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An enantioselective total synthesis of aspergillides A and B

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ABSTRACT

An enantioselective total synthesis of aspergillides A and B has been accomplished on the basis of a unified synthetic strategy that exploits stereodivergent intramolecular oxa-conjugate cyclization and Yamaguchi macrolactonization.

1. Introduction

Kusumi and co-workers have recently reported the isolation and structure characterization of aspergillides A–C.[1] These naturally occurring substances are the secondary metabolites of the marine fungus *Aspergillus ostianus* strain 01F313, cultured in a bromine-modified medium. On the basis of extensive 2D NMR studies and application of the modified Mosher's method, the initially proposed structures of aspergillides A–C were represented by **1**–**3**, respectively (Fig. 1). However, total synthesis of the proposed structure **1** of aspergillide A by Hande and Uenishi disclosed non-identity of the synthetic material with natural aspergillide A.[2] They instead revealed that the spectroscopic properties of synthetic **1** matched exactly those of natural aspergillide B. Thus, the structure of aspergillide A once again fell into the mystery. On the other hand, the absolute stereostructure of aspergillide C (**3**) was unambiguously confirmed by a total synthesis by Nagasawa and Kuwahara.[3] Finally, the Kusumi group unequivocally established the structures of aspergillides A and B to be represented by **4** and **1**, respectively, through X-ray crystallographic analysis of the corresponding 3-bromobenzoate derivatives.[4] The molecular architecture of aspergillides A (**4**) and B (**1**) is characterized by a 14-membered macrolactone embedded with a tetrahydropyran ring. Aspergillide B (**1**) has a 2,6-*trans*-substituted tetrahydropyran ring, which is a quite rare structure in natural products. Moreover, as evident from the X-ray crystallographic analysis by Kusumi and co-workers, the tetrahydropyran ring of these natural products is in an axial-rich chair conformation presumably due to the constraint of the macrocyclic framework. Although aspergillide A (**4**) is the C3-epimer of aspergillide B (**1**), Kusumi and co-workers reported that interconversion between **1** and **4** was not possible.[4] These unique structural aspects combined with the cytotoxic activity against mouse lymphocytic leukemia cells (L1210) with LD_{50} values of 2.0–71 μg/mL render these naturally occurring substances intriguing targets for the synthetic community.[5–7] Herein, we describe in detail our enantioselective total synthesis of aspergillides A and B on the basis of a unified synthetic strategy that exploits stereodivergent intramolecular oxa-conjugate cyclization and Yamaguchi lactonization.[8]

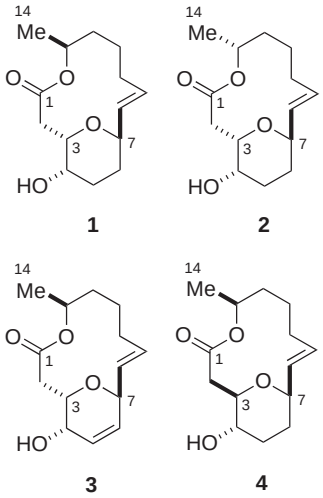

Figure 1. Proposed and correct structures of aspergillides A–C.

2. Results and discussion

2.1. Synthesis plan

Olefin metathesis reaction has emerged as a powerful and versatile tool for the synthesis of macrocycles.[9] There are an increasing number of total syntheses of macrolide natural products, which relied on esterification/ring-closing metathesis (RCM) strategy.[10] In

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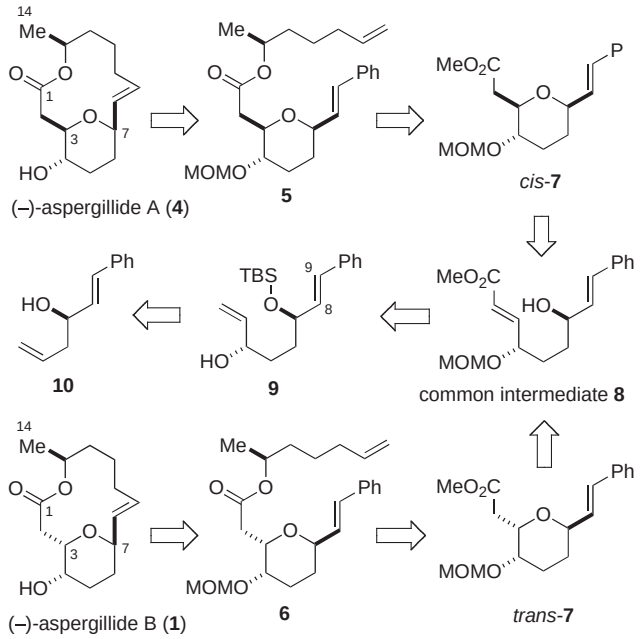
view of the structural resemblance, we planned a unified total synthesis of aspergillides A (**4**) and B (**1**), as summarized in Scheme 1. We envisioned that the 14-membered macrocyclic framework of **4** and **1** could be forged via RCM of dienes **5** and **6**, respectively. The dienes **5** and **6** would in turn be synthesized from the respective tetrahydropyrans *cis*-**7** and *trans*-**7** through esterification. We planned to construct the tetrahydropyrans *cis*-**7** and *trans*-**7** from a common precursor **8** by means of stereodivergent intramolecular oxa-conjugate cyclization.[11,12] Specifically, we expected that energetically more favored *cis*-**7** would be obtained under thermodynamic conditions, while *trans*-**7** would be selectively produced under kinetic conditions.[11] Enoate **8** would be derived from allylic alcohol **9** via chemoselective olefin cross-metathesis (CM),[13] where the C9 phenyl and C7 silyloxy groups would reduce the reactivity of the C8–C9 double bond toward initiation of olefin metathesis.[14] Finally, allylic alcohol **9** could be traced back to homoallylic alcohol **10**.[15]



Scheme 1. Synthesis plan toward aspergillides A and B.

2.2. Synthesis of common intermediate 8

Our synthesis started with silylation of the known homoallylic alcohol **10**, available in one step from (*E*)-cinnamaldehyde via asymmetric allylation,[15] giving silyl ether **11** in quantitative yield (Scheme 2). Chemoselective hydroboration of **11** with disiamylborane followed by oxidative workup delivered alcohol **12**. One-pot oxidation/Wittig homologation of **12** (TEMPO, $PhI(OAc)_2$[16] then $Ph_3P{=}CHCO_2Et$) afforded enoate **13** in high yield and stereoselectivity (95% yield, *E*/*Z*>20:1), which was reduced with DIBALH to afford allylic alcohol **14**. Asymmetric epoxidation of **14** using (+)-diethyl tartrate (DET) as a chiral auxiliary produced epoxy alcohol **15** (89%) as a single diastereomer (judged by 600 MHz ^{1}H NMR). Iodination of **15** followed by zinc reduction cleanly gave secondary allylic alcohol **9** quantitatively. Upon treatment of **9** with methyl acrylate in the presence of 5 mol % of the Grubbs second-generation catalyst (**G-II**)[17] in toluene at room temperature, olefin CM reaction proceeded cleanly to afford enoate **16** in 90% yield as a sole isolable product. It is of particular interest that the possible RCM reaction to yield the corresponding cyclohexene derivative did not take place at all. The plausible rationale for this intriguing reactivity of **9** is summarized in Figure 2. According to the early report

