Natural Product Synthesis

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Total Synthesis of Aspergillide A and B Based on the Transannular Oxy-Michael Reaction**

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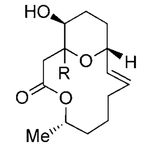
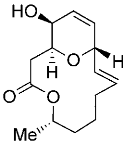
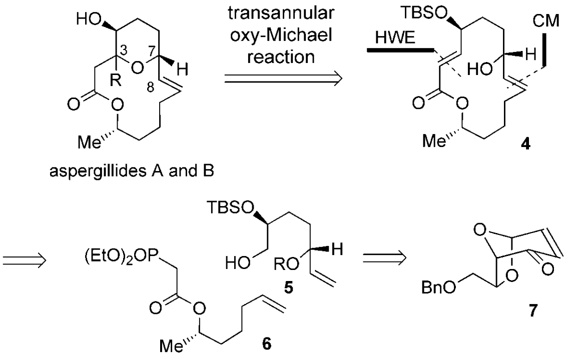
The aspergillides A, B, and C (**1**, **2**, and **3**) comprise a novel class of 14-membered macrolides that were isolated by Kusumi and co-workers from the marine-derived fungus *Aspergillus ostianus* strain 01F313 that was cultured in a medium composed of bromine-modified artificial sea water.[1] Their structures were determined by extensive spectroscopic studies, and their absolute configurations were established by X-ray crystallography (for **1** and **2**) and the modified Mosher method (for **3**).[2] These compounds contain tri-substituted tetrahydro and dihydropyran units and exhibit cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD$_{50}$ values of 2.1, 71.0, and 2.0 μg mL^{-1}, respectively. Because of their intriguing structural features and biological profile, these polyketides have attracted much attention in the synthetic community as targets for total synthesis. To date, four total syntheses of **1**,[3] six of **2**,[3c,4] and two of **3**[5] have been reported. Herein, we describe our total synthesis of the aspergillides A (**1**) and B (**2**) from a common macrolide intermediate by employing an interesting transannular oxy-Michael reaction[6] as the key step.



R=β-H: aspergillide A (**1**)
R=α-H: aspergillide B (**2**)



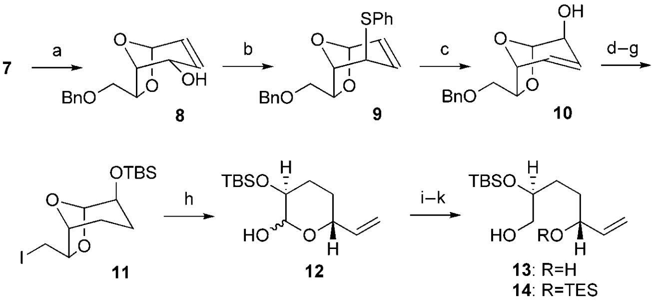
aspergillide C (**3**)



Scheme 1. Retrosynthetic analysis. Bn = benzyl, HWE = Horner–Wadsworth–Emmons, TBS = *tert*-butyldimethylsilyl.

Our strategy for the synthesis of the aspergillides A and B, illustrated in Scheme 1, proposes the formation of the trisubstituted pyran moiety through a base-mediated transannular oxy-Michael reaction from the 14-membered macrolactone **4**. It was thought that stereochemical control at the newly generated stereogenic center at C3 could be achieved by the choice of reaction conditions. The macrolactone **4** could be assembled by using a sequential cross-metathesis and intramolecular Horner–Wadsworth–Emmons reaction of the acyclic precursors **5**, which could be accessed from the chiral building block **7**[7] and compound **6**, which was known in the literature.[8] Two stereogenic centers at the future C4 and C7 positions in **5** would be created by taking advantage of the convex nature of **7**.

The optically pure enone **7** with a bicyclo[3.2.1]octane framework, prepared from 2-furfural by a six-step sequence, served as the starting material for the synthesis of the alkenyl alcohol **14** (Scheme 2). Attempted transformation of **7** into **10** using the Wharton transposition[7,9] gave unsatisfactory results (≈20% yield), prompting us to find another route. Reduction with NaBH$_4$ followed by the Hata reaction[10] of



