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Total synthesis of (+)-aspergillide C

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ABSTRACT

The enantioselective total synthesis of aspergillide C, a member of a novel class of 14-membered macrolides isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313, has been accomplished employing a highly diastereoselective intramolecular oxy-Michael reaction as the key step.

Aspergillide C[1] (**1**), along with aspergillides A (**2**) and B (**3**),[1,2] has been isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313, cultured in a medium composed of bromine-modified artificial sea water, by Kusumi and co-workers. Its structure was determined on the basis of extensive spectroscopic studies and its absolute configuration was assigned by the modified Mosher method and chemical conversion. The key structural feature of the molecule is a novel 14-membered macrolide in which a 2,6-*anti*-dihydropyran moiety, having three stereogenic centers, is incorporated. The aspergillides A–C showed cytotoxicity against mouse lymphocytic leukemia cells (L1210), the most potent activity being found in aspergillide C (**1**) with an LD_{50} value of 2.0 μg/mL. These intriguing chemical structures, combined with their promising biological profiles, have made the aspergillides attractive synthetic targets. To date, four total syntheses of **2**[3] and six of **3**[3c,4] have been reported; however, only two reports on aspergillide C[5] have been published. We report here the total synthesis of (+)-aspergillide C (**1**) employing as the key step a highly diastereoselective intramolecular oxy-Michael (IMOM) reaction of the substrate with a *cis*-epoxide,[6] which may play a key role not only in the stereochemical control during the cycloaddition but also in the further transformation to the allylic alcohol moiety on the pyran ring (Fig. 1).

Our retrosynthetic analysis of aspergillide C is shown in Scheme 1. We envisaged the macrolactonization being achieved in the last stage of the synthesis. The seco acid would be derived from **4**, the IMOM adduct of the hydroxy enoate **5** which can be prepared from *R*-(−)-benzyl glycidyl ether (**6**), via a sequential C8 olefination, transformation of the epoxide to the allyl alcohol, and standard functionalization. From an examination of molecular models, it was thought that the *Z*-enoate (*Z* in **5**) might produce the *syn*-adduct preferentially in the key IMOM reaction; therefore, in order to obtain the requisite *anti*-adduct, we chose the *E*-enoate **5** as the substrate (Scheme 1).

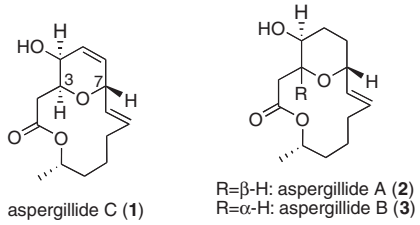
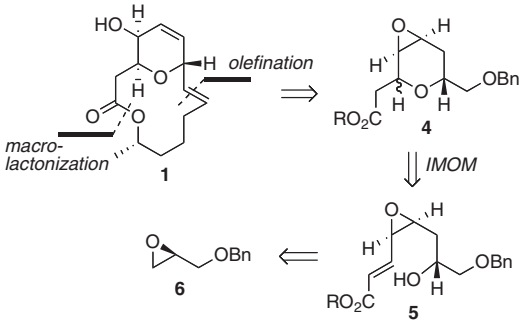


Figure 1.



Scheme 1. Retrosynthetic analysis of aspegillide C.

The substrate **10** for the IMOM reaction was synthesized as shown in Scheme 2. The diene **7**, prepared from *R*-(−)-benzyl glycidyl ether (**6**) via a two-step sequence, was treated with 0.5 mol % of the Grubbs' 2nd generation catalyst in refluxing CH_2Cl_2[7] to give lactone **8**.[8] Diastereoselective epoxidation[9] followed by DIBAL-H reduction and Horner–Wadsworth–Emmons reaction of **9** provided *E*-hydroxy enoate **10** in 64% yield for the six steps (Scheme 2).

The key IMOM reaction of **10** was examined and the results are shown in Table 1. Treatment of a solution of **10** in THF with KH at

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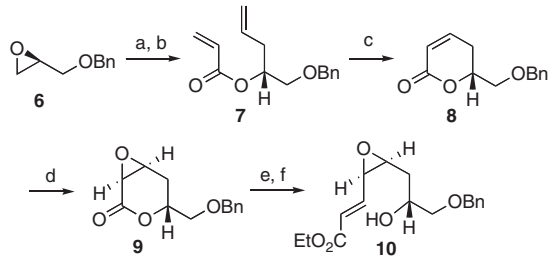
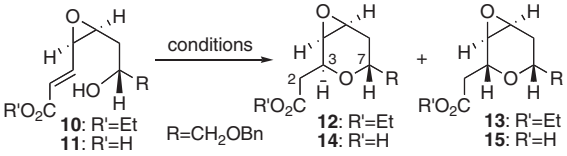


