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Total synthesis of aspergillide B and structural discrepancy of aspergillide A

Sudhir M. Hande, Jun'ichi Uenishi *

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan

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ABSTRACT

Fourteen-membered cytotoxic macrolides **1** and **2** were synthesized from alcohol **10** in 15 steps utilizing stereospecific Pd(II)-catalyzed cyclization of ζ-hydroxy chiral allylic alcohol **7**. Aspergillides A and B were isolated from marine fungus, and their structures were proposed as **1** and **2**, respectively. The synthetic **1** was not matched with aspergillide A but matched with aspergillide B. The chiral center at C-13 position of aspergillide B was revised to be (*S*)-configuration. The key steps of the stereoselective synthesis include the Sharpless asymmetric dihydroxylation, cross-metathesis, stereospecific construction of tetrahydropyran ring of **16** using Pd^{II} catalyst, and the Yamaguchi macrolactonization.

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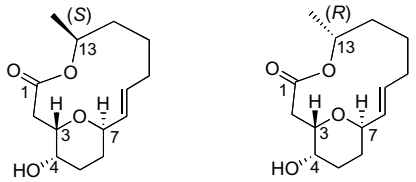
Marine organisms are a rich source of natural products, which contain novel chemical diversity and biological activity. Recently, three 14-membered macrolides, namely aspergillides A, B, and C, were isolated from the marine-derived fungus *Aspergillus ostianus strain* 01F313, cultured in a medium composed of bromine-modified artificial water.[1] The biological assay of these compounds revealed a potent cytotoxicity against mouse lymphocytic leukemia cells (L1210) at 2–70 μg/L (LC50). Although some 14-membered macrolides possessing bridged tetrahydropyran ring have been reported,[2] aspergillides are the first examples of 14-membered macrolides incorporated with a *trans* tetrahydropyran ring.[3]

We were attracted to aspergillides A and B (Fig. 1) because of their unique structural motif and interesting biological activity. The major challenge from the synthetic point of view is the construction of the bridged tetrahydropyran ring with required trans stereochemistry. We envisioned that this goal could be achieved by the Pd^{II}-catalyzed stereospecific synthesis of tetrahydropyrans[4] that we developed for the synthesis of some natural products.[5]



1 (aspergillide A) **2** (aspergillide B)

Figure 1. Proposed structures of aspergillides A and B.

Our approach for the synthesis of aspergillides A and B is outlined in Scheme 1.

The intermediacy seco acids **3** and **4** can be prepared by cross-metathesis of two alkenes **5** and 6-hepten-2-ol **6*S*** or **6*R***. *trans*-2,6-Disubstituted tetrahydropyran **5** will be constructed in 3 steps utilizing the stereospecific SN2′-type cyclization of ζ-hydroxy chiral allylic alcohol **7** by Pd^{II} catalyst. This intermediate is derived by the cross-metathesis of compound **8** and chiral allylic alcohol **9*S***.

Therefore, the initial object was the preparation of compound **8** as shown in Scheme 2.

The synthesis commenced from the known methyl (*E*)-7-hydroxyhept-3-enoate (**10**), which was derived from tetrahydrofurfuryl alcohol in 3 steps.[6] After the protection of the primary alcohol of **10** with TBSCl, alkene **11** was subjected to the Sharpless asymmetric dihydroxylation reaction using AD-mix-α accompanied by lactonization to give the chiral β-hydroxy-γ-lactone **12** in 89% yield.[7]

Protection of the secondary hydroxy group with TBDPSCl and selective deprotection of TBS group by the treatment with $BF_3{\cdot}OEt_2$ at −10 °C afforded **13** in 2 steps in 91% yield. The Swern oxidation of the primary alcohol gave aldehyde **14** in 98% yield. The Wittig olefination of **14** provided **8** in 57% yield along with 16% recovery of starting material.[8]

Next, olefin **8** was subjected to the cross-metathesis reaction[9] with the coupling partner (*S*)-5-phenylpent-1-en-3-ol (**9*S***)[10] to afford **15** in 63% yield[11] along with 12% recovery of **8** (Scheme 3). Desilylation of **15** with TBAF gave the cyclization precursor **7** in 74% yield. The key cyclization of **7** was carried out by the treatment with 15 mol % of $PdCl_2(CH_3CN)_2$ in THF at 0 °C for 45 min. The desired *trans*-(*E*)-tetrahydropyran **16*trans*** was obtained in 76% yield along with **16*cis*** in 3% yield.

