ORGANIC LETTERS

2009
Vol. 11, No. 3
761−764

Enantioselective Total Synthesis of Aspergillide C

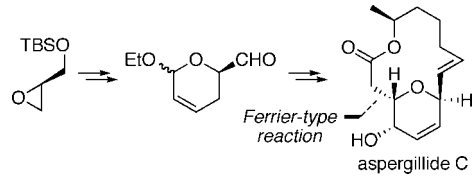
Tomohiro Nagasawa and Shigefumi Kuwahara*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

skuwahar@biochem.tohoku.ac.jp

Received December 4, 2008

ABSTRACT



The first enantioselective total synthesis of aspergillide C, a cytotoxic 14-membered macrolide isolated from the marine-derived fungus *Aspergillus ostianus*, has been accomplished from a commercially available chiral glycidol derivative by a 12-step sequence involving an expeditious preparation of a cyclic acetal intermediate and a trans-selective Ferrier-type two-carbon homologation reaction.

Aspergillides A−C 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 found to exhibit significant cytotoxicity against mouse lymphocytic leukemica cells (L1210) with LD_{50} values of 2.1, 71.0, and 2.0 μg/mL, respectively.[1] Based on spectroscopic analyses including NOESY experiments and the modified Mosher methodology, they proposed structures **1**, **2**, and **3** for aspergillides A, B, and C, respectively (Figure 1). The molecular architectures

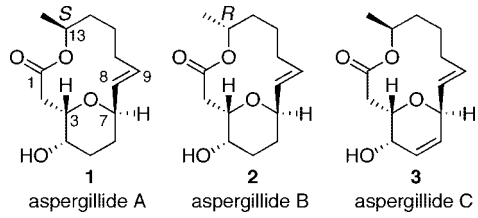


Figure 1. Structures of aspergillides A−C proposed by Kusumi et al.

of aspergillides A−C immediately captured our interest, since the 14-membered macrolide structures incorporating a 2,6-trans-substituted tetrahydro- or dihydropyran ring were totally unprecedented in natural products.[2,3] Quite recently, Uenishi and co-workers achieved the first total synthesis of the proposed structures of aspergillides A and B (**1** and **2**, respectively) and revealed that the spectroscopic and physical data of their synthetic compound **1** matched those reported by Kusumi et al. for aspergillide B, while the data of synthetic **2** were different form those reported either for aspergillide A or for aspergillide B.[4] On the basis of these findings, Uenishi et al. concluded that the genuine structure of aspergillide B must be represented by structure **1** (13S form) and the real structure of aspergillide A should be

(1) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225–228.

(2) For the only synthesis of a non-natural 14-membered macrolide containing a 2,6-*trans*-substituted tetrahydropyran ring, see: Zacuto, M. J.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 5525–5527.

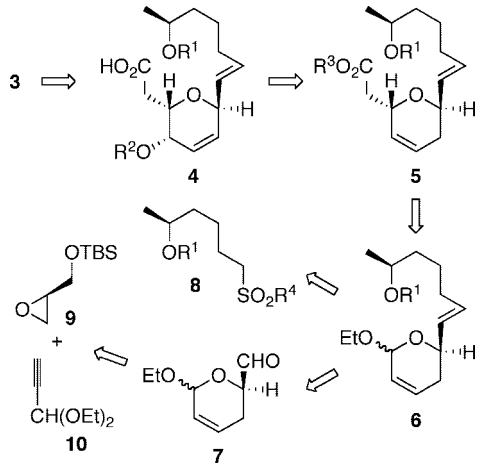
(3) For examples of natural 14-membered macrolides containing a 2,6-*cis*-substituted tetrahydropyran ring either as a hemiacetal or as a nonhemiacetal form, see: (a) Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 8956–8960. (b) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085–11088. (c) Zampella, A.; D'Auria, M. V.; Minale, L. *Tetrahedron* **1997**, *53*, 3243–3248. (d) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415. (e) Tan, L. T.; Márquez, B. L.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 925–928. (f) Luesch, H.; Yoshida, W. Y.; Harrigan, G. G.; Doom, J. P.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 1945–1948. (g) Wright, A. E.; Botelho, J. C.; Guzmán, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412–416. (h) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211–9214.