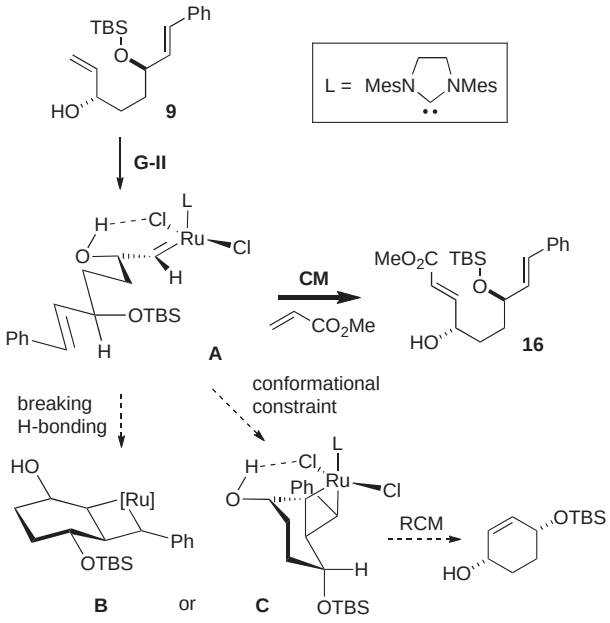
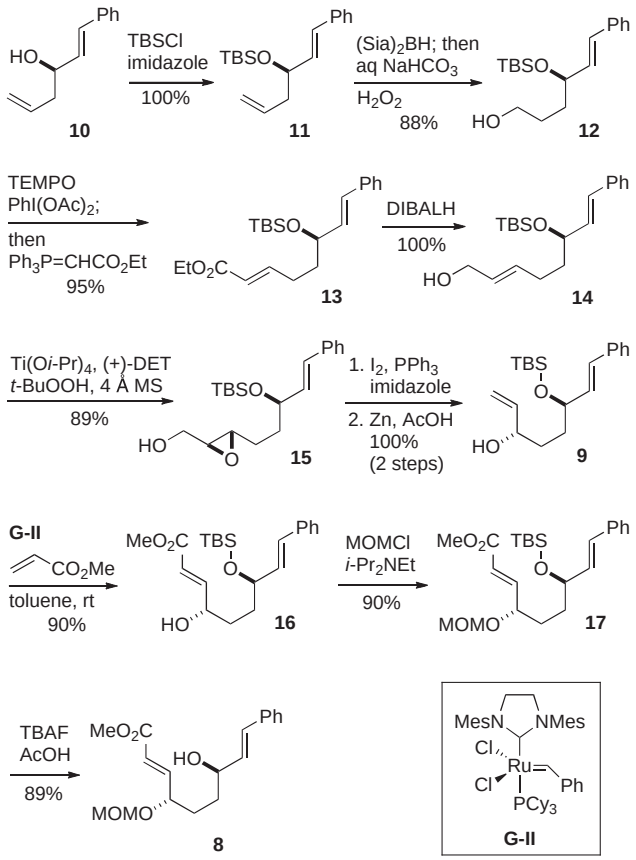


Figure 2. Plausible rationale for chemoselective olefin CM.

by Hoye and Zhao[18] and the recent disclosure from the Hoveyda group,[19] reaction of allylic alcohol **9** with **G-II** catalyst would generate ruthenium alkylidene complex **A**, wherein an H-bonding between the hydroxy group and one of the two chlorine atoms of **G-II** is formed. We envision that this H-bonding would act as a conformational constraint that renders the possible RCM pathway unfavorable. Thus, the CM reaction of **9** would proceed via the ruthenium alkylidene complex **A** in a usual manner, while the ring-closing metathesis of **9** would have to take place via ruthenacyclobutane **B** by breaking the H-bonding and/or highly strained ruthenacyclobutane **C**. Thus, RCM would be energetically less favored than CM in the present case.[20] Protection of enoate **16** as its MOM ether proceeded in 90% yield. Subsequent desilylation using TBAF buffered with AcOH afforded hydroxy enoate **8**, the common intermediate, in 89% yield.

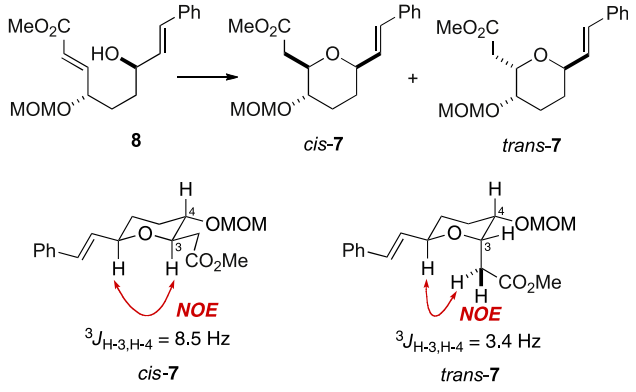
2.3. Intramolecular oxa-conjugate cyclization of 8

With the common intermediate **8** available in a gram-scale, we focused our attention to stereodivergent intramolecular oxa-conjugate cyclization (Table 1). It was quickly revealed that the formation of 2,6-*trans*-tetrahydropyran *trans*-**7** could be efficiently achieved in a highly stereoselective manner. Thus, exposure of **8** to 0.05 equiv of KO*t*-Bu in THF at −78 °C for 30 min furnished *trans*-**7** in 96% yield with an approximately 17:1 diastereoselectivity. In contrast, stereoselective synthesis of 2,6-*cis*-tetrahydropyran *cis*-**7** (entry 1) proved to be difficult than anticipated. In principle, the energetically more favored *cis*-**7** could be produced provided that an efficient thermodynamic equilibration between *cis*-**7** and *trans*-**7** exists. We initially thought that such equilibrium would be possible simply by elevating the reaction temperature. However, we were surprised to find that running the reaction at 0 °C for 2 h only gave a 2.5:1 mixture of *trans*-**7** and *cis*-**7** (entry 2). Extending the reaction time did not improve the stereochemical outcome, and elevating the reaction temperature above 0 °C resulted in low mass recovery due to degradation of the material. Reacting **8** with NaH (1.5 equiv) in THF at room temperature for 2 h gave a 1.4:1 mixture of *trans*-**7** and *cis*-**7** in 98% yield (entry 3), and decomposition of the material was observed on forcing the reaction conditions (e.g., extended reaction times and/or raising the reaction temperature above room temperature). Treatment of **8** with DBU (0.3 equiv) in



Scheme 2. Synthesis of common intermediate **8**.

Table 1
Screening of the reaction conditions[a]