A similar reaction of **8** with (*R*)-alcohol **9*R***[10] gave **15′** in 66% yield[11] along with 7% recovery of **8**. Desilylation with TBAF

* Corresponding author.
E-mail address: juenishi@mb.kyoto-phu.ac.jp (J. Uenishi).

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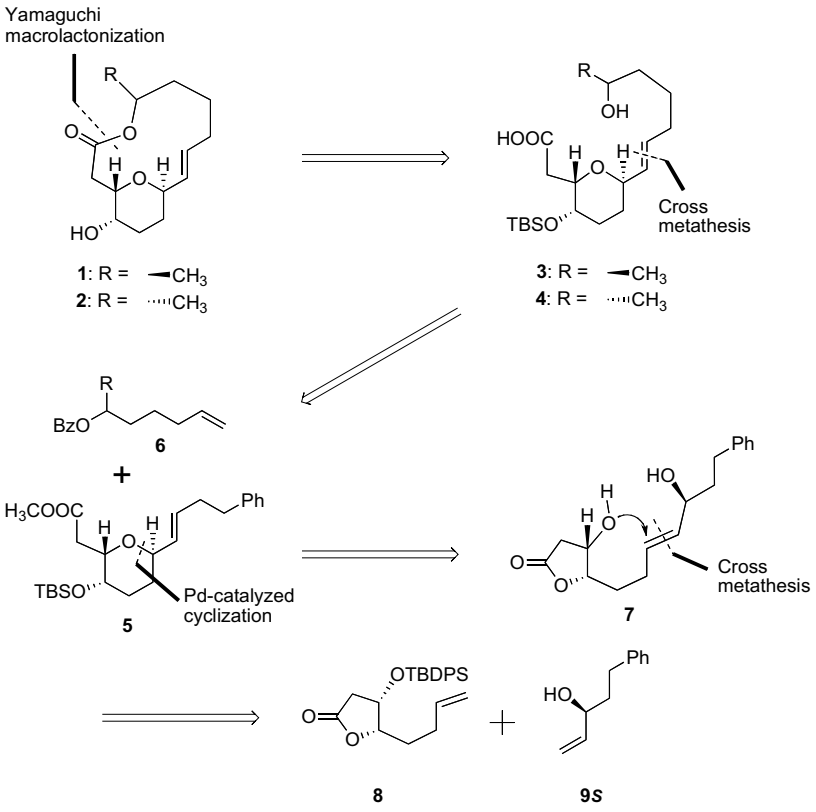
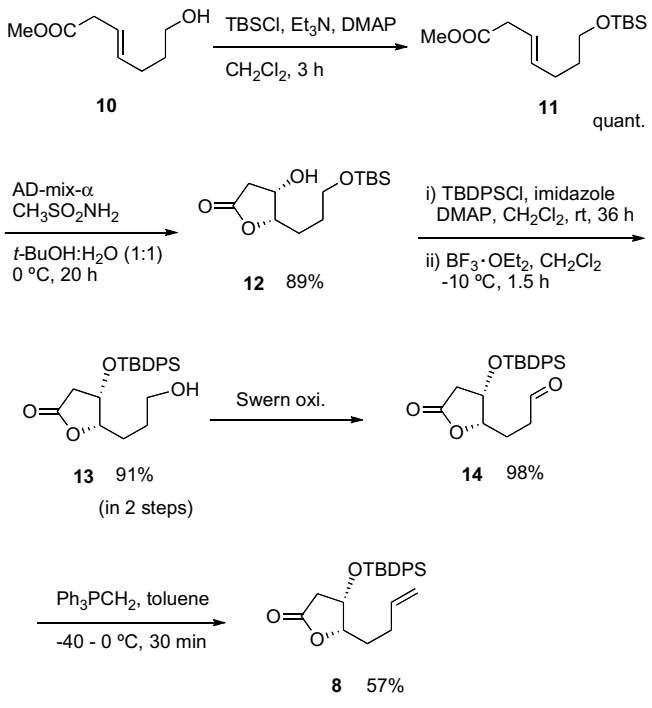


Scheme 1. Retrosynthetic analysis of aspergillides A and B.



