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Stereoselective synthesis of the cytotoxic macrolide aspergillide B

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ABSTRACT

A total, stereoselective synthesis of the cytotoxic macrolide aspergillide B has been performed. A cross metathesis and a C-glycosidation via a Mukaiyama-type aldol reaction were key features of the synthesis. The macrocyclic lactone ring was created by means of the Yamaguchi procedure.

The aspergillides A, B and C (**1**–**3**) are three 14-membered macrolides isolated the last year from a strain of the marine-derived fungus *Aspergillus ostianus* cultivated in a bromine-modified medium.[1,2] The structures of these new compounds were determined by analyses of their 1D and 2D NMR spectra and reported to be as depicted in Figure 1. Their absolute configurations were elucidated by means of the modified Mosher's method as well as with the aid of chemical conversions. Macrolides **1**–**3** were found to show cytotoxic activities in the micromolar range against mouse lymphocytic leukaemia cells (L1210).

The structures of these natural lactones show some unusual features which deserve comment. In a literature perusal, we have found only two examples of naturally occurring, very recently isolated 14-membered macrolides that possess a tetrahydropyran ring not forming part of a hemiacetal or acetal moiety.[3,4] This and the aforementioned bioactivities prompted us to initiate the total synthesis of these compounds.

In the beginning of this year, Uenishi et al. published a synthesis of a compound having structure **1**, then assumed to correspond to aspergillide A.[5] However, these authors found that their synthetic compound had spectral properties identical with those reported for aspergillide B. The latter compound was thus reassigned structure **1**, which led to the need of a new structure assignment for aspergillide A. Still more recently, Kuwahara et al. published a synthesis of aspergillide C and confirmed it to have structure **3**.[6] Structure **2** therefore does not correspond to any natural compound isolated so far.[5]

In the present manuscript, we wish to publish our own synthesis of aspergillide B, now known to have structure **1**.[7] The retrosynthetic concept is depicted in Scheme 1. Hydrolytic opening of the lactone ring gives the protected seco acid **4**. Inverse cross metathesis (CRM) yields the known alcohol **5**[8] and tetrahydropyran **6**. We planned to obtain **6** by means of an anomeric Mukaiyama-type alkylation of a suitable lactol derivative prepared through reduction of lactone **7**. The latter was to be obtained by functional modification of **8**, in turn derived from **9** through a metal-catalyzed double bond migration. Following this, inverse asymmetric allylation to aldehyde **10** and oxidative retro-cleavage of the olefinic bond finally led to the known compound **11**.[9]

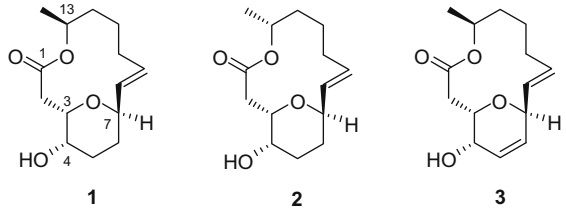

Figure 1. Structures of the aspergillides A–C as reported in the initial publication.

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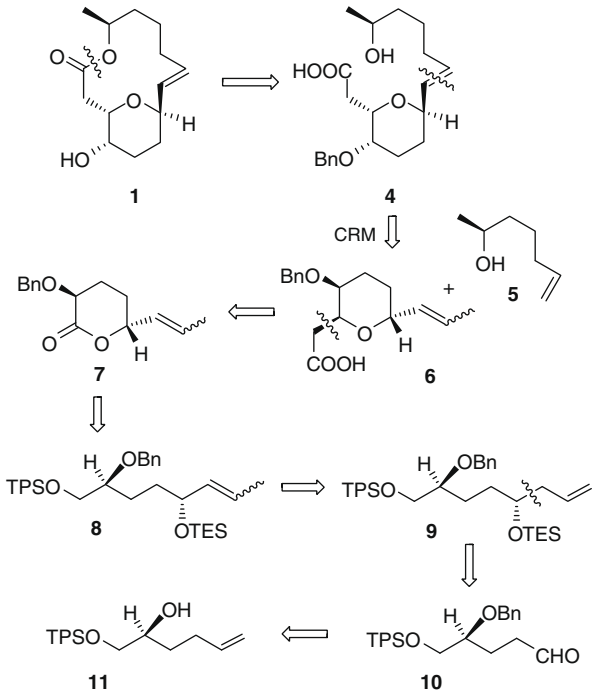
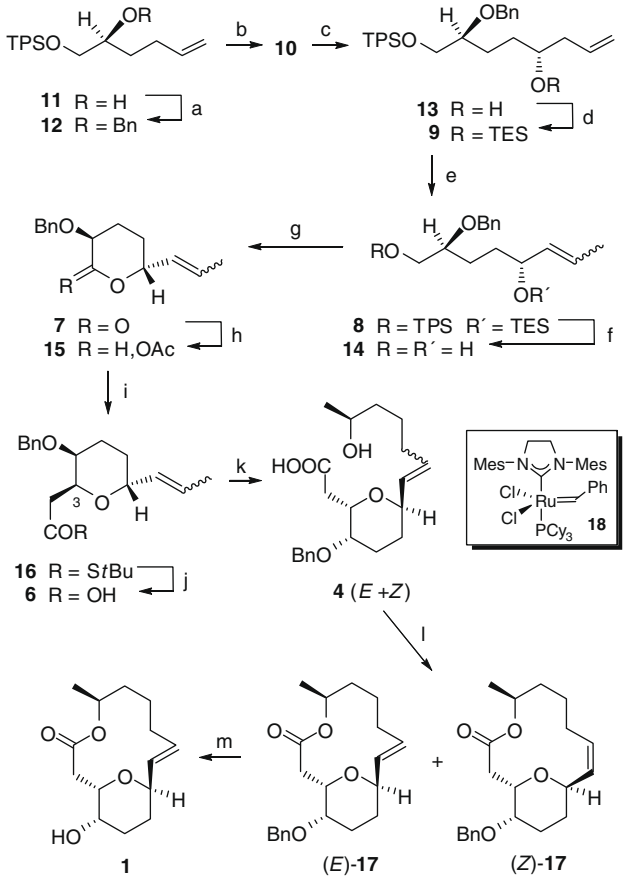