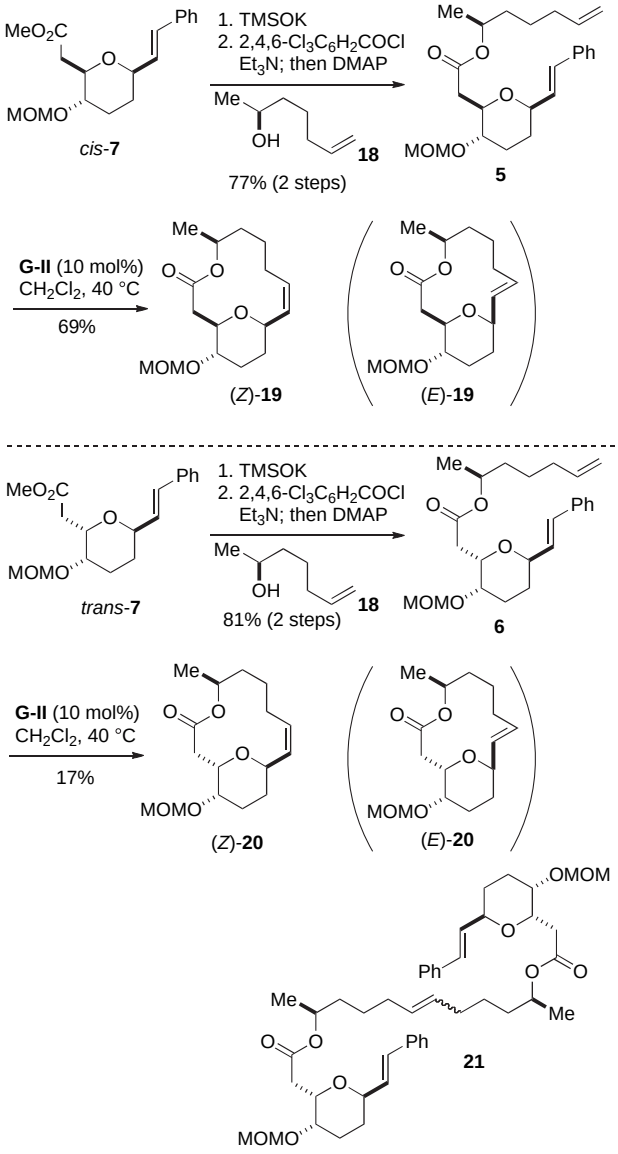
Entry	Reagents and conditions	Yield (%)[a]	*cis*-**7**/*trans*-**7**[b]
1	KO*t*-Bu (0.05 equiv), THF, −78 °C, 30 min	96	1:17
2	KO*t*-Bu (0.2 equiv), THF, 0 °C, 2 h	89	1:2.5
3	NaH (1.5 equiv), THF, room temperature, 2 h	98	1:1.4
4	DBU (0.3 equiv), CH_2Cl_2, room temperature, 99 h	93	1:1.4
5[c]	DBU (10 equiv), toluene, 100 °C, 54 h	85	7:1
6[c]	DBU (10 equiv), toluene, 135 °C, 36 h	81	11:1

[a] Isolated yield of a purified mixture of *cis*-**7** and *trans*-**7**.
[b] The diastereomer ratio was determined on the basis of ^{1}H NMR analysis (500 MHz, $CDCl_3$) on crude reaction mixture.
[c] Performed in a sealed tube.

CH_2Cl_2 at room temperature also resulted in an unsatisfactory diastereoselectivity (entry 4). In contrast to the recent report from the Murga/Marco group,[5b] after several experiments, we were delighted to find that DBU efficiently converted *trans*-**7** into *cis*-**7** under forcing conditions without a sign of material decomposition. Thus, exposure of **8** to DBU (10 equiv) in toluene at 100 °C (sealed tube) afforded *cis*-**7** in 85% yield with 7:1 diastereoselectivity. This result indicated that sufficient thermodynamic equilibration between *cis*-**7** and *trans*-**7** could be achieved under these conditions (entry 5). Further improvement was possible by running the reaction at 135 °C in a sealed tube, giving rise to *cis*-**7** in 81% yield with diastereomer ratio of 11:1 (entry 6). Fortunately, *cis*-**7** and *trans*-**7** could be easily separated by flash chromatography on silica gel. Thus, stereodivergent synthesis of 2,6-*cis*- and 2,6-*trans*-substituted tetrahydropyrans, *cis*-**7** and *trans*-**7**, respectively, from the common intermediate **8** was realized simply by switching the reaction conditions. The stereochemistry of *cis*-**7** and *trans*-**7** was unequivocally established by NOE experiments as shown.

2.4. Construction of the 14-membered macrocyclic framework by esterification/RCM strategy

With both *cis*-**7** and *trans*-**7** in hand, we proceeded to construct the macrocyclic framework of aspergillides A and B (Scheme 3). Saponification of *cis*-**7** with potassium trimethylsilanolate (TMSOK)[21] followed by coupling of the derived carboxylic acid with



Scheme 3. RCM of dienes **5** and **6**.

alcohol **18**[22] under Yamaguchi conditions[23] gave diene **5** in 77% yield for the two steps. RCM of **5** took place smoothly by the action of 10 mol % of **G-II** catalyst in CH_2Cl_2 at 40 °C. However, (*Z*)-isomer (*Z*)-**19** was exclusively isolated in 69% yield; no trace amount of the desired (*E*)-**19** was detected. A similar result was obtained when the reaction was carried out in toluene at 70 °C.[5b,24] On the other hand, RCM of diene **6**, similarly prepared from *trans*-**7**, also produced (*Z*)-isomer (*Z*)-**20** in low yield (17%), along with several unidentified products. Changing the solvent to toluene did not improve the result, and the use of the Grubbs first-generation catalyst (**G-I**)[25] only provided dimer **21** in 23% yield (38% based on recovered **6**).

Here, we attempted to account for the outcome of the RCM of diene **5** on the basis of conformational analysis by NOE experiments and theoretical calculations.[26] First, the conformational property of diene **5** and macrolactone (*Z*)-**19** was analyzed on the basis of NOE experiments. As illustrated in Figure 3, it was found that both of the tetrahydropyran rings of **5** and (*Z*)-**19** exist in a stable chair conformation with all the substituents being equatorially disposed (i.e., 'equatorial-rich' chair conformer), suggesting that the conformation of the tetrahydropyran did not change during the RCM process. In contrast, according to the X-ray crystallographic analysis by Kusumi and co-workers, the tetrahydropyran ring of aspergillide A (**4**) is in a chair conformation, where all of the substituents are axially oriented (i.e., 'axial-rich' chair conformer). Molecular modeling by conformational searches (MMFF) and geometry optimization (HF/6-31G*//PM3) suggested that the tetrahydropyran ring of (*E*)-**19** adopts essentially the same conformation as that of **4**, possibly because of the constraint of the macrocycle (Fig. 4). Thus, it is likely that the configuration of the C8–C9 double bond plays a critical role in defining the conformation of the tetrahydropyran ring of (*E*)-**19** and (*Z*)-**19**, and vice versa. The formation of (*Z*)-**19** would be preferred under kinetic conditions, because the pathway to (*E*)-**19** should suffer from an energetic penalty arising from conformational flipping of the tetrahydropyran ring (i.e., 'equatorial-rich' chair conformer→'axial-rich' chair conformer). In addition, (*Z*)-**19** would be also thermodynamically more favored than (*E*)-**19** because repulsive interactions between the substituents on the tetrahydropyran are present within (*E*)-19,[25] and this is also supported by calculations at HF/6-31G*//PM3 level, which indicated that (*Z*)-**19** is considerably more stable than (*E*)-**19** (ΔE=13.0 kcal/mol). Thus, the kinetic product (*Z*)-**19** would not isomerize to (*E*)-**19** under the reaction conditions.

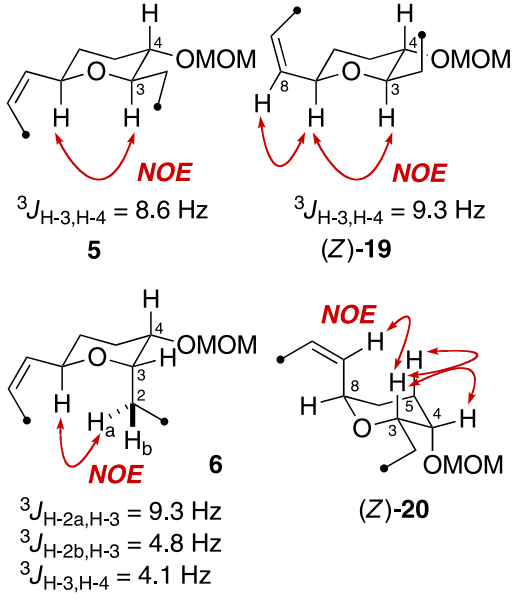


Figure 3. Conformations of the tetrahydropyran rings of **5**, **6**, (*Z*)-**19**, and (*Z*)-**20**.

