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Note

Enantioselective Synthesis of Aspergillide B

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The enantioselective synthesis of aspergillide B, a 14-membered macrocyclic cytotoxin, was achieved in a 49% yield *via* 7 steps from a synthetic intermediate of aspergillide C. The spectroscopic data and specific rotation value for the synthetic material matched those of natural aspergillide B.

Key words: aspergillide; cytotoxic; macrolide; enantioselective synthesis

Aspergillides A–C, which exhibit significant cytotoxicity against mouse lymphocytic leukemica cells (L1210), were recently isolated by Kusumi and co-workers from a bromine-modified 1/2PD (potato-dextrose) culture medium of the marine-derived fungus, *Aspergillus ostianus* strain 01F313, and their structures were proposed to be heptaketidic 14-membered macrolides based on extensive spectroscopic analyses.[1] The structural proposal for aspergillides A and B was, however, revealed to be incorrect by the synthesis of the proposed structures by Uenishi and co-workers.[2] They concluded that the genuine structure of aspergillide B must be represented by structure **1** (Fig. 1), and the real structure of aspergillide A should be reinvestigated.[2] We also took an interest in the unique structures of aspergillides A–C proposed by Kusumi *et al.*, which featured a 14-membered macrolide structure incorporating a 2,6-*trans*-substituted tetrahydro- or dihydropyran ring,[3] and embarked on their total synthesis. We recently completed the enantioselective total synthesis of the proposed structure of aspergillide C (**2**), and confirmed its structure.[3] In this note, we describe a new synthesis for aspergillide B (**1**) from a synthetic intermediate of **2**.

As shown in Scheme 1, our synthesis of **1** began with the saponification of **5** and subsequent *in-situ* iodolactonization of the resulting carboxylate salt to give **6**; olefinic ester **5** in turn was prepared according to our previously reported procedure, using **3** and **4** as chiral sources.[3] Reductive elimination of iodolactone **6** proceeded smoothly, affording **7** in a 90% yield from **5**. Hydrolysis of the lactone moiety of **7** with lithium hydroxide in aqueous THF gave a mixture containing the corresponding hydroxy carboxylate. The mixture was concentrated to dryness, dissolved in DMF, and treated with TBSOTf, imidazole and DMAP to give a bis-silylated intermediate, the TBS ester group of which was then selectively hydrolyzed by directly adding water to the reaction mixture to afford **8** in an 89% yield from **7**.[3] Oxidative deprotection of the PMB group with DDQ gave hydroxy carboxylic acid **9** in a 77% yield. Finally, seco acid **9** was subjected to the known two-step sequence involving Yamaguchi lactonization and TBS deprotection to afford aspergillide B (**1**) in an 80% yield.[2] The ^{1}H- and ^{13}C-NMR spectra of **1**, obtained as a microcrystalline solid (mp 82.5–83.5 °C), were identical with those reported for natural aspergillide B, and the specific rotation of **1** {$[\alpha]^{25}_D$ −108 (*c* 0.175, MeOH)} showed good agreement with reported data {$[\alpha]^{31}_D$ −97.2 (*c* 0.27, MeOH),[1] $[\alpha]^{20}_D$ −90.0 (*c* 0.10, MeOH)[2]}.

Experimental

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer, using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C), unless otherwise stated. Optical rotation values were measured with a Horiba Septa-300 polarimeter, and mass spectra were obtained with a Jeol JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

*(3aS,5R,7aS)-5-[(1E,6S)-6-(4-Methoxybenzyloxy)-1-heptenyl]hexahydrofuro[3,2-*b*]pyran-2-one (7).* To a stirred solution of **5** (30.7 mg, 79.0 μmol) in THF (0.15 ml) was added a solution of NaOH (9.7 mg, 0.23 mmol) in water (50 μl) at room temperature. The mixture was stirred at 40 °C for 5 h and then cooled to room temperature. To the mixture were successively added a solution of $NaHCO_3$ (67.9 mg, 0.808 mmol) in water (1 ml) and a solution of I_2 (26.8 mg, 0.106 mmol) and KI (67.8 mg, 0.408 mmol) in water (1 ml). After being stirred overnight in the dark, the mixture was quenched with satd. $Na_2S_2O_3$ aq. and extracted with $CHCl_3$. The resulting extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give **6** (42.5 mg) as a yellow oil which was then taken up in toluene (2.0 ml). To the solution was successively added Bu_3SnH (30.0 μl, 0.108 mmol) and a solution of Et_3B (1 M in hexane, 45.0 μl, 45 μmol) at −30 °C. After being stirred at −30 °C for 30 min under an oxygen atmosphere, the mixture was quenched with satd. $NaHCO_3$ aq. and extracted with EtOAc. The resulting extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give 26.6 mg (90%) of **7** as a pale yellow oil. $[\alpha]^{23}_D$ −34.5 (*c* 1.18, $CHCl_3$); IR ν_{max}: 1782 (vs), 1612 (m), 1513 (s), 1246 (s), 1034 (s); ^{1}H-NMR δ: 1.18 (3H, d, J = 6.0 Hz, 7′-H_3), 1.37–1.61 (5H, m), 1.97–2.11 (5H, m), 2.50 (1H. dd, J = 17.3, 1.1 Hz, 3-H), 2.65 (1H, dd, J = 17.3, 4.4 Hz, 3-H), 3.46–3.55 (1H, m, 6′-H), 3.80 (3H, s, OCH_3), 4.33–4.40 (3H, m, 3a-H, 7a-H, 5-H), 4.37 (1H, d, J = 11.3 Hz, Ar–CH), 4.51 (1H, d, J = 11.3 Hz, Ar–CH), 5.57 (1H, ddt, J = 15.7, 4.9, 1.4 Hz, 1′-H), 5.71 (1H, ddt, J = 15.7, 1.4, 6.6 Hz, 2′-H), 6.84–6.90 (2H, m, Ar–H), 7.23–