Scheme 2.

afforded diol **7′** in 67% yield, and successive cyclization of **7′** gave **16*cis*** predominantly in 80% yield along with **16*trans*** in 2% yield. The minor isomers were supposed to be produced via the *anti*-oxypalladation process discussed in the previous paper.[4c] These structures are confirmed by the nOe experiments, as shown in Figure 2.

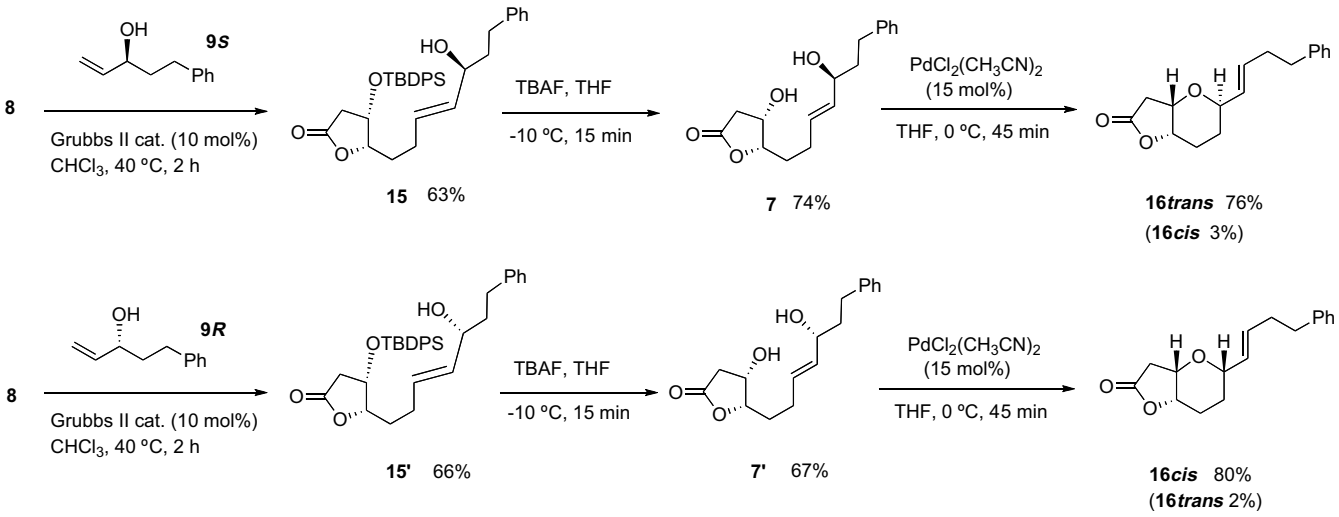
Thus, after all three stereocenters on the tetrahydropyran ring of **16*trans*** were set with requisite stereochemistries, the five-membered lactone ring was subjected to open as shown in Scheme 4.

Methanolysis of **16*trans*** by treatment with sodium methoxide in absolute methanol and successive silylation of the axial hydroxy group with TBSOTf in the presence of 2,6-lutidine in CH_3CN[12] gave **5** in 60% yield in two steps. The required heptenol side chain on the tetrahydropyran ring for the seco acid **3** was introduced through a second cross-metathesis of the sequence with (*S*)-hept-6-en-2-yl benzoate (**6*S***).[13a] In fact, cross-metathesis of **5** with **6*S*** in the presence of 10 mol % of Grubbs-II catalyst afforded **17*S*** as a sole product in 73% yield.[11] Hydrolysis of benzoate and methyl ester of **17S** was performed in one step to give **3** in 91% yield. The standard Yamaguchi macrolacton-zation[14] of **3** provided **18*S*** in 86% yield. The stereo-chemistry of the *trans* tetrahydropyran ring of **18*S*** was reconfirmed by its characteristic nOe as shown in Figure 3.

The final deprotection of silyl ether by the treatment of **18*S*** with TBAF gave **1** in 96% yield. However, surprisingly, after comparison of the spectroscopic data of **1** with those of the natural products, we found that all the data of **1**[15] including specific rotation matched well with those of aspergillide B rather than those of aspergillide A, as reported in the original literature.[1] Based on these results, we concluded that aspergillide B must have the C-13(*S*) configuration rather than the C-13(*R*) configuration.

At this point, we assumed that aspergillide A might posses the C-13(*R*) configuration and sought to prove this by the synthesis of **2**. Since we have the key common intermediate **5**, only the replacement of coupling partner from (*S*)-benzoate **6*S*** to (*R*)-benzoate **6*R***[13d] in metathesis reaction and the repetition of the same four-step sequence would give compound **2** as shown in Scheme 5.