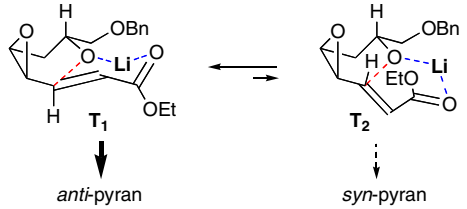
Scheme 2. Synthesis of hydroxy enoate **10**. Reagents and conditions: (a) vinylmagnesium chloride, CuI (0.1 equiv), THF, 0 °C, 1 h; (b) acryloyl chloride, EtMgBr, THF, rt, 1.5 h, quant (2 steps); (c) Grubbs' 2nd cat. (0.5 mol %), CH_2Cl_2, reflux, 6 h, 96%; (d) H_2O_2 (30% aq), NaOH (aq), MeOH, 0 °C, 1 min, 74%; (e) DIBAL-H, toluene, −78 °C, 1 h; (f) $(EtO)_2POCH_2CO_2Et$, DBU, NaI, THF, −40 °C, 1 h, 90% (2 steps).

Table 1
IMOM reaction of **10**



Entry	Conditions	Yield (%)	Product ratio
1	KH (1.3 equiv), THF, −78 °C, 3 h	74	**12**/**13** = 1.3:1
2	NaHMDS (1.3 equiv), THF, −60 °C, 0.5 h	48	**12**/**13** = 1.3:1
3	LiHMDS (1.3 equiv), THF, −50 °C, 3 h	13	**12**/**13** = 2.5:1
4	LiOH·H_2O (2 equiv), THF/H_2O = 3:1, rt, 12 h	94	**14**
5	NaOH (2 equiv), THF/H_2O = 3:1, rt, 9 h	79[a]	**14**/**15** = 6.1:1[b]
6	KOH (2 equiv), THF/H_2O = 3:1, rt, 11 h	85[a]	**14**/**15** = 6.3:1[b]

[a] The uncyclized carboxylic acid **11** was obtained in 8% (entry 4) and 10% (entry 5) yield, respectively.
[b] The ratio was determined by ^{1}H NMR.



Scheme 3. Transition state for the IMOM reaction.

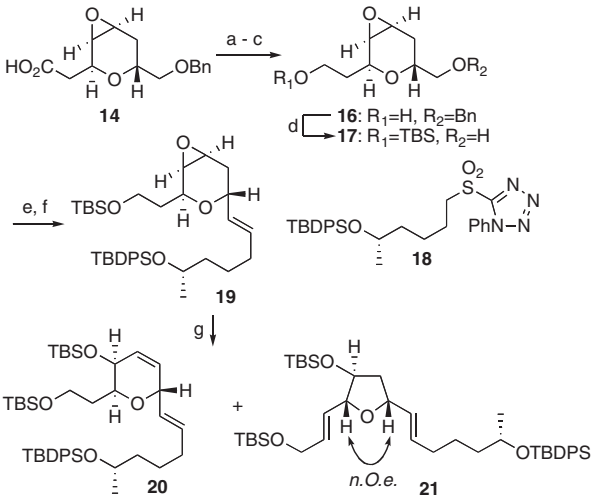
−78 °C for 3 h produced the cycloadduct as a separable 1.3:1 mixture of *anti* **12** and *syn* **13** pyran isomers in 74% yield (entry 1). When the reaction was conducted in the presence of NaHMDS and LiHMDS as bases, the yields obtained were poorer (entries 2 and 3).[10]

Since the use of LiHMDS resulted in a slight increase in the formation of the requisite *anti*-pyran **12**, we focused our attention on lithium bases for the cycloaddition. After numerous attempts, we isolated pyran carboxylic acid **14** with the *anti*-configuration as a single product in 94% yield after conducting the reaction with LiOH·H_2O in THF/H_2O (3:1) at room temperature. To compare the effect of counter cation, we examined the reaction using NaOH and KOH as bases under the similar conditions (entries 5 and 6). Both cases resulted in the formation of a diastereomeric mixture of the carboxylic acids (**14** and **15**) in slightly lower yields and diastereoselectivities along with a small amount of the uncyclized carboxylic acid **11**.[11] It was found that addition of water was essential for acceleration of the reaction and for obtaining the *anti*-adduct with higher yield and diastereoselectivity, however, the role of it remains unclear (Table 1).

