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A Unified Total Synthesis of Aspergillides A and B

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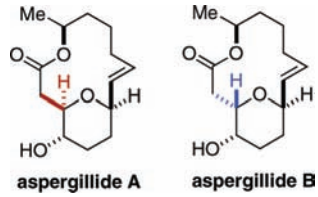
ABSTRACT



An enantioselective total synthesis of aspergillides A and B has been accomplished based on a unified strategy, wherein a hydroxy-directed, highly chemoselective olefin cross-metathesis and a diastereoselective intramolecular oxa-conjugate cyclization were employed to forge the 2,6-substituted tetrahydropyran substructure.

Aspergillides A−C were isolated from the marine fungus *Aspergillus ostianus* strain 01F313, cultured in a bromine-modified medium by Kusumi and co-workers.[1] These natural products are characterized by a 14-membered macrolactone core structure embedded with a 2,3,6-trisubstituted tetrahydropyran ring. Kusumi et al. initially proposed the structures of aspergillides A−C as **1**−**3**, respectively, on the basis of extensive NMR analysis and the modified Mosher's method (Figure 1). However, chemical synthesis of the proposed structure of **1** by the Uenishi group revealed nonidentity of synthetic **1** with natural aspergillide A.[2] Instead, the spectroscopic properties of synthetic **1** matched those of natural aspergillide B. Soon thereafter, the Kusumi group unequivocally determined the correct structure of natural aspergillides A and B to be represented by structures **4** and **1**, respectively, through X-ray crystallographic analysis.[3] The intriguing molecular structure and the cytotoxic properties of aspergillides against mouse lymphocytic leukemia cells (L1210) with LD_{50} values of 2.0−71 μg/mL have led to significant interest from synthetic chemists.[2,4−6] Herein we report our total synthesis of aspergillides A and B (i.e., (−)-**4** and (−)-**1**, respectively) based on a unified strategy.

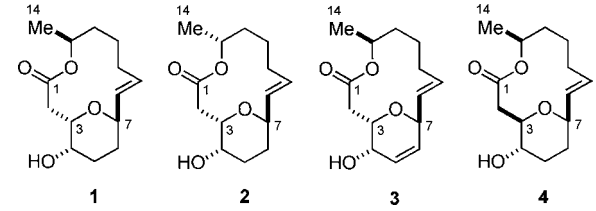


Figure 1. Proposed and corrected structures of aspergillides.

Our synthesis plan toward (−)-aspergillide A (**4**) is summarized in Scheme 1. The 14-membered macrolactone

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

(2) Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189–192.

(3) Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett.* **2009**, *38*, 384.

(4) Total synthesis of aspergillide A: (a) Nagasawa, T.; Kuwahara, S. *Tetrahedron Lett.* **2010**, *51*, 875–877. (b) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2010**, *75*, 1775–1778.

(5) Total synthesis of aspergillide B: (a) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783–3785. (b) Nagasawa, T.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1893–1894. (c) Liu, J.; Xu, K.; He, J.; Zhang, L.; Pan, X.; She, X. *J. Org. Chem.* **2009**, *74*, 5063–5066.

(6) Total synthesis of aspergillide C: Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761–764. Formal synthesis of aspergillide C: Panarese, J. D.; Waters, S. P. *Org. Lett.* **2009**, *11*, 5086–5088.