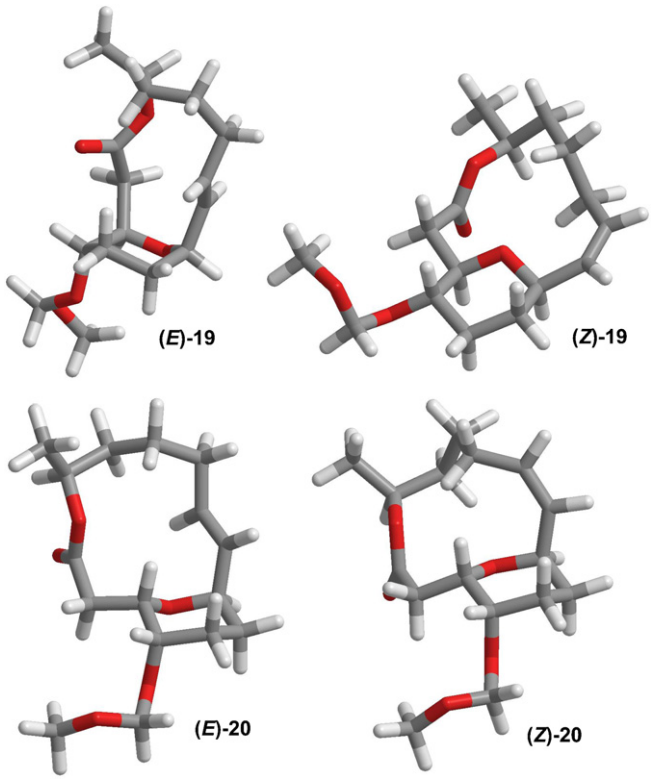
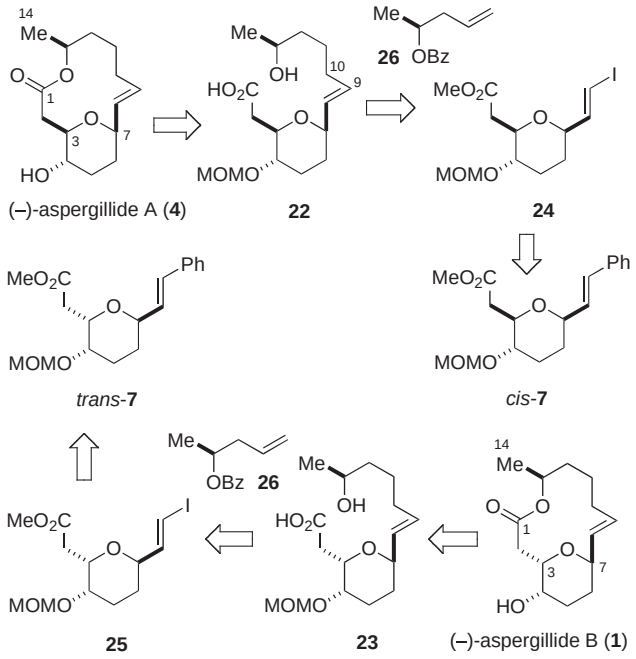


Figure 4. Geometrically optimized structures of (*E*)-**19**, (*Z*)-**19**, (*E*)-**20**, and (*Z*)-**20** at HF/6-31G*//PM3 level of theory.

We have also investigated the conformation of diene **6** and macrolactones (*E*)-**20** and (*Z*)-**20**. On the basis of $^3J_{H,H}$ values and an NOE experiment, the tetrahydropyran ring of **6** would be in a chair conformation with the C4 and C7 substituents being equatorially oriented (i.e., 'equatorial-rich' chair conformer). By contrast, NOE experiments on macrolactone (*Z*)-**20** showed that the tetrahydropyran ring of (*Z*)-**20** adopts a chair conformation with the C4 and C7 substituents being axially disposed (i.e., 'axial-rich' chair conformer), presumably due to the macrocyclic constraint. Thus, the tetrahydropyran ring of diene **6** would have to flip to 'axial-rich' chair conformer during the RCM process, which makes the RCM of **6** difficult to achieve and may account for the low yield of (*Z*)-**20**. Interestingly, theoretical calculations at HF/6-31G*//PM3 level revealed that (*E*)-**20** is energetically more stable than (*Z*)-**20** (ΔE=13.0 kcal/mol) (Fig. 4). The preferential formation of energetically less stable (*Z*)-**20** suggests that the RCM of **6** proceeded under kinetic control. We think that isomerization of (*Z*)-**20** to the energetically more stable (*E*)-isomer was retarded presumably because the C8–C9 double bond is sterically encumbered and could not react with ruthenium methylidene complex, an active propagation catalyst of RCM.

2.5. Completion of the total synthesis of aspergillides A and B by Suzuki–Miyaura coupling/macrolactonization strategy

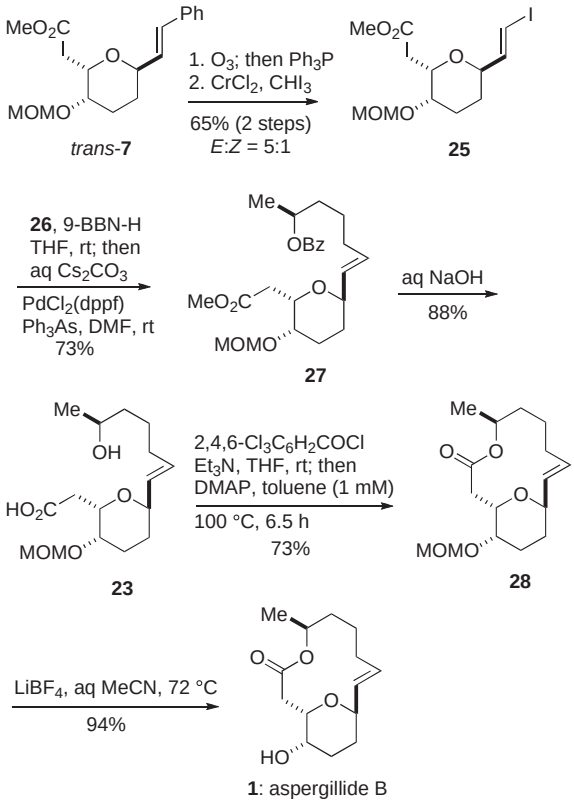
Based on the disappointing results of the RCM of dienes **5** and **6**, we envisaged that a prerequisite for the success of the total synthesis of aspergillides A and B would be the formation of the C8–C9 double bond with correct configuration prior to the construction of the macrocyclic framework. Accordingly, we thought that it would be possible to construct the macrocycle via macrolactonization (Scheme 4). Thus, **4** and **1** would be synthesized from *cis*-**7** and *trans*-**7**, respectively, via the formation of the C9–C10 double bond



Scheme 4. Revised synthesis plan for aspergillides A and B.

