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 reaction mixture matched those of natural aspergillide B.

Key words: aspergillide; cytotoxic; macrolide; enantioselective synthesis

Aspergillides A–C, which exhibit significant cytotoxicity against mouse lymphocytic leukemia 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 ostiarius strain 01F313, and their structures were proposed to be heptaketidic 14-membered macrolides based on extensive spectroscopic analyses.\(^3\) 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 dihydropropyran 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 carboxylic acid 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 carboxylic acid. The mixture was concentrated to dryness, dissolved in DMF, and treated with TBSOT, 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 [\([\alpha]_D^{25}\)] = \(-108.0 (c 0.175, MeOH)]\(^1\) gave good agreement with reported data [\([\alpha]_D^{25}\)] = \(-97.2 (c 0.27, MeOH)], \([\alpha]_D^{25}\)] = \(-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.

\((3S,5R,7aS)-5\{(\text{E},\text{E})\}-6-(4\text{-Methoxybenzoyloxy})-1\text{-heptenyl}\}\text{hydrofuro[3,2-}c_1\text{3}\text{4}\text{3}]\text{2,3-bipyrane-2(1H)}\text{one (7). To a stirred solution of 5 (30.7 mg, 79.0 \mu\text{mol}) in THF (0.15 ml) was added a solution of NaOH (9.7 mg, 0.25 mmol) in water (50 \mu\text{l}) at room temperature. The mixture was stirred at 40 °C for 5 h and then cooled to room temperature. The mixture was 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\(_2\)SO\(_4\) 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 washed up in toluene (2.0 ml). To the solution was successively added Bu\(_3\)SnH (30.1 \mu\text{mol}) and a solution of Et\(_3\)B (1.3 \mu\text{mol}) in hexane, 45.0 \mu\text{mol}, 45 \mu\text{l} 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 deliver 26.6 mmol (90\%) of 7 as a pale yellow oil. [\([\alpha]_D^{25}\)] = −34.5 (c 1.18, CHCl\(_3\)); IR \(\nu_{\text{max}}\) : 1782 (vs), 1612 (m), 1513 (s), 1246 (s), 1034 (s); \(^1\H-NMR \delta : 1.18 (3H, d, J = 6.0 Hz, 7-H\(_4\)), 1.37–1.61 (5H, m), 1.97–2.11 (5H, m), 2.50 (1H, dd, J = 17.3, 3.4 Hz, 3-H\(_4\)), 2.65 (1H, dd, J = 17.3, 4.4 Hz, 3-H\(_4\)), 3.46–3.55 (1H, m, 6'-H\(_3\)), 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\(_3\)), 4.51 (1H, d, J = 11.3 Hz, Ar-CH\(_3\)), 5.57 (1H, ddt, J = 15.7, 4.9, 1.4 Hz, 1'-H\(_3\)), 5.71 (1H, ddt, J = 15.7, 1.4, 6.6 Hz, 2'-H\(_3\)), 6.84–6.90 (2H, m, Ar-H), 7.23–
solution of 7-benzyloxy)-1-heptenyl]tetrahydropyran-2-yl}acetic acid (0.06 (3H, s, SiCH₃)).

The mixture was diluted with water and extracted with a pale yellow oil. Upon concentration, 80% 499 (26.7 mg, 70.6 mmol) in THF (0.10 ml) was added a 0.290 mmol) at room temperature. After 2 h, the mixture was stirred for 1 h. The mixture was diluted with water and extracted with CH₂Cl₂, and the extract was washed with brine, dried (MgSO₄), and concentrated in vacuo.

The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give 13.2 mg (77%) of 9 as a pale yellow oil. [α]D²⁰ = −27.9 (c 0.185, CHCl₃); IR νmax: 3420 (br s), 3000 (br w), 1713 (s), 1104 (s), 836 (s); ¹H-NMR δ: 0.09 (3H, s, SiiCH₂), 0.69 (3H, s, SiCH₃), 0.89 (9H, s, Si(CH₃)₃), 1.18 (3H, d, J = 6.0 Hz), 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, 3H, 3-H₃), 2.72 (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, 3-H, 6-H), 4.17–4.29 (2H, 2-H, 6-H), 5.48 (1H, br dd, J = 15.7, 5.8 Hz, 1-H), 5.68 (1H, dd, J = 15.7, 11.1, 1.6, 6.6 Hz, 2-H⁺); ¹³C-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 C₁₂H₂₂O₅Si, 387.2566; found, 387.2564 (M⁺).

(1S,3S,6R)-3-(3-tetradymethylsilyl)-6-{[(1S,6S)-6-hydroxy-1-heptynyl]tetrahydropyran-2-yl}acetic acid (8). To a stirred solution of 7 (26.2 mg, 70.0 mmol) in THF (0.10 ml) was added a solution of LiOH·H₂O (3.4 mg, 77 mmol) in water (30 μl) at room temperature. After 2 h, the mixture was concentrated in vacuo to give a lithium carbonate 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 (20 μl) was added, and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with CH₂Cl₂. The extract was washed with brine, dried (MgSO₄), 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. [α]D²⁰ = −11.3 (c 0.780, CHCl₃); IR νmax: 3000 (br m), 1711 (s), 1513 (m), 1248 (s), 835 (s); ¹H-NMR δ: 0.05 (3H, s, SiCH₃), 0.06 (3H, s, Si(CH₃)₂), 0.89 (9H, s, Si(CH₃)₃), 1.17 (3H, d, J = 6.3 Hz, 7°-H₃), 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, OCH₃), 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); ¹³C-NMR δ = −5.1, −4.9, 17.9, 19.5, 24.8, 25.7 (3C), 27.2, 27.3, 33.2, 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 (El) m/z: calcd. for C₁₀H₁₆O₃Si, 506.3064; found, 506.3069 (M⁺).