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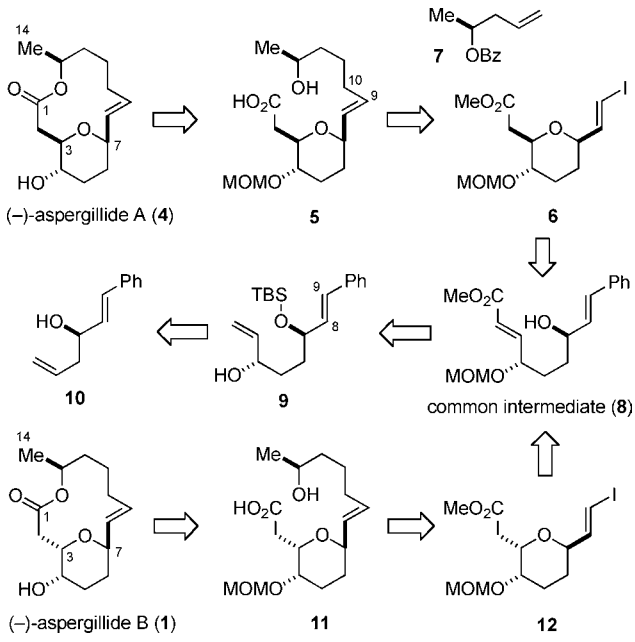
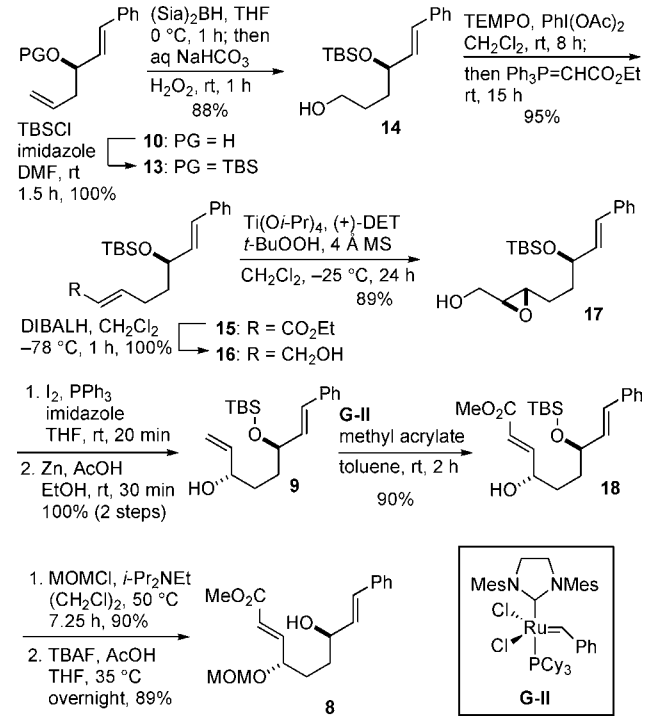
Scheme 1. Unified Synthesis Plan toward **1** and **4**



Scheme 2. Synthesis of Common Intermediate **8**



core of **4** was planned to be accessed by macrolactonization of hydroxy acid **5**. The C9−C10 bond of **5** would be formed via Suzuki−Miyaura coupling[7] of vinyl iodide **6** and an alkylborane derived from olefin **7**. We expected that the 2,6-*cis*-tetrahydropyran **6** would be efficiently constructed via an intramolecular oxa-conjugate cyclization of enoate **8** under *thermodynamic* conditions.[8] In turn, **8** was traced back to allylic alcohol **9** by planning a chemoselective olefin cross-metathesis (CM),[9] where the phenyl and silyloxy groups would reduce the reactivity of the C8−C9 double bond toward initiation of olefin cross-metathesis. We envisioned that (−)-aspergillide B (**1**) could also be synthesized according to the above synthesis plan, except that the 2,6-*trans*-tetrahydropyran subunit **12** would be derived from **8** by an intramolecular oxa-conjugate cyclization under *kinetic* conditions. Thus, both **1** and **4** were planned to be synthesized from the common intermediate **8**.[10]

The synthesis of the key intermediate **8** is illustrated in Scheme 2. The known homoallylic alcohol **10**[11] was protected with TBSCl/imidazole to give silyl ether **13** in 100% yield. Chemoselective hydroboration of the terminal olefin of **13** with disiamylborane followed by oxidative workup afforded alcohol **14** in 88% yield. TEMPO/$PhI(OAc)_2$ oxidation[12] of **14** and one-pot Wittig reaction afforded enoate **15** in 95% yield (E/Z > 20:1). DIBALH reduction of **15** gave allylic alcohol **16** in 100% yield, which was subjected to Sharpless asymmetric epoxidation using (+)-DET as a chiral auxiliary to yield epoxy alcohol **17** (89% yield). Iodination under standard conditions followed by zinc reduction of the derived iodo-epoxide afforded allylic alcohol **9** in 100% yield for the two steps. Chemoselective olefin CM of **9** with methyl acrylate under the influence of 5 mol % of the Grubbs second-generation catalyst (G-II)[13] proceeded smoothly to deliver enoate **18** in 90% yield without affecting the styrene moiety (E/Z > 20:1). No trace amount of the possible ring-closing metathesis (RCM) product was detected. The observed remarkable chemoselectivity can be ascribed to H-bonding of the allylic alcohol with the chlorine atom of the Grubbs catalyst, which results in the formation of an unfavorable conformational constraint for the RCM (Figure 2).[14] Thus, the CM of **9** would occur via the Ru-alkylidene complex **A** in an open-chain conformation, while the RCM of **9** would have to proceed via ruthenacyclobutane **B** by breaking the H-bonding within **A** and/or highly strained ruthenacyclobutane **C**. Protection of the hydroxy group within **18** (MOMCl, i-Pr_2NEt, 90% yield) and removal of

(7) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695. (d) Suzuki, A. *Chem. Commun.* **2005**, 4759–4763.