Scheme 2. Synthesis of the alkenyl alcohol **14**. Reagents and conditions: a) NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, RT, 1 h, 98%; b) PhSSPh, *n*Bu$_3$P, pyridine, 60 °C, 16 h, 86%; c) *m*CPBA, CH$_2$Cl$_2$, −78 °C, 1.5 h; then (MeO)$_3$P, EtOH, reflux, 6 h, 71%; d) TBSCl, imidazole, DMAP, CH$_2$Cl$_2$, RT, 1 h, 94%; e) H$_2$, Pd(OH)$_2$-C, THF, 60 °C, 8 h, 99%; f) MsCl, Et$_3$N, CH$_2$Cl$_2$, RT, 1 h; g) LiI, THF, reflux, 8 h, 94% (over 2 steps); h) Zn, EtOH, reflux, 3 h, 94%; i) LiBH$_4$, THF, 0 °C, 2 h, quant.; j) PivCl, Et$_3$N; then TESCl, DMAP, CH$_2$Cl$_2$, RT, 1 h; k) LiBH$_4$, THF, 0 °C, 3 h, 96% (over 2 steps, based on recovered diol **13**). DMAP = 4-dimethylaminopyridine, *m*CPBA = *m*-chloroperoxybenzoic acid, Ms = methanesulfonyl, Piv = pivaloyl, TES = triethylsilyl, THF = tetrahydrofuran.

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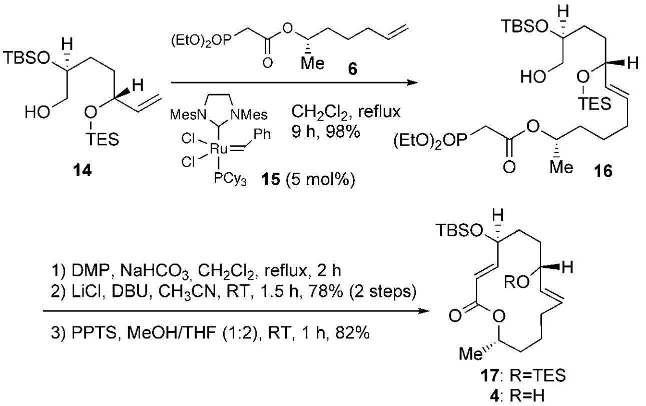
the resulting **8** produced the inverted sulfide **9**, which was treated with *m*CPBA and $(MeO)_3P$ in ethanol at reflux[11] to give the alcohol **10** in 60% yield from **7**. After protection of the alcohol moiety as the TBS ether, sequential hydrogenation, debenzylation, mesylation, and iodination gave the iodide **11**, which was reduced with zinc in ethanol at reflux to afford the hemiacetal **12** in good overall yield as a 1.5:1 mixture of diastereoisomers at the acetal carbon atom. Reduction with $LiBH_4$ gave the diol **13**, the primary and the secondary alcohols of which were sequentially protected as the pivalate and the TES ether, respectively. The pivalate was reduced with $LiBH_4$ to give the alkenyl alcohol **14**.

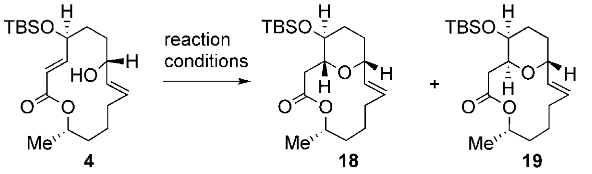
Cross-metathesis[12] of **14** with the phosphonoacetate **6**,[8] prepared from (*R*)-2-methyloxirane through a two-step sequence, in the presence the second-generation Grubbs catalyst (5 mol%) in methylene chloride at reflux provided the coupled product as the *E* alkene (>20:1) in 98% yield (Scheme 3). Oxidation of **16** with Dess–Martin periodinane and a subsequent intramolecular Horner–Wadsworth–Emmons reaction[13] gave the macrolactone **17** in 78% yield over the two steps. Selective removal of the TES ether was realized by treatment with PPTS to afford the requisite **4**, a substrate ready for the transannular cyclization.



Scheme 3. Synthesis of the macrolactone **4**. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMP = Dess–Martin periodinane, PPTS = pyridinium 4-toluenesulfonate.

