Tetrahedron Letters 51 (2010) 875–877

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of aspergillide A from a synthetic intermediate of aspergillide B

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ARTICLE INFO

Article history:
Received 13 November 2009
Revised 7 December 2009
Accepted 8 December 2009
Available online 11 December 2009

Keywords:
Aspergillide
Cytotoxic
Macrolide
Epimerization

ABSTRACT

The first synthesis of aspergillide A, a cytotoxin produced by a marine-derived fungus, has been achieved from a synthetic intermediate of aspergillide B by using a proline-mediated epimerization of a 2,6-trans-substituted tetrahydropyran-2-acetaldehyde intermediate into the corresponding cis-isomer via a retro-oxy-Michael/oxy-Michael sequence as the key transformation.

In the course of screening for bioactive substances from marine-derived fungi, Kusumi and co-workers isolated three cytotoxic compounds, aspergillides A–C, from a bromine-modified 1/2PD (potato-dextrose) culture medium of *Aspergillus ostianus* strain 01F313, and proposed their structures to be 14-membered macrolides **I**, **II**, and **III**, respectively, based on spectroscopic analyses including NOESY experiments and the modified Mosher method (Fig. 1).[1] The proposed structure of aspergillide C (**III**) was confirmed by our total synthesis,[2] while the stereochemical assignment of aspergillides A and B was found to be incorrect through the total synthesis of **I** and **II** by Hande and Uenishi.[3] They revealed that the physical and spectral data of their synthetic compound **I** were identical to those reported by Kusumi and co-workers for aspergillide B, and the data of synthetic **II** did not match those reported either for aspergillide A or for aspergillide B. These results enabled them to conclude that the genuine structure of aspergillide B must be **2** (Fig. 2), and the real structure of aspergillide A should be reinvestigated. Ooi and co-workers answered the question regarding the structure of aspergillide A by means of X-ray crystallographic analysis of its *m*-bromobenzaoate derivative, which clarified that aspergillide A was the C3 epimer of aspergillide B (compound **1**, Fig. 2) possessing a 3,7-cis relationship as well as 3*R* absolute configuration.[4]

Prompted by the unique molecular architecture of aspergillides A (**1**), B (**2**), and C (**III**), the latter two of which possess a very rare 2,6-trans-substituted tetrahydro- and dihydropyran structural unit, respectively, embedded in a 14-membered macrolide structure,[5] three additional syntheses of **2**[6] and an additional synthesis of **III**[7] have been published. However, no report concerning the synthesis of aspergillide A (**1**) has appeared to date. We describe herein the first synthesis of aspergillide A via a proline-mediated isomerization of a 2,6-trans-substituted tetrahydropyran-2-acetaldehyde intermediate into the corresponding cis-isomer.

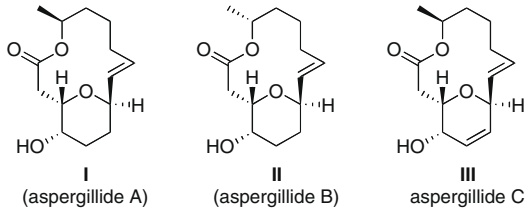

Figure 1. Originally proposed structures of aspergillides A (**I**), B (**II**), and C (**III**).

Since aspergillide A (**1**) and aspergillide B (**2**) are epimeric to each other at the alkoxy-bearing C3 position β to the lactone carbonyl, we envisaged that they might be interconvertible via a retro-oxy-Michael/oxy-Michael equilibrium sequence. Concerned about the possible formation of a γ-lactone from **2** through the intramolecular attack of the C4 hydroxyl to the carbonyl group

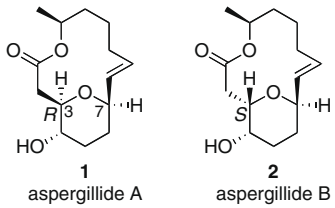

Figure 2. Revised stereochemistries of aspergillides A and B.

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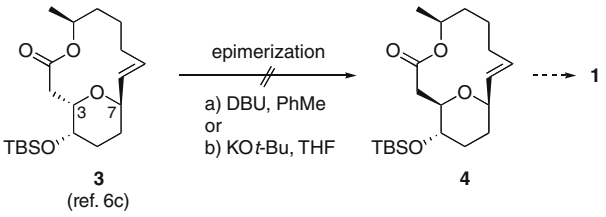
doi:10.1016/j.tetlet.2009.12.032

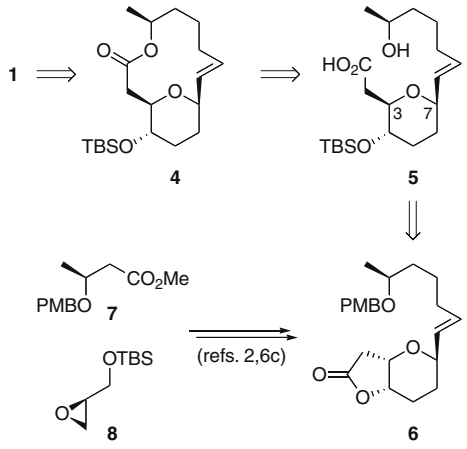


Scheme 1. Attempted epimerization of TBS-protected aspergillide B (**3**) to TBS-protected aspergillide A (**4**).