In fact, a four-step sequence from **5** gave compound **2** in 39% yield. However, the spectroscopic data and the specific rotation



Scheme 3.

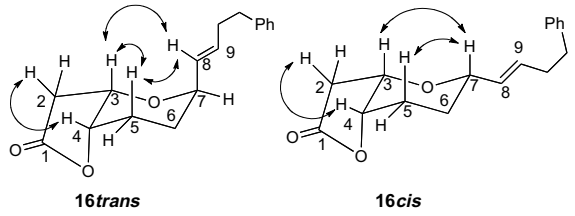


Figure 2. Key nOes observed in **16*trans*** and **16*cis***.

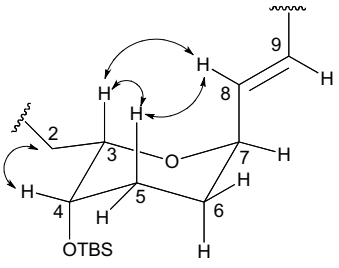
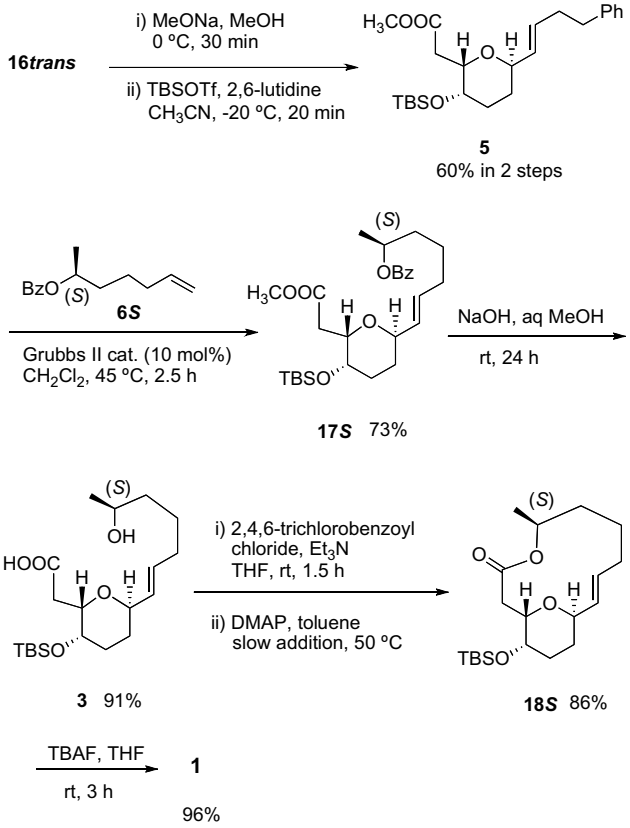
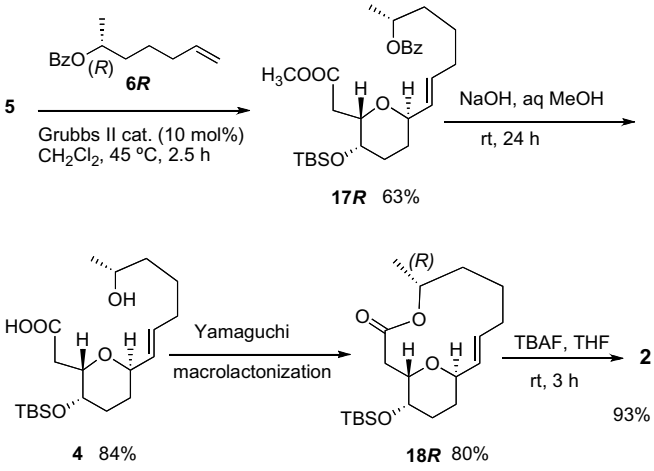


Figure 3. NOe relations observed in **18S**.



Scheme 4.



Scheme 5.

of **2** were totally different from those of aspergillide A.[15] These results prompted us to conclude that compound **2** is not the structure of aspergillide A.[1]

In summary, we have achieved the first enantioselective synthesis of **1** as a revised structure of aspergillide B. The proposed structure of aspergillide A is found to be incorrect and its structure remains unclear. Besides these findings, this synthesis also underlined the efficiency and importance of our methodology for the stereospecific construction of chiral non-racemic tetrahydropyran

ring that would allow easy access to the related natural products of the biological importance. Synthesis of additional analogs, determination of the correct structure of aspergillide A,[16] and their biological tests are in progress.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.115.