(8) For discussions on the stereochemical outcome of intramolecular oxa-conjugate addition, see: (a) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570–4583. (b) Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73–82.

(9) For a review, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.

(10) Although aspergillide A (**4**) is the C3-epimer of aspergillide B (**1**), Kusumi et al. reported that interconversion between **1** and **4** was not possible (ref 3). Accordingly, **1** and **4** have to be synthesized independently.

(11) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem.−Eur. J.* **2003**, *9*, 4405–4413.

(12) Mico, A. D.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

(13) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(14) (a) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379. (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125.

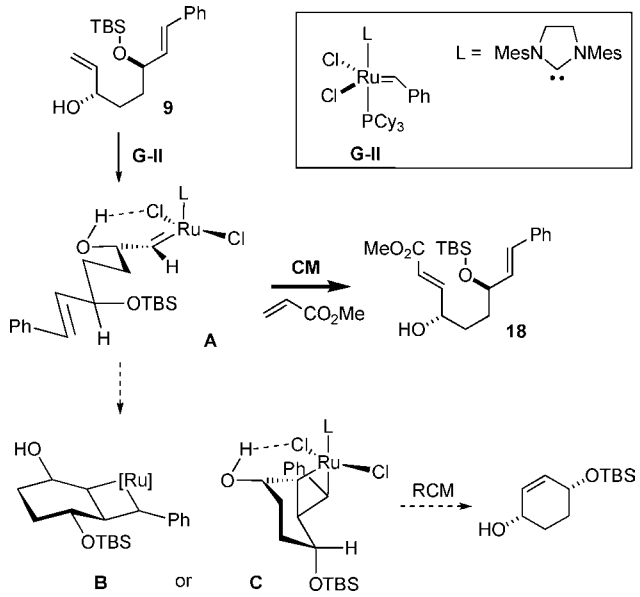
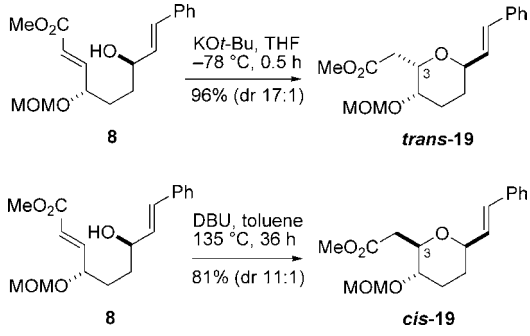


Figure 2. Plausible rationale for chemoselective CM of **9**.

the TBS group with TBAF buffered with AcOH led to enoate **8** (89% yield).

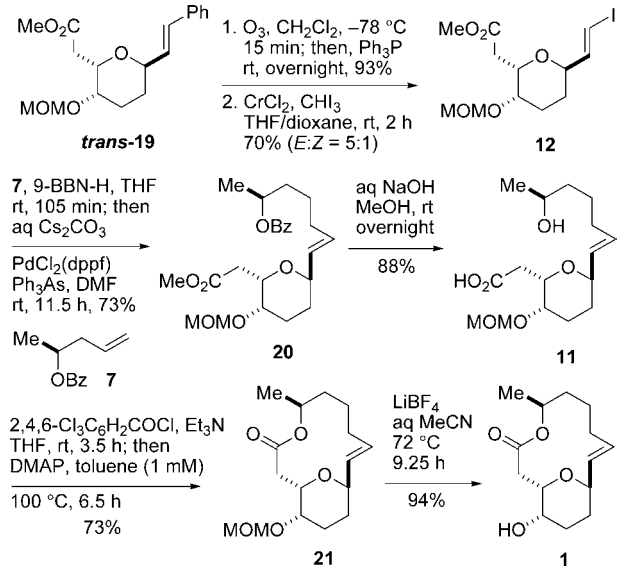
Intramolecular oxa-conjugate cyclization of **8** by exposure to KO*t*-Bu (0.05 equiv) in THF at −78 °C for 30 min gave rise to 2,6-*trans*-tetrahydropyran *trans*-**19** in 96% yield with excellent diastereoselectivity (dr = 17:1) (Scheme 3). In contrast, treatment of **8** with DBU in toluene at 135 °C afforded thermodynamically favored 2,6-*cis*-tetrahydropyran (*cis*-**19**) in 81% yield with high diastereoselectivity (dr = 11:1). The stereochemistries of *cis*-**19** and *trans*-**19** were established by NOE experiments. Thus, either *syn*-**19** or *anti*-**19** could be synthesized from **8** in a stereoselective manner simply by switching the reaction conditions.