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Abbreviations: PMB, *p*-methoxybenzyl; TBS, *tert*-butyldimethylsilyl; TBSOTf, *tert*-butyldimethylsilyl trifluoromethanesulfonate; imid, imidazole; DMAP, 4-(dimethylamino)pyridine; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

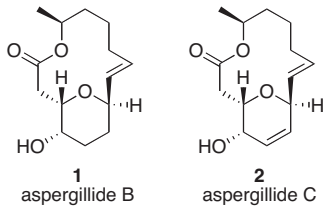
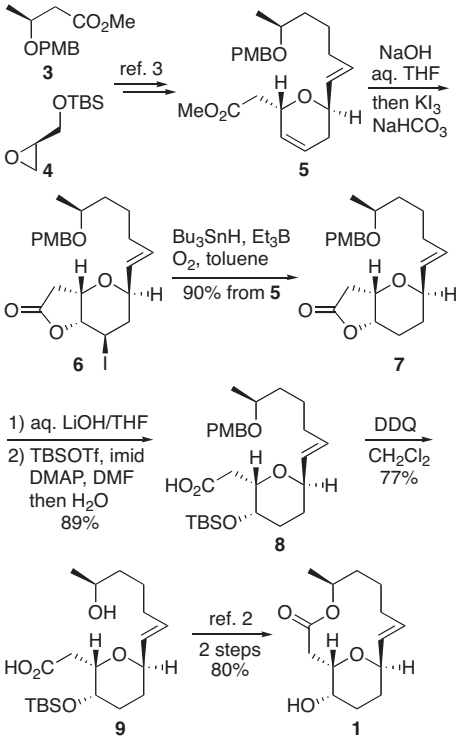


Fig. 1. Structures of Aspergillides B and C.



Scheme 1. Synthesis of Aspergillide B.

7.29 (2H, m, Ar–H); ^{13}C-NMR δ: 19.5, 20.6, 22.1, 24.9, 32.4, 36.1, 38.0, 55.2, 67.2, 69.9, 71.7, 74.2, 76.9, 113.8 (2C), 127.4, 129.2 (2C), 131.2, 134.4, 159.2, 176.2; HRMS (EI) *m/z*: calcd. for $C_{22}H_{30}O_5$, 374.2093; found, 374.2095 (M^+).

*{(2S,3S,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(1*E*,6*S*)-6-(4-methoxybenzyloxy)-1-heptenyl]tetrahydropyran-2-yl}acetic acid (**8**).* To a stirred solution of **7** (26.2 mg, 70.0 µmol) in THF (0.10 ml) was added a solution of LiOH•H_2O (3.4 mg, 77 µmol) in water (30 µl) at room temperature. After 2 h, the mixture was concentrated *in vacuo* to give a lithium carboxylate salt as a pale yellow solid which was then dissolved in DMF (0.2 ml). To the solution were successively added a solution of imidazole (26.7 mg, 0.392 mmol) and DMAP (6.0 mg, 49 µmol) in DMF (0.25 ml) and TBSOTf (68 µl, 0.290 mmol) at room temperature. After 2 h, water (2.0 µl) was added, and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give 31.5 mg (89%) of **8** as a pale yellow oil. $[\alpha]^{23}_D$ −11.3 (*c* 0.780, $CHCl_3$); IR ν_{max}: 3000 (br m), 1711 (s), 1513 (m), 1248 (s), 835 (s); ^{1}H-NMR δ: 0.05 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.17 (3H, d, J = 6.3 Hz, 7″-H_3), 1.32–1.68 (6H, m), 1.72–1.83 (1H, m), 1.85–1.96 (1H, m), 2.01 (2H, br q, J = 6.6 Hz), 2.61 (1H, dd, J = 15.7, 4.9 Hz, 2-H), 2.73 (1H, dd, J = 15.7, 8.8 Hz, 2-H), 3.43–3.53 (1H, m, 6″-H), 3.76–3.86 (1H, m, 3′-H), 3.80 (3H, s, OCH_3), 4.13–4.20 (1H, m, 2′-H), 4.22–4.29 (1H, m, 6′-H), 4.37 (1H, d, J = 11.4 Hz, Ar–CH), 4.49 (1H, d, J = 11.4 Hz, Ar–CH), 5.45 (1H, br dd, J = 15.7, 5.5 Hz, 1′-H), 5.66 (1H, ddt, J = 15.7, 1.1, 6.6 Hz, 2″-H), 6.84–6.90 (2H, m, Ar–H), 7.23–7.29 (2H, m, Ar–H); ^{13}C-NMR δ: −5.1, −4.9, 17.9, 19.5, 24.8, 25.7 (3C), 27.2, 27.3, 32.3, 33.4, 36.0, 55.2, 67.6, 69.9, 70.9, 72.2, 74.3, 113.8 (2C), 129.3 (2C), 129.4, 131.2, 133.3, 159.2, 176.4; HRMS (EI) *m/z*: calcd. for $C_{28}H_{46}O_6Si$, 506.3064; found, 506.3069 (M^+).