10.1021/ol802803x CCC: $40.75
Published on Web 01/07/2009

reinvestigated. Prompted by the unique structural features and significant cytotoxicity of aspergillides, we also embarked on their total synthesis. As part of our synthetic studies on aspergillides, we describe herein the first total synthesis of aspergillide C (**3**) from a commercially available glycidol derivative via 12 steps, which confirmed the structure of aspergillide C proposed by Kusumi et al.

Our retrosynthetic analysis of aspergillide C (**3**) is shown in Scheme 1. We considered that the target molecule **3** should

Scheme 1. Retrosynthetic Analysis of Aspergillide C (**3**)

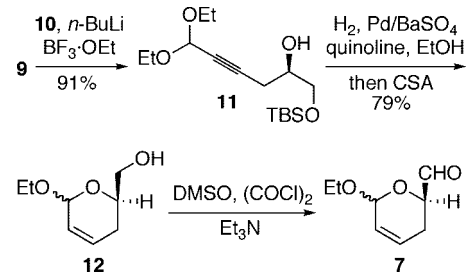


be obtained via macrolactonization of seco acid **4**, the protected allylic alcohol moiety of which in turn would be installable through halolactonization of **5** followed by dehydrohalogenation of the resulting halolactone intermediate and hydrolytic cleavage of the lactone ring. To construct the 2,6-trans-substituted dihydropyran structure in **5**, we planned to utilize a Ferrier-type reaction between cyclic acetal **6** and a silyl ketene acetal. The *E* double bond in the side chain of **6** would be formed by the Julia olefination of aldehyde **7** with sulfone **8**. The cyclic acetal **7** seemed to be readily prepared via epoxide ring-opening of commercially available epoxide **9** with known acetylenic compound **10**.

According to the synthetic plan, we began our synthesis of **3** with the preparation of the cyclic acetal **7** (Scheme 2). Exposure of the epoxide **9**[5] to the lithium acetylide generated from **10**[6] with *n*-BuLi in the presence of $BF_3{\cdot}OEt_2$ afforded **11**.[7] The acetylenic alcohol **11** was then subjected to catalytic hydrogenation conditions using Lindlar's catalyst in EtOH to semihydrogenate the triple bond. After checking the disappearance of **11** by TLC monitoring, a catalytic amount

(4) Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189–192.
(5) (a) Pospísil, J.; Markó, I. E. *Tetrahedron Lett.* **2006**, *47*, 5933–5937. (b) Jamieson, A. G.; Sutherland, A. *Org. Lett.* **2007**, *9*, 1609–1611. (c) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.
(6) Le Coq, A.; Gorgues, A. *Org. Synth.* **1980**, *59*, 10–15.
(7) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394. (b) Fernández-González, M.; Alonso, R. *J. Org. Chem.* **2006**, *71*, 6767–6775.

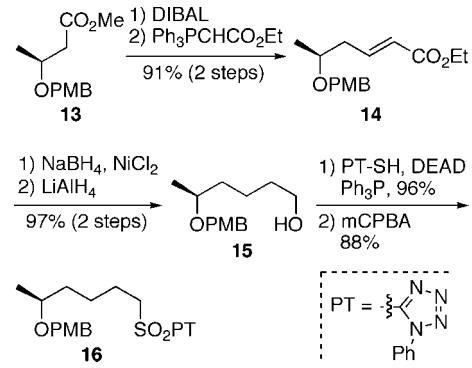
Scheme 2. Three-Step Preparation of **7**



of camphorsulfonic acid was added to the reaction mixture, which induced the formation of the 6-membered cyclic acetal ring as well as the removal of the TBS protecting group, giving a 79% yield of the desired product **12** in one pot as a 15:1 epimeric mixture with the anomerically favored α-epimer predominating.[8] Thus, the preparation of **12** was achieved in only two steps (72% yield) from the commercially available siloxy epoxide **9**.[9,10] The alcohol **12** was then oxidized smoothly to aldehyde **7**, which set the stage for chain-elongation by the Julia olefination reaction.