Scheme 3. Intramolecular Oxa-Conjugate Cyclization of **8**

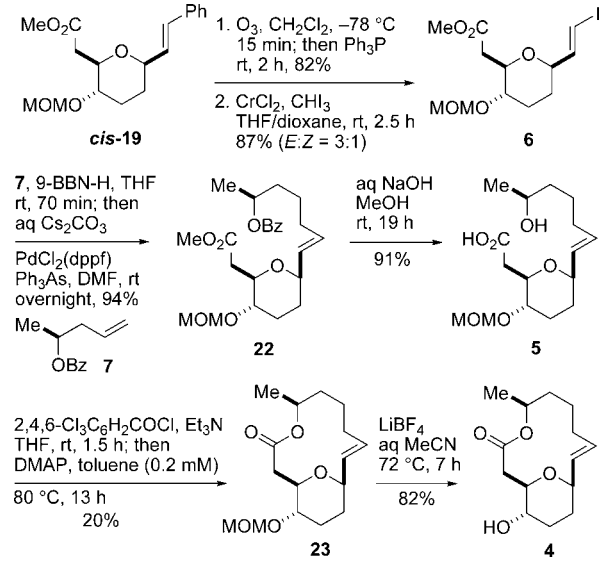


Completion of the total synthesis of (−)-aspergillide B (**1**) is illustrated in Scheme 4. Ozonolysis of the double bond of *trans*-**19** followed by Takai olefination[15] of the derived aldehyde gave (*E*)-vinyl iodide **12** as the major isomer (*E*/*Z*

Scheme 4. Total Synthesis of Aspergillide B (**1**)



Scheme 5. Total Synthesis of Aspergillide A (**4**)



= ca. 5:1) in good overall yield. The minor *Z*-isomer was removed by flash chromatography on silica gel. Suzuki−Miyaura coupling of **12** with an alkylborane, derived from olefin **7**, under the influence of the $PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$ catalyst system and aqueous Cs_2CO_3 (DMF, room temperature)[16] afforded *E*-olefin **20** in 73% yield. Hydrolysis gave hydroxy acid **11** in 88% yield, whose macrolactonization under Yamaguchi conditions[17] (2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF;

(15) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.

(16) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.

(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

then DMAP, toluene, 100 °C) successfully delivered the 14-membered macrolactone **21** in 73% yield. Finally, cleavage of the MOM group with $LiBF_4$ (aq CH_3CN, 72 °C)[5c] furnished synthetic (−)-aspergillide B (**1**) in 94% yield, whose spectroscopic properties (^1H, ^{13}C NMR, IR, HRMS) as well as specific rotation ($[\alpha]_D$) were in full accordance with those reported for natural (−)-**1**.[1]

Total synthesis of (−)-aspergillide A (**4**) was accomplished from *cis*-**19** in a similar manner to that described for (−)-**1** (Scheme 5).[18] The spectroscopic properties and specific rotation of synthetic (−)-**4** matched with those of the authentic sample.

In conclusion, we have accomplished the total synthesis of aspergillides A and B based on a unified strategy that involves (i) a hydroxy-directed, highly chemoselective olefin cross-metathesis reaction of allylic alcohol **9** and (ii) a diastereoselective intramolecular oxa-conjugate cyclization of **8** to construct either 2,6-*cis*- or 2,6-*trans*-substituted tetrahydropyran substructure.

Acknowledgment. We thank Professors Shigefumi Kuwahara (Tohoku University) and Takenori Kusumi (Tokyo Institute of Technology) for providing us with copies of ^1H and ^{13}C NMR spectra of aspergillides A and B. This work was supported in part by a Grant-in-Aid for Scientific Research from MEXT, Japan.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) It should be noted, however, that macrolactonization of **5** proved to be a difficult task, giving **23** in only 20% yield. At higher concentrations (1 mM or above), only a trace amount of **23** was formed and the major product was the corresponding dimer. The difficulty associated with the macrolactonization of **5** can be ascribed to the conformation of the 2,3,6-trisubstituted tetrahydropyran of **23**, which adopts a chair conformation with all three substituents being axially disposed (ref 3). In contrast, the tetrahydropyran of **5** is in a chair conformation with all three substituents occupying equatorial positions. Thus, it is likely that the energetically favored "all-equatorial" chair conformer of the tetrahydropyran ring of **5** would have to flip to the energetically disfavored "all-axial" chair conformer before the macrolactonization took place. To suppress the undesired dimerization, the reaction had to be performed under high-dilution conditions (0.2 mM). However, at the same time, a significant amount of **5** was decomposed under these conditions, resulting in the low yield of **23**.