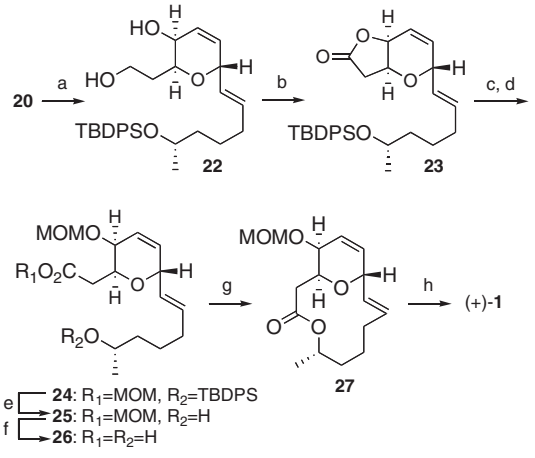
In the cases of entries 4–6, the formation of **12** can be monitored by TLC analysis. In addition, treatment of carboxylic acid **11**, prepared from **10**, with the conditions of entries 4 provided a trace amount of the cyclized product **14**. These indicated that the IMOM reaction would proceed before hydrolysis of the ester moiety. As a possible mechanism, the high *anti*-selectivity of the cycloaddition (Table 1, entry 4) can be explained by comparing the two possible lithium-chelated transition states T_1 and T_2, in which the less strained six-membered chair-like transition state T_1 might predominate, and the *anti*-pyran would be generated as the sole product (Scheme 3). The stereochemistry in **14** was established by the diagnostic ^{1}H–1H NOE between the C2 and C7 protons and by the vicinal coupling constant ($J_{3,4}$ = 3.8 Hz).

With the desired *anti*-pyran **14** in hand, we next examined its conversion to the dihydropyran **20**. Reduction of the carboxylic acid followed by silylation of the resulting primary alcohol moiety in **16** and debenzylation gave **17**. IBX oxidation[12] gave the aldehyde, which was subjected to Kocienski-Julia olefination[13] with **18**[4d] in the presence of LiHMDS to provide **19** as *E*-olefin (>10:1). Various conditions for the direct conversion of the epoxide to allylic alcohol in **19** were examined (LDA, $LiNEt_2$;[14] LiTMP, Et_2AlCl;[15] $Al(O^iPr)_3$;[16] etc.), but none provided the desired product. The conversion was successfully achieved by treatment of **19** with TBSOTf, Hunig's base, and DBU[17] to give the desired dihydropyran **20** in 51% yield, accompanied by 20% of the chromatographically separable rearranged product **21**. The *syn*-stereochemistry on the tetrahydrofuran ring of **21** was confirmed by NOE experiments (Scheme 4).

Selective deprotection of the two TBS ethers in **20** followed by oxidation of the primary alcohol moiety with catalytic TEMPO and $PhI(OAc)_2$ provided lactone **23**. Standard functional group transformations of **23** via a four-step sequence of reactions produced hydroxy acid **26**, which was exposed to Yamaguchi macrolactonization conditions to give lactone **27**. Finally, acidic hydrolysis produced aspergillide C (**1**), {$[\alpha]_D^{28}$ = +77.5(*c* 0.11, MeOH); lit.[1] $[\alpha]_D^{25}$ = +66.2 (*c* 0.19, MeOH); lit.[5a] $[\alpha]_D^{25}$ = +83 (*c* 0.14,



Scheme 4. Synthesis of **20**. Reagents and conditions: (a) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C, 15 min; (b) $NaBH_4$, EtOH, 0 °C, 2 h, 87% from **10**; (c) TBSOTf, DBU, CH_2Cl_2, −78 °C, 2 min, 95%; (d) $Pd(OH)_2$–C, EtOH, cyclohexene, 60 °C, 24 h, 94%; (e) IBX, *t*BuOH, 60 °C, 1 h; (f) **18**, LiHMDS, DMF/HMPA (4:1), rt, 1 h, 54% (2 steps); (g) TBSOTf, iPr_2NEt then DBU, benzene, rt, 2 h, 51% for **20**, 20% for **21**.



Scheme 5. Synthesis of (+)-**1**. Reagents and conditions: (a) 3 M HCl, THF, rt, 2 h, 90%; (b) TEMPO (10 mol %), $PhI(OAc)_2$, CH_2Cl_2, rt, 1.5 h, 93%; (c) $LiOH{\cdot}H_2O$, THF/H_2O (1:1), rt, 3 h; (d) MOMCl, iPr_2NEt, CH_2Cl_2, 0 °C, 2 h, 90% (2 steps); (e) HF·pyridine, THF/pyridine (1:1), 0 °C, 8 h, 90%; (f) $LiOH{\cdot}H_2O$, THF/H_2O (1:1), rt, 3 h; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 2 h then 4-DMAP, toluene, 80 °C, 5 h (76%, 2 steps); (h) 6 M HCl, THF, rt, 3 h, 49%.

MeOH)}, the spectroscopic properties of which matched those reported for the natural product (Scheme 5).

In summary, we have completed an enantioselective total synthesis of (+)-aspergillide C (**1**) using an efficient and highly diastereoselective IMOM reaction of the substrate with a *cis*-epoxide and an *E*-enoate as the key step. It was found that addition of water is important in promoting the IMOM reaction and providing higher yield and diastereoselectivity. In addition, we demonstrated that a *cis*-epoxide on the pyran ring can play a key role in assembling the hydroxy dihydropyran moiety of the natural product. Our synthetic studies described here may contribute to the synthesis of other related natural products.

Acknowledgments

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