.

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