Scheme 1. Retrosynthetic analysis of aspergillide B (**1**).

Scheme 2 shows the details of the synthesis. Alcohol **11**[9] was benzylated to **12** under mild, nonbasic conditions.[10] Ozonolytic cleavage of the olefinic bond yielded aldehyde **10**, which was first purified and then subjected to Brown's asymmetric allylboration.[11] This gave homoallyl alcohol **13** in a very high diastereomeric purity (dr >95:5 by NMR), which was subsequently protected as its triethylsilyl derivative **9**. Isomerization of the terminal olefinic bond to the internal position was achieved by means of the catalytic method of Wipf et al.[12] With the aid of this procedure, compound **9** was converted into its isomer **8** in high yield.[13] Compound **8** was obtained as a ~9:1 *E*/*Z* mixture[14,15] which proved to be difficult to separate and was thus carried as such until the last step of the synthesis. Cleavage of the two silyl groups and selective oxidation of the primary alcohol with $PhI(OAc)_2$/TEMPO[16] afforded δ-lactone **7**. Reduction of **7** (DIBAL) followed by acetylative quenching yielded the acetylated lactol **15** as a mixture of stereoisomers,[17] which were not separated. The mixture was subsequently treated with the trimethylsilyl enolate of *tert*-butyl thioacetate[18] in the presence of BF_3-etherate and TMSOTf.[19] This furnished the *trans*-2,6-disubstituted[20] tetrahydropyran **16** in 55% yield, accompanied by its epimer at C-3 (21%, not depicted in Scheme 2). Alkaline hydrolysis of **16** provided acid **6** in high yield.

Treatment of **6** with 5 equiv of olefinic alcohol **5** in the presence of 20% of ruthenium catalyst **18** caused cross metathesis[21] and afforded hydroxy acid **4** in 89% yield as a 7:3 *E*/*Z* mixture. Macrolactonization was performed on the mixture by means of the Yamaguchi procedure[22] and gave a separable mixture of (*E*)- and (*Z*)-**17**. Cleavage of the benzyl group in the former was performed with DDQ[23] in wet CH_2Cl_2 and yielded lactone **1**, which showed physical and spectral properties[24] identical to those published for aspergillide B.[1,5]

In summary, the cytotoxic macrolide aspergillide B has been synthesized in a stereoselective way. As recently reported by Hande and Uenishi,[5] its actual structure has been found to be **1** (Fig. 1), the structure initially and erroneously proposed for aspergillide A.