The preparation of sulfone segment **16** corresponding to the C9−C14 portion of aspergillide C was conducted in a straightforward manner from known ester **13**[11] via six steps (Scheme 3). Reduction of **13** with DIBAL gave an aldehyde

Scheme 3. Preparation of Sulfone Segment **16**

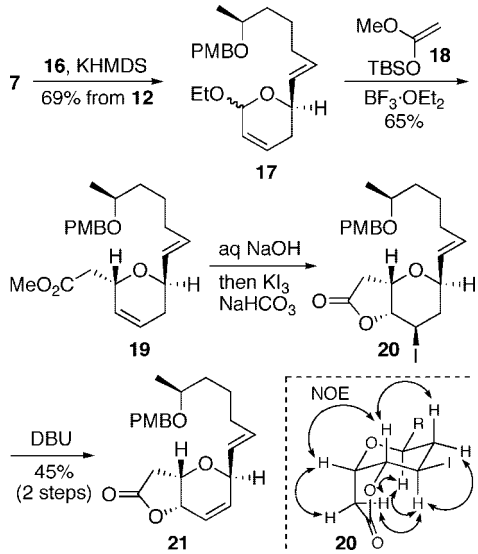


intermediate, which was then converted to unsaturated ester **14** by the Wittig reaction. Chemoselective reduction of the double bond of **13** was effected smoothly by use of $NaBH_4$/$NiCl_2$ in MeOH,[12] and the resulting ester was further reduced with $LiAlH_4$ to give alcohol **15** in excellent yield. Conversion of **15** to the Kocienski-type sulfone **16** was carried out uneventfully according to the literature procedure.[13]

(8) The stereochemical assignment to each epimer was supported by comparison of the ^{1}H NMR data of the epimeric mixture with those reported for analogous compounds: Jurczak, J.; Bauer, T. *Tetrahedron* **1986**, *42*, 5045–5052.
(9) For the preparation of the (2*S*,6*S*)-stereoisomer of **12** from tri-*O*-acetyl-D-glucal in five steps, see: Valverde, S.; Hernandez, A.; Herradon, B.; Rabanal, R. M.; Martin-Lomas, M. *Tetrahedron* **1987**, *43*, 3499–3504.

With the two segments **7** and **16** in hand, we moved on to their coupling by the Julia−Kocienski reaction and elaboration of the resulting product to lactone intermediate **21** bearing the carbon skeleton and functionalities corresponding appropriately to those of aspergillide C (**3**) (Scheme 4). The

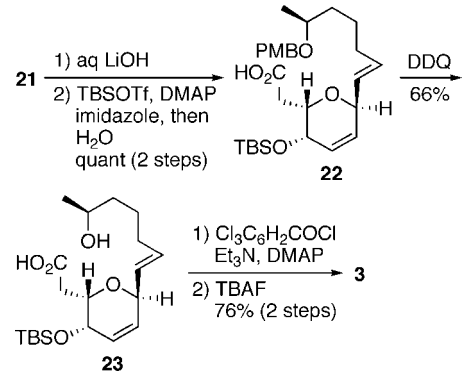
Scheme 4. Preparation of Lactone Intermediate **21**



coupling of **7** and **16** was conducted by exposing **7** to the potassium anion generated from **16** according to Kocienski's procedure to afford **17** as a 10:1 *E*/*Z* mixture favoring the desired *E* isomer.[13] Installation of an acetate unit at the anomeric position of **17** was effected by the Ferrier-type reaction using silyl ketene acetal **18**[14] in the presence of BF_3•OEt_2 in CH_3CN,[15] delivering the desired trans-substituted ester **19** and its cis isomer in isolated yields of 65% and 25%, respectively,[16] after chromatographic separation.[17] The olefinc ester **19** was hydrolyzed with an aqueous NaOH solution, and the resulting reaction mixture was directly treated with KI_3/$NaHCO_3$ to give iodolactone **20**, the stereochemistry of which was assigned from its NOE correlations (see the conformational diagram in Scheme 4). Dehydroiodination of **20** was found to be problematic due to side reactions triggered probably by deprotonation at the α-position of the lactone carbonyl (for example, retro-oxy-Michael cleavage of the dihydropyran ring).[18] In the event, this transformation was carried out using DBU in THF at room temperature to give **21** in a moderate overall yield of 45% from **19**; heating the reaction mixture led to a complex mixture of products.