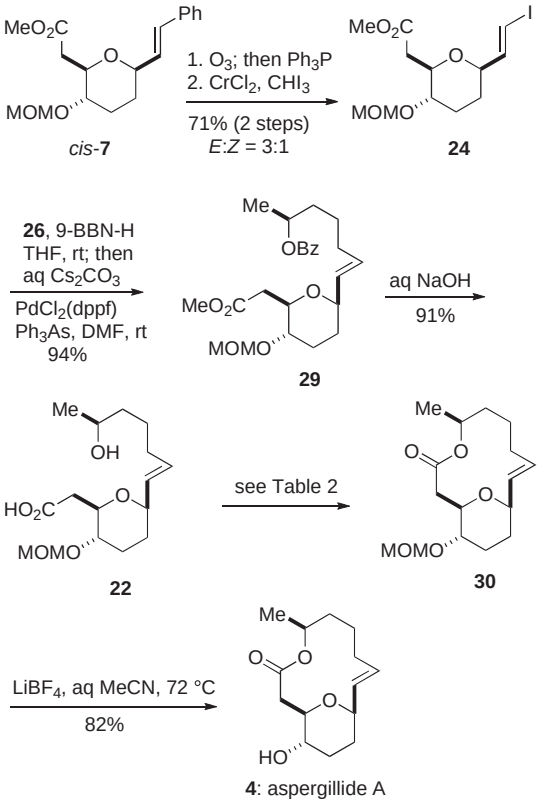
by means of Suzuki–Miyaura coupling[27] and subsequent macrolactonization to forge the whole framework (i.e., Suzuki–Miyaura coupling/macrolactonization strategy).

Completion of the total synthesis of aspergillide B (**1**) is summarized in Scheme 5. Ozonolysis of the double bond of *trans*-**7** followed by Takai olefination ($CrCl_2$, CHI_3, THF/1,4-dioxane, rt)[28] gave (*E*)-vinyl iodide **25** in 65% yield (*E*/*Z*=ca. 5:1) for the two steps. Suzuki–Miyaura coupling of **25** with an alkylborane derived from olefin **26**[29] under Johnson conditions (aqueous Cs_2CO_3, $PdCl_2$(dppf), Ph_3As, THF/DMF, rt)[30] proceeded without incident to deliver *trans*-olefin **27** in 73% yield. Hydrolysis of **27** gave hydroxy acid **23** in 88% yield, which was cyclized under Yamaguchi conditions (2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt; then slow addition (6.5 h) to DMAP, toluene (1 mM), 100 °C) to provide macrolactone **28** in 73% yield. Finally, deprotection of the MOM group using $LiBF_4$ (aqueous CH_3CN, 72 °C)[6c] furnished synthetic aspergillide B (**1**), whose spectroscopic properties and optical rotation value were in full accordance with those of the natural product.



Scheme 5. Completion of the total synthesis of aspergillide B.

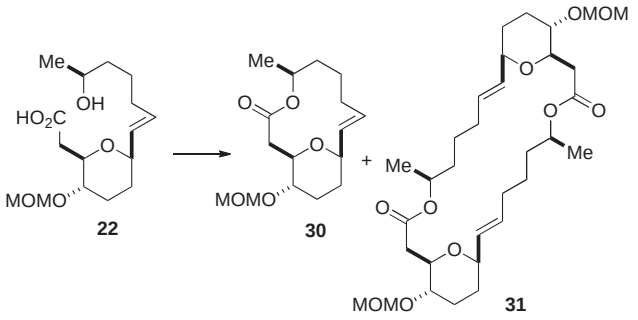
The total synthesis of aspergillide A (**4**) was similarly completed as depicted in Scheme 6. The spectroscopic data and specific rotation of synthetic **4** matched exactly those reported for the natural product. However, we found it difficult to forge the macrolactone **30**



Scheme 6. Completion of the total synthesis of aspergillides A.

due to competitive formation of dimeric product **31** and degradation of the material. We examined several reaction conditions as summarized in Table 2. Our first attempt was to perform the macrolactonization under essentially the same conditions as those used for **23** (2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, room temperature; then slow addition (5 h) to DMAP, toluene (1 mM), 100 °C), but unfortunately the only isolable product was dimer **31** (entry 1). Only a trace amount of **30** was detected by LC/MS analysis of a crude mixture. To suppress the undesired dimerization, a solution of a mixed anhydride generated in situ from hydroxy acid **22** was added slowly over a period of 8.5 h to a solution of DMAP in toluene at 100 °C, resulting in the formation of the desired lactone **30** in 12% yield, along with dimer **31** in 28% yield (entry 2). This result suggested that the macrolactonization had to be performed under high-dilution conditions (<1 mM) with careful slow addition technique. Further optimization of the reaction conditions (2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, room temperature; then slow addition (13 h) to DMAP, toluene (0.2 mM), 80 °C) improved the yield of **30** up to 20% (entry 3). However, at the same time, a significant amount of **22** was decomposed under these conditions, resulting in low mass recovery. The difficulties associated with the macrolactonization of **22** can be

Table 2
Screening of the reaction conditions of Yamaguchi macrolactonization



Entry	Reagents and Conditions	Yield (%)	
		30	**31**
1	2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, room temperature; then DMAP, toluene (1 mM), 100 °C (added over 5 h)[a]	Trace	29
2	2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, room temperature; then DMAP, toluene (0.8 mM), 100 °C (added over 8.5 h)[a]	12	28
3	2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, room temperature; then DMAP, toluene (0.2 mM), 80 °C (added over 13 h)[a]	20	Trace

[a] Syringe pump addition.

reasoned by the fact that the energetically favored 'all-equatorial' chair conformer of the tetrahydropyran ring of **22** would have to flip to the energetically disfavored 'all-axial' chair conformer during the macrolactonization process.

3. Conclusion

We have successfully completed the enantioselective total synthesis of aspergillides A and B by exploiting a unified strategy. Highly chemoselective olefin CM of secondary allylic alcohol **9** with methyl acrylate was realized by the assistance of the H-bonding formed within the ruthenium alkylidene species **A**. Stereodivergent synthesis of 2,6-*cis*- and 2,6-*trans*-substituted tetrahydropyrans (*cis*-**7** and *trans*-**7**, respectively) was achieved simply by switching the reaction conditions. Due to the unique strained molecular architecture, the esterification/RCM strategy has proven to be unsuitable for the construction of the macrocyclic framework of these natural products. The total synthesis of aspergillides A and B was eventually accomplished by exploiting Suzuki–Miyaura coupling/macrolactonization strategy.

4. Experimental section

4.1. General remarks

All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Chemical shift values of ^1H and ^{13}C NMR spectra are reported in parts per million (δ) downfield from tetramethylsilane with reference to internal residual solvent [^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0)] unless otherwise noted. Coupling constants (J) are reported in hertz (Hz). The following abbreviations were used to designate the multiplicities: s=singlet; d=doublet; t=triplet; m=multiplet; br=broad.