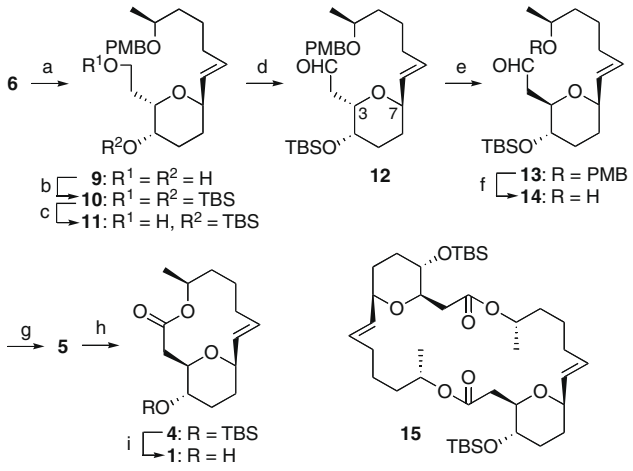
during the attempt to directly epimerize **2** into **1**, we chose the TBS-protected form of **2** (compound **3**, Scheme 1), the penultimate intermediate in Uenishi's and our syntheses of aspergillide B,[3,6c] as the substrate for the epimerization. Thus, the 3,7-trans isomer **3** was first subjected to DBU in toluene in the hope of obtaining the corresponding 3,7-cis isomer **4**, the TBS ether of **1**. The basic treatment, however, did not afford the desired product **4** even at elevated temperatures, resulting only in the recovery of the starting material **3**. The use of KO*t*-Bu as a stronger base also brought no fruitful outcome, giving only the starting material at room temperature or a complex mixture at 45 °C.[8]

Faced with the difficulty to epimerize the 3,7-trans macrolactone **3** into the corresponding cis-isomer **4**, we next planned to prepare 3,7-cis-substituted seco acid **5** beforehand and then macrolactonize it into **4** (Scheme 2). As a possible precursor of **5**, we chose 3,7-trans-substituted lactone **6** since it was known to be obtainable very efficiently from **7** and **8** in our previous synthesis of aspergillide B (**2**),[2,6c] and the requisite stereochemical inversion at the C3 position of **6** on its way to **5** was expected to be possible from literature precedents by conducting an appropriate epimerization reaction on a suitable intermediate before macrolactonization.[9]

The elaboration of **6** to **1** commenced with the reductive opening of the lactone ring of **6** with $LiAlH_4$ to give diol **9**. Protection of the two hydroxyl groups of **9** to bis-TBS ether **10** was followed by selective removal of the protecting group at the primary hydroxyl, affording **11** in 86% yield for the three steps (Scheme 3). Oxidation of the resulting alcohol with Dess–Martin's periodinane proceeded smoothly to furnish aldehyde **12**, which set the stage for the key transformation in the present synthesis, the epimerization at the C3 position of the 3,7-trans-substituted intermediate **12** to the corresponding 3,7-cis isomer **13**. The conversion of **12** into **13** was realized very efficiently by the Massi–Dondoni protocol using proline as the epimerization catalyst.[10] Thus, the treatment of **12** with D-proline for 1 h at 0 °C and for an additional 3 h at 60 °C gave a 95:5 epimeric mixture of **13** and **12** in 81% yield favoring the desired 3,7-cis isomer **13**.[11] After deprotection of the PMB group of **13** by DDQ oxidation, the resulting product **14** was oxidized to the seco acid **5** by the Pinnick oxidation. Unexpectedly, the macrolactonization of **5** into **4** was found to be problematic in contrast to the case of the corresponding 3,7-trans seco acid, which underwent smooth macrolactonization under the Yamaguchi lactonization conditions and led, after deprotection, to aspergillide B (**2**) in previous synthetic studies.[3,6c] On treatment of **5** with 2-methyl-6-nitrobenzoic anhydride in the presence of DMAP in CH_2Cl_2 at room temperature for 28 h (Shiina's method),[12] no desired product **4** was obtained, but instead dimeric macrodiolide **15** was isolated in 22% yield. Gerlach's modification of the Corey–Nicolaou macrolactonization (PySSPy, Ph_3P, $AgBF_4$, PhMe, 110 °C, 54 h)[13] and modified Mukaiyama's lactonization conditions (2-bromo-1-ethylpyridinium tetrafluoroborate, Et_3N, MeCN, 90 °C, 6 h)[14] both gave complex mixtures. The only successful result was obtained when the seco acid **5** was subjected to Yamaguchi's conditions ($Cl_3C_6H_2COCl$, Et_3N, THF, then DMAP, PhMe, 81 °C, 8 h; substrate concentration, 0.8 mM),[15] which gave the desired product **4** in 30% yield along with 19% of the dimeric product **15**.[16,17] Unfortunately, all attempts to improve the chemical yield of **4** by varying the reaction conditions (mainly, reaction temperature, and concentration) were unsuccessful and could not exceed the above-mentioned yield (30%). Finally, the TBS-protecting group of **4** was removed with TBAF to give aspergillide A (**1**) as a crystalline solid (mp 64.5–65.5 °C) after chromatographic purification. The specific rotation and spectral data of **1** were in good agreement with those reported in the literature.[1,18]