Scheme 2. Reagents and conditions: (a) BnBr, Ag_2O, Et_2O, rt, 3 d (83%); (b) O_3, CH_2Cl_2, −80 °C, 30 min, then Ph_3P, rt, 2 h (78%); (c) allylBIpc$_2$ from (−)-DIP-Cl and allylmagnesium bromide, Et_2O, −90 °C, 2 h (dr >95:5); (d) TESOTf, Et_3N, CH_2Cl_2, −80 °C, 2 h (77% overall from **10**); (e) cat. **18** (5% molar), *N*-trityl allylamine, EtN*i*Pr$_2$, CH_2Cl_2, Δ, 16 h (96%, *E*/*Z* 9:1); (f) TBAF, THF, rt, 16 h (98%); (g) $PhI(OAc)_2$, TEMPO (cat.), 0 °C, 16 h (84%); (h) DIBAL, CH_2Cl_2, −80 °C, 2 h, then addition of Ac_2O, py, DMAP, 14 h (93%); (i) CH_2=C(OTMS)S*t*Bu, 4 Å MS, $BF_3{\cdot}Et_2O$, TMSOTf, MeCN, 16 h, −18 °C (55%); (j) NaOH, aq MeOH, rt, 16 h (94%); (k) **5** (5 equiv), cat. **18** (20% molar), CH_2Cl_2, Δ, 6 h (89%, *E*/*Z* 7:3); (l) $Cl_3C_6H_2COCl$, Et_3N, THF, rt, 1.5 h, then DMAP, toluene, 50 °C, 6 h (57%); (m) DDQ, CH_2Cl_2/H_2O 10:1, rt, 20 h (51%). *Abbreviations*: Bn, benzyl; TPS, *tert*-butyldiphenylsilyl; TES, triethylsilyl.

Acknowledgements

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Aoki, M.; Sakai, N.; Fujimoto, N.; Kawashima, A. *Tetrahedron Lett.* **2009**, *50*, 108–110.
5. Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189–192. The compound with structure **2** was also synthesized by these authors and found to be different from aspergillide A.
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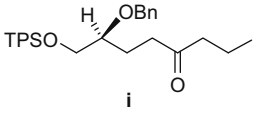
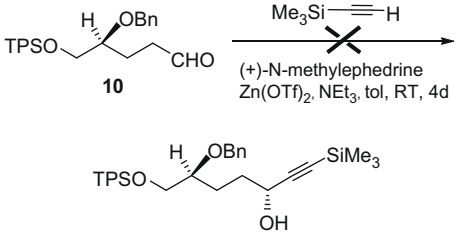
13. Protection of the free OH group in compound **13** was crucial. Attempts at double bond isomerization in **13** under various conditions gave only ketone **i** in low yield.



i

14. Both *E*/*Z* isomers were synthetically productive. In order to avoid working with mixtures, however, we tried to convert compound **8** into its nor-methyl derivative (vinyl instead of propenyl) by means of cross metathesis under an ethylene atmosphere.[12a] This goal was achieved but yields were not satisfactory (50–55% at <1 mmol scale) and difficult to reproduce at a larger scale.
15. We also made attempts at obtaining the aforementioned vinyl derivative by means of asymmetric ethynylation of aldehyde **10** (Frantz, D. E.; Fässler, R.; Carreira, E. M., *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807) followed by semihydrogenation of the triple bond. Unfortunately, the ethynylation step proved to be too slow (mainly starting materials in the reaction mixture after 4 days) and was abandoned.