Having secured the properly functionalized lactone intermediate **21**, we proceeded to the final stage of the synthesis (Scheme 5). Hydrolysis of the lactone **21** with aq LiOH (1.2

Scheme 5. Completion of the Synthesis of Aspergillide C (**3**)



equiv) in THF gave a lithium carboxylate salt, which after evaporation of the water-containing solvent under reduced pressure, was treated with 4.5 equiv of TBSOTf in DMF in presence of DMAP and imidazole.[19] TLC monitoring of the reaction indicated that both the carboxylate anion and the hydroxyl group of the carboxylate intermediate were protected smoothly to give a bis-TBS intermediate. Fortunately, addition of a small amount of water to the reaction mixture brought about selective deprotection of the TBS ester group, giving **22** in quantitative yield over the two steps. The PMB protecting group of **22** was then removed by DDQ oxidation, and the resulting seco acid **23** was subjected to the Yamaguchi lactonization conditions to furnish **3** as a white crystalline solid (mp 115.5−116 °C) after deprotection of the TBS ether group. The ^{1}H and ^{13}C NMR of **3** were identical with those reported for natural aspergillide C, and the specific rotation of **3** {$[\alpha]^{25}_D$ +83 (*c* 0.14, MeOH)} was equal in sign to that of natural aspergillide C {$[\alpha]^{25}_D$ +66.2 (*c* 0.19, MeOH)},[1]

(10) For the preparation of analogous compounds of **12** by asymmetric hetero-Diels−Alder approaches, see: (a) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820. (b) Bauer, T.; Chapuis, C.; Jezewski, A.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1391–1404. (c) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885–1893. (d) Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Tetrahedron:Asymmetry* **2004**, *15*, 3189–3194.

(11) (a) Li, S.; Xu, R.; Bai, D. *Tetrahedron Lett.* **2000**, *41*, 3463–3466. (b) Nakano, M.; Kikuchi, W.; Matsuo, J.; Mukaiyama, T. *Chem. Lett.* **2001**, 424–425. (c) Andrus, M. B.; Shih, T.-L. *J. Org. Chem.* **1996**, *61*, 8780–8785. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

(12) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817–820.

(13) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

(14) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

(15) (a) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413–9436. (b) Gaertzen, O.; Misske, A. M.; Wolbers, P.; Hoffmann, H. M. R. *Synlett* **1999**, 1041–1044. (c) Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, 2777–2785.

(16) For theoretical studies on stereoselectivity in this type of substitution reaction, see: (a) Yang, M. T.; Woerpel, K. A *J. Org. Chem.* **2009**, *74*, 545–553. (b) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907–4910.

(17) At this stage, a small amount of the *Z*-isomer of **19** originating from the 10:1 *E*/*Z* selectivity in the conversion of **7** to **17** could be removed by column chromatography.

(18) The difficulty in this dehydroiodination step would be ascribable to the fact that the *β*-elimination of **20** demands the transition state to adopt an energetically unfavorable conformation in which the iodine atom and the olefinic side chain are in a 1,3-diaxial relationship.

(19) (a) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083–6089. (b) Jayasundera, K. P.; Brodie, S. J.; Taylor, C. M. *Tetrahedron* **2007**, *63*, 10077–10082.

although the magnitude of the former was considerably larger than the latter.

In conclusion, the first total synthesis of aspergillide C (**3**) was accomplished in 7.3% overall yield from the commercially available chiral glycidol derivative **9** via 12 steps (or 7.5% from the known ester **13** through 15 steps) using the one-pot preparation of cyclic acetal **12** from acetylenic alcohol **11** and the Ferrier-type two-carbon homologation of **17** to **19** as the key transformations. The synthesis of the revised structure of aspergillide B (**1**) from the iodolactone **20** is now underway.

Acknowledgment. This work was financially supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 16380075). We also thank Ms. Yamada (Tohoku University) for measuring the NMR and mass spectra.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802803X