*{(2S,3S,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(1*E*,6*S*)-6-hydroxy-1-heptenyl]-tetrahydropyran-2-yl}acetic acid (**9**).* To a stirred mixture of **8** (22.5 mg, 44.4 µmol) in CH_2Cl_2 (0.4 ml)/1 M phosphate buffer (pH 7.0, 0.2 ml) was added DDQ (22.2 mg, 94.9 µmol) at room temperature. After 12 h, additional DDQ (15.9 mg, 67.9 µmol) was added, and the mixture was stirred for 4 h. The mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1–1:0) to give 13.2 mg (77%) of **9** as a pale yellow oil. $[\alpha]^{22}_D$ −27.9 (*c* 0.815, $CHCl_3$); IR ν_{max}: 3402 (br w), 3000 (br w), 1713 (s), 1104 (s), 836 (s); ^{1}H-NMR δ: 0.05 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.18 (3H, d, J = 6.0 Hz, 7″-H_3), 1.36–1.52 (5H, m), 1.57–1.69 (1H, m), 1.74–1.84 (1H, m), 1.88–1.97 (1H, m), 2.00–2.10 (2H, m, 3″-H_2), 2.56 (1H, dd, J = 15.6, 4.4 Hz, 2-H), 2.72 (1H, dd, J = 15.6, 9.3 Hz, 2-H), 3.75–3.85 (2H, m, 3′-H, 6″-H), 4.17–4.29 (2H, m, 2′-H, 6′-H), 5.48 (1H, br dd, J = 15.7, 5.8 Hz, 1″-H), 5.68 (1H, ddt, J = 15.7, 1.1, 6.6 Hz, 2″-H); ^{13}C-NMR δ: −5.1, −4.8, 17.9, 23.2, 24.9, 25.7 (3C), 27.0, 27.2, 32.1, 33.8, 38.4, 67.7, 68.0, 70.9, 72.1, 129.5, 133.3, 176.3; HRMS (FAB) *m/z*: calcd. for $C_{20}H_{39}O_5Si$, 387.2566; found, 387.2564 ($[M + H]^+$).

*(1S,5S,9E,11R,14*S*)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]-pentadec-9-en-3-one (**1**).* Compound **1** was prepared from **9** in an 80% yield *via* 2 steps according to the procedure reported in ref. 2. Mp 82.5–83.5 °C; $[\alpha]^{25}_D$ −108 (*c* 0.175, MeOH); IR ν_{max}: 3437 (br m), 2930 (s), 1724 (vs), 1183 (m), 1023 (s); ^{1}H-NMR (C_6D_6) δ: 0.99 (1H, dddd, J = 14.0, 4.9. 2.5, 1.2 Hz, 6-H), 1.06 (3H, d, J = 6.3 Hz, 5-CH_3), 1.27–1.44 (3H, m), 1.46–1.68 (3H, m), 1.68–1.91 (2H, m), 1.86–1.96 (1H, br, OH), 1.98–2.09 (1H, m, 8-H), 2.12 (1H, dd, J = 13.7, 1.9 Hz, 2-H), 2.72 (1H, dd, J = 13.7, 11.5 Hz, 2-H), 3.21 (1H, br s, 14-H), 4.08 (1H, br d, J = 11.5 Hz, 1-H), 4.28–4.34 (1H, m, 11-H), 5.04–5.14 (1H, m, 5-H), 5.39 (1H, br dd, J = 15.7, 4.4 Hz, 10-H), 6.19 (1H, dddd, J = 15.7, 10.9, 4.9, 1.9 Hz, 9-H); ^{13}C-NMR (C_6D_6) δ: 19.0, 22.4, 25.1, 27.6, 30.6, 31.9, 39.7, 67.2, 69.5, 69.7, 71.4, 129.0, 138.2, 169.9; HRMS (EI) *m/z*: calcd. for $C_{14}H_{22}O_4$, 254.1518; found, 254.1520 (M^+).

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