*4.1.1. Silyl ether **11**.* To a solution of homoallylic alcohol **10** (2.59 g, 14.9 mmol) in DMF (50 mL) were added imidazole (2.03 g, 29.8 mmol) and TBSCl (3.14 g, 20.8 mmol). The reaction mixture was stirred at room temperature for 1.5 h before the reaction was quenched with H_2O. The resultant mixture was extracted with diethyl ether, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (3% EtOAc/hexanes) gave silyl ether **11** (4.29 g, 100%) as a colorless clear oil: $[\alpha]_D^{18}$ +28.4 (*c* 1.00 in $CHCl_3$); IR (film) 2955, 2929, 2856, 1254, 1071, 966, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J*=7.8 Hz, 2H), 7.30 (dd, *J*=7.8, 7.8 Hz, 2H), 7.21 (dd, *J*=7.8, 7.8 Hz, 1H), 6.50 (d, *J*=15.6 Hz, 1H), 6.19 (dd, *J*=15.6, 6.0 Hz, 1H), 5.83 (m, 1H), 5.10–5.02 (m, 2H), 4.31 (ddd, *J*=6.0, 6.0, 6.0 Hz, 1H), 2.39–2.29 (m, 2H), 0.91 (s, 9H), 0.075 (s, 3H), 0.051 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 134.9, 132.8, 129.1, 128.5 (×2), 127.3, 126.4 (×2), 117.0, 73.3, 43.1, 25.9 (×3), 18.3, −4.3, −4.7; HRMS (ESI) calcd for $C_{18}H_{28}OSiNa$ [(M+Na)$^+$] 311.1802, found 311.1804.

*4.1.2. Alcohol **12**.* To a solution of 2-methyl-2-butene (4.10 mL, 38.7 mmol) in THF (100 mL) cooled to 0 °C was added $BH_3\cdot SMe_2$ (1.9 M solution in THF, 10.1 mL, 19.2 mmol), and the resultant solution was stirred at 0 °C for 1 h. To this solution was added a solution of silyl ether **11** (4.26 g, 14.8 mmol) in THF (20+10 mL rinse). The resultant solution was stirred at 0 °C for 1 h before it was treated with saturated aqueous $NaHCO_3$ solution (20 mL) and 30% aqueous H_2O_2 solution (10 mL). The resultant mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous Na_2SO_3, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–15% EtOAc/hexanes) gave alcohol **12** (3.98 g, 88%) as a colorless clear oil: $[\alpha]_D^{25}$ +42.2 (*c* 1.00 in $CHCl_3$); IR (film) 3349, 2952, 2928, 2884, 2856, 1254, 1058, 836, 775, 692 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J*=7.2 Hz, 2H), 7.30 (dd, *J*=7.2, 7.2 Hz, 2H), 7.21 (dd, *J*=7.2, 7.2 Hz, 1H), 6.48 (d, *J*=15.8 Hz, 1H), 6.16 (dd, *J*=15.8, 6.5 Hz, 1H), 4.35 (m, 1H), 3.68–3.59 (m, 2H), 1.87 (br m, 1H), 1.73–1.59 (m, 4H), 0.91 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 132.7, 129.4, 128.5 (×2), 127.4, 126.3 (×2), 73.3, 63.0, 34.9, 28.3, 25.9 (×3), 18.2, −4.3, −4.8; HRMS (ESI) calcd for $C_{18}H_{30}O_2SiNa$ [(M+Na)$^+$] 329.1907, found 329.1917.

*4.1.3. Enoate **13**.* To a solution of alcohol **12** (3.95 g, 12.9 mmol) in CH_2Cl_2 (100 mL) were added $PhI(OAc)_2$ (5.40 g, 16.8 mmol) and TEMPO (0.40 g, 2.6 mmol), and the resultant solution was stirred at room temperature for 8 h. To this solution was added $Ph_3P{=}CHCO_2Et$ (6.74 g, 19.3 mmol), and the resultant solution was stirred at room temperature for 15 h. The reaction mixture was diluted with EtOAc and washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution/saturated aqueous $Na_2S_2O_3$ solution, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (3% EtOAc/hexanes) gave enoate **13** (4.61 g, 95%) as a colorless clear oil: $[\alpha]_D^{28}$ +19.7 (*c* 0.40 in $CHCl_3$); IR (film) 2954, 2929, 2856, 1720, 1257, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J*=8.4 Hz, 2H), 7.30 (dd, *J*=8.4, 8.4 Hz, 2H), 7.22 (dd, *J*=8.4, 8.4 Hz, 1H), 6.97 (ddd, *J*=15.6, 6.8, 6.8 Hz, 1H), 6.48 (d, *J*=15.6 Hz, 1H), 6.12 (dd, *J*=15.6, 6.8 Hz, 1H), 5.81 (d, *J*=15.6 Hz, 1H), 4.29 (ddd, *J*=6.8, 6.8, 6.8 Hz, 1H), 4.16 (q, *J*=6.8 Hz, 2H), 2.34–2.22 (m, 2H), 1.78–1.64 (m, 2H), 1.26 (t, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 149.0, 136.9, 132.6, 129.6, 128.6 (×2), 127.5, 126.4 (×2), 121.4, 72.7, 60.1, 36.5, 27.8, 25.9 (×3), 18.2, 14.3, −4.2, −4.8; HRMS (ESI) calcd for $C_{22}H_{34}O_3SiNa$ [(M+Na)$^+$] 397.2169, found 397.2176.

*4.1.4. Allylic alcohol **14**.* To a solution of enoate **13** (4.58 g, 12.2 mmol) in CH_2Cl_2 (100 mL) cooled to −78 °C was added DIBALH (1.02 M solution in hexanes, 35.0 mL, 35.7 mmol). The resultant

solution was stirred at −78 °C for 1 h before the reaction was quenched with MeOH. The resultant mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution and stirred vigorously at room temperature until the layers became clear. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–15% EtOAc/hexanes) gave allylic alcohol **14** (4.10 g, 100%) as a colorless clear oil: $[\alpha]_D^{27}$ +24.7 (*c* 1.00 in $CHCl_3$); IR (film) 3341, 2952, 2928, 2855, 1087, 966, 835, 775, 692 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J*=7.3 Hz, 2H), 7.30 (dd, *J*=7.3, 7.3 Hz, 2H), 7.21 (dd, *J*=7.3, 7.3 Hz, 1H), 6.47 (d, *J*=15.8 Hz, 1H), 6.14 (dd, *J*=16.1, 6.5 Hz, 1H), 5.70 (m, 1H), 5.64 (m, 1H), 4.27 (ddd, *J*=6.5, 6.5, 6.5 Hz, 1H), 4.07 (dd, *J*=5.6, 5.6 Hz, 2H), 2.19–2.05 (m, 2H), 1.72–1.56 (m, 2H), 1.25 (m, 1H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 133.1, 133.0, 129.2, 129.1, 128.5 (×2), 127.3, 126.3 (×2), 73.0, 63.8, 37.7, 27.9, 25.9 (×3), 18.2, −4.2, −4.8; HRMS (ESI) calcd for $C_{20}H_{32}O_2SiNa$ [$(M+Na)^+$] 355.2064, found 355.2077.