10

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17. Compound **15** is a ca. 2:1 mixture of anomers, each of which being a ca. 9:1 mixture of *E*/*Z* geometric isomers. The ^{1}H NMR spectrum shows four doublets in the δ 6.50–5.50 range with the expected coupling constant values. Major anomer: δ 5.64 (d, J = 7.9 Hz; *E* isomer) and 5.59 (d, J = 7.9 Hz; *Z* isomer); minor anomer: δ 6.38 (d, J = 3.1 Hz; *E* isomer) and 6.33 (d, J = 3.1 Hz; *Z* isomer).
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24. Compounds (*E*)-**17** and (*Z*)-**17** were separated on a silica gel column using hexanes–EtOAc mixtures as the eluent (gradient from 95:5 to 90:10). Compound **1** was purified on a silica gel column using a 70:30 mixture of hexanes–EtOAc. Physical and spectral data of (*E*)-**17**, (*Z*)-**17** and **1**:(*E*)-**17**: oil; R_f on a silica gel TLC plate (hexanes–EtOAc, 80:20): 0.21; $[\alpha]_D$ −56.3 (*c* 1.5; $CHCl_3$); IR ν_{max} 1732 (lactone C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (5H, br m, arom. H), 6.19 (1H, dddd, J = 15.5, 10.8, 4.8, 1.8 Hz; H-9), 5.64 (1H, br dd, J = 15.5, 4 Hz; H-8), 5.06 (1H, m; H-13), 4.72 (1H, d, J = 12.5 Hz; benzyl), 4.49 (1H, m; H-7), 4.40 (1H, d, J = 12.5 Hz; benzyl), 4.18 (1H, br d, J = 11 Hz; H-3), 3.32 (1H, br s; H-4), 2.64 (1H, dd, J = 14, 11 Hz; H-2), 2.25–2.15 (2H, m; H-6, H-10), 2.10 (1H, dd, J = 14, 1.7 Hz; H-2′), 2.05–1.90 (2H, m; H-5, H-10′), 1.85–1.75 (2H, m; H-11, H-12), 1.70–1.55 (2H, br m; H-5′, H-12′), 1.45–1.30 (2H, br m; H-6′, H-11′), 1.17 (3H, d, J = 6.5 Hz; Me-C13); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C-1), 138.6 (aromatic quat. C), 137.7 (C-9), 128.8 (C-8), 128.3, 127.9, 127.6 (aromatic), 73.1 (C-4), 71.2 (C-7), 70.5 (benzyl CH_2), 69.9 (C-13), 69.0 (C-3), 39.9 (C-2), 31.7 (C-12), 30.6 (C-10), 24.8 (C-11), 23.0 (C-6), 22.9 (C-5), 19.1 (Me-C13).
(*Z*)-**17**: oil; R_f on a silica gel TLC plate (hexanes–EtOAc, 80:20): 0.33; $[\alpha]_D$ −28.4 (*c* 0.5; $CHCl_3$); IR ν_{max} 1729 (lactone C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (5H, br m, arom. H), 5.69 (1H, br tt, $J \sim$ 10.2, 2.5 Hz; H-9), 5.46 (1H, br d, J = 10.5 Hz; H-8), 4.88 (1H, m; H-13), 4.68 (1H, d, J = 12.2 Hz; benzyl), 4.63 (1H, m; H-7), 4.40 (1H, d, J = 12.2 Hz; benzyl), 4.16 (1H, dt, J = 11.8, 2.2 Hz; H-3), 3.30 (1H, br s; H-4), 2.86 (1H, dd, J = 15.2, 11.8 Hz; H-2), 2.76 (1H, m; H-10), 2.20–2.10 (2H, m; H-2′, H-6), 2.00 (1H, dq, J = 14, 3.5 Hz; H-5), 1.90 (1H, br d, $J \sim$ 15 Hz; H-10′), 1.80–1.50 (5H, br m; H-5′, H-11, H-11′, H-12, H-12′), 1.34 (1H, br dq, $J \sim$ 13, 2.5 Hz; H-6′), 1.18 (3H, d, J = 6.3 Hz; Me-C13); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C-1), 138.5 (C-9 + aromatic quat. C), 128.3 (aromatic), 128.2 (C-8), 127.8, 127.6 (aromatic), 72.5 (C-4), 72.1 (C-13), 70.5 (benzyl CH_2), 69.4 (C-3), 69.3 (C-7), 38.4 (C-2), 32.8 (C-12), 27.2 (C-11), 24.7 (C-10), 24.6 (C-6), 22.1 (C-5), 21.7 (Me-C13).
1: oil; R_f on a silica gel TLC plate (hexanes–EtOAc, 60:40): 0.15; $[\alpha]_D$ −88.2 (*c* 0.26; MeOH), lit.[1] $[\alpha]_D$ −97.2 (*c* 0.27; MeOH), lit.[5] $[\alpha]_D$ −90 (*c* 0.1; MeOH); IR ν_{max} 3400 (br, OH), 1732 (lactone C=O) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.19 (1H, dddd, J = 15.5, 10.8, 4.8, 1.8 Hz; H-9), 5.64 (1H, br dd, J = 15.5, 4 Hz; H-8), 5.09 (1H, m; H-13), 4.30 (1H, m; H-7), 4.08 (1H, br d, J = 11.4 Hz; H-3), 3.22 (1H, br s; H-4), 2.71 (1H, dd, J = 13.8, 11.6 Hz; H-2), 2.12 (1H, dd, J = 14, 1.7 Hz; H-2′), 2.04 (1H, dddd, J = 13.5, 10.5, 4.8, 2.2 Hz; H-10), 1.85–1.75 (2H, br m; H-6, H-10′), 1.65–1.50 (3H, br m; H-5, H-11, H-12), 1.45–1.30 (3H, br m; H-5′, H-11′, H-12′), 1.07 (3H, d, J = 6.4 Hz; Me-C13), 1.00 (1H, dddd, J = 14, 4.5, 2.5, 1.3 Hz; H-6′); ^{13}C NMR (125 MHz, C_6D_6) δ 169.9 (C-1), 138.2 (C-9), 129.1 (C-8), 71.6 (C-7), 69.9 (C-3), 69.7 (C-13), 67.3 (C-4), 39.9 (C-2), 32.1 (C-12), 30.7 (C-10), 27.8 (C-5), 25.3 (C-11), 22.6 (C-6), 19.2 (Me-C13).