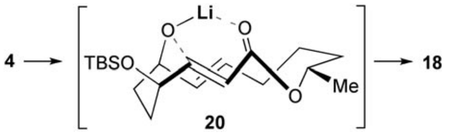
With the macrolactone in hand, we next investigated the crucial transannular oxy-Michael reaction (Table 1). Treatment of **4** with DBU in acetonitrile at reflux provided in 50% yield a 1:6 mixture of the cyclized *syn*- and *anti*-pyrans **18** and **19**, which were separable by column chromatography (entry 1). When LiCl was used with DBU, the reaction proceeded faster, and the cycloadduct was obtained quantitatively and with 7:1 *syn* selectivity (entry 2). Encouraged by this result, we next proceeded to examine more closely the reaction conditions. It turned out that the best result was obtained by treatment of **4** with DBU and LiCl in acetonitrile at room temperature for 1.5 hours, and provided a quantitative amount of the *syn*-adduct **18** as a single product (entry 3). This result can be explained by invoking the lithium-chelated transition-state **20**, in which the conformation is quite similar to the crystal structure[2] of aspergillide A, as shown in Scheme 4. From these results it was thought that the *anti*-isomer **19** might be the thermodynamic product. Consequently, for the selective formation of **19**, we examined the reaction under the conditions described in entry 1. Prolonged reaction times did not result in increased yields of the desired *anti* adduct; rather decomposition was observed. Treatment of **4** with KH in THF at 0 °C for 0.5 hours produced the pyrans in a ratio of 1.6:1 in 90% yield (entry 4). However, prolonged exposure (2 h) of **4** to the same reaction conditions resulted in the exclusive formation of **19** in comparable yield (entry 5). It was also determined that the reaction could be accelerated (≈0.5 h) by the addition of [18]crown-6 to give the *anti*-adduct **19** in 96% yield (entry 6). Thus, we have demonstrated that the diastereoselectivity of the addition could be altered completely by changing the reaction conditions.

Table 1: Transannular oxy-Michael reaction of **4**.



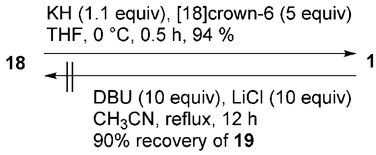
Entry	Reaction conditions	Yield [%][a]	18/19
1	DBU (10 equiv), CH_3CN, reflux, 10 h	50	1:6
2	DBU (10 equiv), LiCl (10 equiv) CH_3CN, reflux, 2 h	quant.	7:1
3	DBU (10 equiv), LiCl (10 equiv), CH_3CN, RT, 1.5 h	quant.	1:0
4	KH (1.1 equiv), THF, 0 °C, 0.5 h	90	1.6:1
5	KH (1.1 equiv), THF, 0 °C, 2 h	91	0:1
6	KH (1.1 equiv), [18]crown-6 (5 equiv), THF, 0 °C, 0.5 h	96	0:1

[a] Yield of isolated product.



Scheme 4. Transition state for the conversion of **4** into **18**.

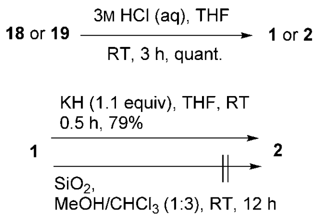
To prove the thermodynamic preference, interconversion between **18** and **19** was attempted (Scheme 5). Exposure of the *syn*-adduct **18** to the conditions shown in entry 6 provided the *anti*-isomer **19** in 94% yield;[14] on the other hand, treatment of **19** under the conditions of entry 2 for 12 hours



Scheme 5. Attempted interconversion.

resulted in 90 % recovery of the starting material. From these results, the *anti*-isomer **19** was found to be thermodynamically favored.

Both macrocyclic pyrans **18** and **19** were independently treated with acidic conditions (3 M aqueous HCl in THF at room temperature for 3 h) to give quantitatively the aspergillides A (**1**) and B (**2**), which were spectroscopically identical to the natural products (Scheme 6 and the Supporting Information). Furthermore, the attempted conversion of natural aspergillide A into aspergillide B under the same conditions as for **18** was also successful. In addition, exposure of **1** to the isolation conditions (SiO$_2$ in MeOH/CHCl$_3$ (1:3) at room temperature) did not produce **2** at all, which indicated that aspergillide B is not an artifact.



Scheme 6. Completion of the total syntheses and attempted conversions.

In summary, the total synthesis of the aspergillides A and B has been accomplished in a longest linear sequence of 17 steps in 30 % and 28 % yield, respectively, from readily accessible bicyclic chiral building blocks. The unique features of this work include the first application of a highly efficient and diastereoselective transannular oxy-Michael reaction for the construction of the *syn* and *anti* tetrahydropyrans, which are the penultimate intermediates for the natural products. From a common 14-membered macrolactone, this synthesis is the first demonstration of the successful conversion of the *syn* pyran into the *anti* isomer, including the conversion of the natural aspergillide A into aspergillide B by employing basic conditions for a short period of time. The transannular oxy-Michael strategy developed here would be applicable to the synthesis of other related natural products.

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