*4.1.5. Epoxy alcohol **15**.* To a solution of allylic alcohol **14** (1.13 g, 3.40 mmol) in CH_2Cl_2 (30 mL) were added 4 Å molecular sieves (1.00 g) and (+)-DET (0.18 g, 0.87 mmol), and the resultant mixture was cooled to −25 °C. To this mixture was added Ti(O*i*-Pr)$_4$ (0.200 mL, 0.676 mmol), and the resultant mixture was stirred at −25 °C for 30 min. To this mixture was added *t*-BuOOH (5.0 M solution in isooctane, 1.40 mL, 7.00 mmol), and the resultant mixture was stirred at −25 °C for 24 h. The reaction was quenched with saturated aqueous Na_2SO_4 solution. The resultant mixture was allowed to warm to room temperature with vigorous stirring and then filtered through a pad of Celite. The filtrate was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–20% EtOAc/hexanes) gave epoxy alcohol **15** (1.05 g, 89%) as a colorless clear oil: $[\alpha]_D^{27}$ +19.9 (*c* 1.00 in $CHCl_3$); IR (film) 3419, 2953, 2928, 2856, 967, 836, 776, 692 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J*=7.2 Hz, 2H), 7.30 (dd, *J*=7.2, 7.2 Hz, 2H), 7.21 (dd, *J*=7.2, 7.2 Hz, 1H), 6.48 (d, *J*=15.8 Hz, 1H), 6.13 (dd, *J*=15.8, 6.2 Hz, 1H), 4.31 (m, 1H), 3.89 (ddd, *J*=12.6, 5.3, 2.6 Hz, 1H), 3.60 (ddd, *J*=12.6, 7.2, 4.8 Hz, 1H), 2.97 (m, 1H), 2.91 (m, 1H), 1.78–1.54 (m, 5H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 132.8, 129.4, 128.5 (×2), 127.4, 126.3 (×2), 73.0, 61.6, 58.4, 55.9, 34.5, 27.4, 25.9 (×3), 18.2, −4.2, −4.8; HRMS (ESI) calcd for $C_{20}H_{32}O_3SiNa$ [$(M+Na)^+$] 371.2013, found 371.2023.

*4.1.6. Allylic alcohol **9**.* To a solution of epoxy alcohol **15** (1.02 g, 2.93 mmol) in THF (25 mL) were added imidazole (0.40 g, 5.9 mmol), Ph_3P (1.15 g, 4.38 mmol), and I_2 (1.12 g, 4.41 mmol). The reaction mixture was stirred at room temperature for 20 min before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution. The resultant mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude iodo-epoxide was used in the next reaction without further purification.

To a solution of the above iodo-epoxide in EtOH (25 mL) were added zinc powder (1.92 g, 29.4 mmol) and AcOH (0.335 mL, 5.85 mmol). The reaction mixture was stirred at room temperature for 30 min before the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was filtered through a pad of Celite, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–15% EtOAc/hexanes) gave allylic alcohol **9** (0.97 g, 100% for the two steps) as a colorless clear oil: $[\alpha]_D^{28}$ +49.8 (*c* 1.00 in $CHCl_3$); IR (film) 3364, 2953, 2928, 2885, 2856, 1070, 967, 836, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J*=7.2 Hz, 2H), 7.30 (dd, *J*=7.2, 7.2 Hz, 2H), 7.21 (dd, *J*=7.2, 7.2 Hz, 1H), 6.47 (d, *J*=15.8 Hz, 1H), 6.16 (dd, *J*=15.8, 6.5 Hz, 1H), 5.85 (ddd, *J*=17.0, 10.3, 5.3 Hz, 1H), 5.21 (dd, *J*=17.0, 1.2 Hz, 1H), 5.08 (d, *J*=10.3 Hz, 1H), 4.32 (ddd, *J*=5.3, 5.3, 5.3 Hz, 1H), 4.10 (m, 1H), 2.07 (br s, 1H), 1.74–1.56 (m, 4H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 137.0, 132.8, 129.4, 128.5 (×2), 127.4, 126.4 (×2), 114.6, 73.5, 73.2, 34.3, 32.6, 25.9 (×3), 18.3, −4.3, −4.8; HRMS (ESI) calcd for $C_{20}H_{32}O_2SiNa$ [$(M+Na)^+$] 355.2064, found 355.2059.

*4.1.7. Enoate **16**.* To a solution of allylic alcohol **9** (150.2 mg, 0.4517 mmol) in toluene (4.5 mL) and methyl acrylate (2.5 mL) was added the Grubbs second-generation catalyst (14.3 mg, 0.0228 mmol). After being stirred at room temperature for 2 h, the reaction mixture was exposed to air for 1.5 h, treated with Et_3N (10 drops), and then filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–20% EtOAc/hexanes) gave enoate **16** (158.7 mg, 90%) as a colorless oil: $[\alpha]_D^{28}$ +55.2 (*c* 1.00 in $CHCl_3$); IR (film) 3444, 2952, 2928, 2856, 1725, 1256, 1070, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.32–7.27 (m, 2H), 7.22 (m, 1H), 6.93 (dd, *J*=15.5, 4.5 Hz, 1H), 6.47 (d, *J*=16.0 Hz, 1H), 6.14 (dd, *J*=15.5, 6.0 Hz, 1H), 6.06 (dd, *J*=16.0, 1.0 Hz, 1H), 4.40–4.28 (m, 2H), 3.72 (s, 3H), 2.68 (br d, *J*=3.5 Hz, 1H), 1.80–1.58 (m, 4H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 150.4, 136.7, 132.2, 129.8, 128.6 (×2), 127.5, 126.4 (×2), 119.7, 73.4, 71.0, 51.6, 34.2, 32.0, 25.9 (×3), 18.3, −4.3, −4.8; HRMS (ESI) calcd for $C_{22}H_{34}O_4SiNa$ [$(M+Na)^+$] 413.2119, found 413.2128.

*4.1.8. MOM ether **17**.* To a solution of enoate **16** (146.5 mg, 0.3751 mmol) in $ClCH_2CH_2Cl$ (5 mL) were added *i*-Pr_2NEt (1.29 mL, 7.50 mmol) and MOMCl (0.285 mL, 3.75 mmol), and the resultant solution was stirred at 50 °C for 7.25 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed successively with H_2O, 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (3–10% EtOAc/hexanes) gave MOM ether **17** (147.0 mg, 90%) as a colorless clear oil: $[\alpha]_D^{26}$ +1.3 (*c* 1.0 in CH_2Cl_2); IR (film) 2952, 2929, 2887, 2856, 1728, 1257, 1037, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.32–7.27 (m, 2H), 7.21 (m, 1H), 6.80 (dd, *J*=15.5, 6.5 Hz, 1H), 6.46 (d, *J*=15.5 Hz, 1H), 6.12 (dd, *J*=16.0, 7.0 Hz, 1H), 5.97 (dd, *J*=16.0, 1.0 Hz, 1H), 4.60 (d, *J*=6.5 Hz, 1H), 4.56 (d, *J*=6.5 Hz, 1H), 4.27 (m, 1H), 4.20 (m, 1H), 3.72 (s, 3H), 3.34 (s, 3H), 1.77–1.52 (m, 4H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 148.1, 136.9, 132.9, 129.3, 128.5 (×2), 127.4, 126.4 (×2), 121.5, 94.6, 75.2, 73.3, 55.7, 51.6, 33.7, 30.4, 25.9 (×3), 18.2, −4.2, −4.8; HRMS (ESI) calcd for $C_{24}H_{38}O_5SiNa$ [$(M+Na)^+$] 457.2381, found 457.2389.

*4.1.9. Alcohol **8**.* To a solution of MOM ether **17** (127.8 mg, 0.2940 mmol) in THF (0.5 mL) were added TBAF (1.0 M solution in THF, 4.40 mL, 4.40 mmol) and AcOH (0.265 mL, 4.63 mmol), and the resultant solution was stirred at 35 °C overnight. The reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl solution, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–30% EtOAc/hexanes) gave alcohol **8** (83.6 mg, 89%) as a colorless clear oil: $[\alpha]_D^{28}$ −35.3 (*c* 1.00 in $CHCl_3$); IR (film) 3422, 2949, 1720, 1276, 1149, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2H),

7.32–7.27 (m, 2H), 7.22 (m, 1H), 6.81 (dd, *J*=15.5, 6.5 Hz, 1H), 6.55 (d, *J*=15.5 Hz, 1H), 6.18 (dd, *J*=16.5, 7.0 Hz, 1H), 5.98 (br d, *J*=15.5 Hz, 1H), 4.62 (d, *J*=7.0 Hz, 1H), 4.58 (d, *J*=7.0 Hz, 1H), 4.30–4.22 (m, 2H), 3.72 (s, 3H), 3.36 (s, 3H), 1.94 (br s, 1H), 1.80–1.55(m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 147.8, 136.5, 132.0, 130.5, 128.6 (×2), 127.7, 126.4 (×2), 121.7, 94.7, 75.0, 72.7, 55.8, 51.7, 32.6, 30.7; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ [(M+Na)$^+$] 343.1516, found 343.1518.