Scheme 2. Synthetic plan for aspergillide A (**1**) from known compound **6**.



Scheme 3. Conversion of **6** into aspergillide A (**1**). Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 1 h; (b) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (c) CSA (0.2 equiv), CH_2Cl_2/MeOH, 0 °C, 1 h (86%, three steps); (d) Dess–Martin's periodinane, $NaHCO_3$, CH_2Cl_2, rt, 5 h (97%); (e) D-proline (0.3 equiv), MeOH, 0 °C, 1 h, then 60 °C, 3 h (81%); (f) DDQ, phosphate buffer (pH 7.0), CH_2Cl_2, rt, 8 h (80%); (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C, 7 h (97%); (h) $Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C to rt, 2 h, then DMAP, PhMe, 80 °C, 8 h (30%); (i) TBAF, THF, rt, 2 h (76%).

In conclusion, the first synthesis of aspergillide A (**1**) was accomplished from **6**, an intermediate in our total synthesis of aspergillide B, by using the proline-mediated epimerization of the 3,7-trans-substituted cyclic intermediate **12** into the corresponding cis-isomer **13** as the key step. Efforts to develop a more efficient synthetic route to **1**, including the improvement of the macrolactonization step, are now underway and will be reported in due course.

Acknowledgments

We thank Ms. Yamada (Tohoku University) for measuring NMR and MS spectra. This work was supported, in part, by a Grant-in-

Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 19380065).

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9. For examples of related epimerization reactions, see: (a) Tatsuta, K.; Suzuki, Y.; Toriumi, T.; Furuya, Y.; Hosokawa, S. *Tetrahedron Lett.* **2007**, *48*, 8018–8021; (b) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, *61*, 11679–11685; (c) Wang, Z.; Shao, H.; Lacroix, E.; Wu, S.-H.; Jennings, H. J.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105; (d) Shao, H.; Wang, Z.; Lacroix, E.; Wu, S.-H.; Jennings, H. J.; Zou, W. *J. Am Chem. Soc.* **2002**, *124*, 2130–2131; (e) Michelet, V.; Adiey, K.; Bulic, B.; Genêt, J.-P.; Dujardin, G.; Rossignol, S.; Brown, E.; Toupet, L. *Eur. J. Org. Chem.* **1999**, 2885–2892.
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18. *Physical and spectral data for* **1**: mp 64.5–65.5 °C; $[\alpha]_D^{23}$ −59 (*c* 0.13, $CHCl_3$)(lit.[1] $[\alpha]_D^{27}$ −59.5 (*c* 0.45, $CHCl_3$); IR: *ν* 3495 (m), 1735 (s), 1665 (w), 1011 (s), 976 (s); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.21 (3H, d, *J* = 6.8 Hz), 1.38–1.44 (1H, m), 1.48–1.57 (2H, m), 1.70–1.76 (1H, m), 1.79–1.87 (1H, m), 1.89–1.99 (2H, m), 2.08–2.17 (1H, m), 2.17–2.26 (2H, m), 2.28–2.34 (1H, m), 2.40 (1H, dd, *J* = 15.6, 4.4 Hz), 2.65 (1H, dd, *J* = 15.6, 13.2 Hz), 3.59 (1H, br s), 4.23–4.29 (1H, m), 4.27 (1H, br s), 4.93–5.00 (1H, m), 5.72 (1H, ddd, *J* = 15.1, 9.3, 3.4 Hz), 5.81 (1H, ddd, *J* = 15.1, 8.8, 2.0 Hz); ^{13}C NMR (125 MHz) *δ* 18.6, 21.7, 22.0, 23.7, 31.1, 32.2, 40.5, 66.8, 71.2, 71.5, 74.0, 132.1, 137.1, 170.0; HRMS (EI) *m*/*z* calcd for $C_{14}H_{22}O_4$ (M^+) 252.1518, found 252.1522.