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15. Compound **1**; $[\alpha]_D^{21}$ − 82.5 (*c* 0.16, $CHCl_3$), $[\alpha]_D^{20}$ − 90.0 (*c* 0.10, MeOH); R_f = 0.4 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 6.19 (dddd, 1H, *J* = 15.7, 10.8, 4.8, 1.8 Hz, H-9), 5.38 (br.dd, 1H, *J* = 15.7, 4.4 Hz, H-8), 5.09 (m, 1H, H-13), 4.30 (m, 1H, H-7), 4.08 (br.d, 1H, *J* = 11.3 Hz, H-3), 3.21 (br, 1H, H-4), 2.71 (dd, 1H, *J* = 13.7, 11.3 Hz, H-2), 2.12 (dd, 1H, *J* = 13.7, 1.8 Hz, H-2), 2.04 (dddd, 1H, *J* = 13.3, 11.0, 4.9, 2.2 Hz), 1.86 (br, 1H), 1.78 (m, 1H), 1.74 (m, 1H), 1.61 (m, 1H), 1.55 (m, 1H), 1.52 (m, 1H), 1.37 (m, 1H), 1.34 (m, 1H), 1.31 (m, 1H), 1.07 (d, 3H, *J* = 6.4 Hz), 0.99 (dddd, 1 H, *J* = 14.1, 4.8, 2.4, 1.2 Hz); ^{13}C NMR (100 MHz, C_6D_6) 169.8, 138.2, 129.0, 71.5, 69.8, 69.5, 67.2, 39.9, 32.0, 30.7, 27.8, 25.3, 22.6, 19.1; IR (film, cm^{-1}) 3431, 2927, 2854, 1732, 1454, 1259; MS (FAB) *m*/*z* 255 (M + H$^+$). HRMS calcd for $C_{14}H_{23}O_4$ (M+H$^+$): 255.1596: Found; *m*/*z* 255.1593. *Compound* **2**; $[\alpha]_D^{23}$ −48.7 (*c* 0.16, $CHCl_3$); R_f = 0.42 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (dddd, 1H, *J* = 15.3, 10.6, 4.4, 1.8 Hz, H-9), 5.61 (ddd, 1H, *J* = 15.3, 4.4, 1.2 Hz, H-8), 4.66 (ddq, 1H, *J* = 6.1, 6.1, 2.7 Hz, H-13), 4.53 (m, 1H, H-7), 4.10 (dt, 1H, *J* = 7.7, 1.3 Hz, H-3), 3.56 (br.d, 1H, *J* = 6.4 Hz, H-4), 2.54 (dd, 1H, *J* = 16.3, 7.9 Hz, H-2), 2.42 (dd, 1H, *J* = 16.3, 1.6 Hz, H-2), 2.03–2.22 (m, 3H), 1.92–2.05 (m, 2H), 1.84 (m, 2H), 1.76 (m, 1H), 1.71 (m, 1H), 1.43 (dddd, 1H, *J* = 14.3, 4.1, 2.8, 1.1 Hz), 1.29 (d, 3H, *J* = 6.4 Hz), 1.12 (dddd, 1H, *J* = 13.6, 4.2, 2.4, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 172.7, 139.0, 126.9, 73.5, 72.1, 68.6, 68.6, 40.3, 33.2, 32.2, 27.3, 26.0, 22.5, 20.3; IR (film, cm^{-1}) 3425, 2924, 2854, 1724, 1454, 1262; MS (FAB) *m*/*z* 277 (M+Na$^+$). HRMS calcd for $C_{14}H_{22}O_4Na$ (M+Na$^+$): 277.1416: Found; *m*/*z* 277.1412. Asperigillide A lit.; $[\alpha]_D^{31}$ −59.5 (*c* 0.45, $CHCl_3$).[1] Asperigillide B lit.; $[\alpha]_D^{31}$ −97.2 (*c* 0.27, MeOH).[1]
16. We are now anticipating that the structure of aspergillide A might possess *cis* tetrahydropyran ring, which would be formed from **1** through ring-opening and ring-closing steps by retro-*O*-Michael reaction and *O*-Michael reaction. Based on this assumption, further efforts for the structural determination of aspergillide A are under way by the synthesis.