*4.1.10. Tetrahydropyran trans-**7**.* To a solution of alcohol **8** (107.1 mg, 0.3343 mmol) in THF (4.5 mL) cooled to −78 °C was added dropwise a solution of KO*t*-Bu (1.9 mg, 0.017 mmol) in THF (0.3 mL). After being stirred at −78 °C for 0.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–30% EtOAc/hexanes) gave a 17:1 mixture of *trans*-**7** and *cis*-**7** (102.4 mg, 96%). Separation of these diastereomers was achieved by flash chromatography on silica gel (1% diethyl ether/benzene) to give tetrahydropyran *trans*-**7** (96.4 mg, 90%) as a colorless clear oil: $[\alpha]_D^{18}$ +3.4 (*c* 1.0 in $CHCl_3$); IR (film) 2948, 1738, 1149, 1104, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2H), 7.32–7.27 (m, 2H), 7.21 (m, 1H), 6.61 (dd, *J*=16.5, 1.5 Hz, 1H), 6.21 (dd, *J*=16.0, 4.5 Hz, 1H), 4.70 (d, *J*=7.0 Hz, 1H), 4.62 (d, *J*=7.5 Hz, 1H), 4.50 (m, 1H), 4.38 (ddd, *J*=8.0, 5.0, 3.5 Hz, 1H), 3.73–3.66 (m, 4H), 3.37 (s, 3H), 2.78 (dd, *J*=15.5, 9.0 Hz, 1H), 2.60 (dd, *J*=15.5, 5.5 Hz, 1H), 2.08 (m, 1H), 1.94–1.76 (m, 2H), 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.7, 131.4, 128.9, 128.5 (×2), 127.6, 126.4 (×2), 95.3, 71.8, 71.5, 70.3, 55.7, 51.7, 34.9, 25.9, 23.9; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ [(M+Na)$^+$] 343.1516, found 343.1518.

*4.1.11. Tetrahydropyran cis-**7**.* To a solution of **8** (61.1 mg, 0.191 mmol) in toluene (3.0 mL) placed in a tube was added DBU (0.285 mL, 1.91 mmol). The tube was sealed and heated at 135 °C for 36 h. The reaction mixture was cooled to 0 °C and neutralized with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–20% EtOAc/hexanes) gave an 11:1 mixture of *cis*-**7** and *trans*-**7** (49.7 mg, 81%) as a colorless clear oil. Further purification by flash chromatography on silica gel (1.5% diethyl ether/benzene) gave pure tetrahydropyran *cis*-**7** (42.7 mg, 70%) as a colorless clear oil: $[\alpha]_D^{24}$ +88.5 (*c* 1.00 in $CHCl_3$); IR (film) 2948, 1740, 1150, 1107, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J*=7.5 Hz, 2H), 7.27 (dd, *J*=7.5, 7.5 Hz, 2H), 7.20 (dd, *J*=7.5, 7.5 Hz, 1H), 6.53 (d, *J*=16.0 Hz, 1H), 6.15 (dd, *J*=16.0, 5.5 Hz, 1H), 4.71 (d, *J*=7.0 Hz, 1H), 4.60 (d, *J*=7.0 Hz, 1H), 4.04 (m, 1H), 3.78 (ddd, *J*=8.5, 8.5, 4.0 Hz, 1H), 3.68 (s, 3H), 3.40–3.29 (m, 4H), 2.83 (dd, *J*=15.5, 4.0 Hz, 1H), 2.51 (dd, *J*=15.5, 8.5 Hz, 1H), 2.27 (m, 1H), 1.85 (m, 1H), 1.62–1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.7, 130.3, 129.4, 128.4 (×2), 127.5, 126.4 (×2), 95.2, 77.7, 77.3, 75.2, 55.6, 51.6, 38.1, 31.1, 29.9; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ [(M+Na)$^+$] 343.1516, found 343.1519.

*4.1.12. Ester **5**.* To a solution of 2,6-*cis*-tetrahydropyran *cis*-**7** (117.6 mg, 0.3675 mmol) in THF (4 mL) was added TMSOK (141.4 mg, 1.102 mmol). The resultant mixture was stirred at room temperature for 4 h before being quenched with H_2O and acidified with 1 M aqueous HCl solution (pH=ca. 4). The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a pad of silica gel (eluted with 30–50% EtOAc/hexanes) to give a carboxylic acid (110.9 mg), which was used in the next reaction without further purification.

To a solution of the above material (110.9 mg) in THF (4 mL) cooled to 0 °C were added Et_3N (0.100 mL, 0.717 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.075 mL, 0.48 mmol). The resultant mixture was stirred at room temperature for 80 min. The solvent was removed under reduced pressure, and the residue was taken up in benzene (3 mL). To this mixture was added a solution of alcohol **18** (62.0 mg, 0.544 mmol) and DMAP (132.8 mg, 1.087 mmol) in benzene (2 mL), and the resultant mixture was stirred at room temperature for 90 min. The reaction mixture was diluted with EtOAc, washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10% EtOAc/hexanes) gave ester **5** (112.9 mg, 77% for the two steps) as a colorless oil: $[\alpha]_D^{26}$ +78.5 (*c* 0.92 in benzene); IR (film) 2937, 1732, 1451, 1377, 1298, 1191, 1107, 1038, 966, 915, 747, 695 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J*=7.2 Hz, 2H), 7.27 (dd, *J*=7.9, 7.2 Hz, 2H), 7.19 (dd, *J*=7.9, 7.9 Hz, 1H), 6.54 (d, *J*=16.1 Hz, 1H), 6.15 (dd, *J*=16.1, 5.5 Hz, 1H), 5.72 (m, 1H), 5.00–4.91 (m, 2H), 4.88 (m, 1H), 4.72 (d, *J*=6.8 Hz, 1H), 4.60 (d, *J*=6.8 Hz, 1H), 4.02 (m, 1H), 3.77 (ddd, *J*=8.6, 8.6, 3.8 Hz, 1H), 3.37 (s, 3H), 3.35 (m, 1H), 2.83 (dd, *J*=15.1, 4.1 Hz, 1H), 2.48 (dd, *J*=15.1, 8.6 Hz, 1H), 2.27 (m, 1H), 2.01–1.96 (m, 2H), 1.84 (m, 1H), 1.61–1.32 (m, 6H), 1.19 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 138.5, 136.8, 130.2, 129.5, 128.4 (×2), 127.5, 126.4 (×2), 114.6, 95.2, 77.64, 77.61, 75.2, 70.8, 55.6, 38.7, 35.4, 33.4, 31.1, 29.9, 24.6, 20.0, 14.2; HRMS (ESI) calcd for $C_{24}H_{34}O_5Na$ [(M+Na)$^+$] 425.2298, found 425.2302.

*4.1.13. (Z)-Olefin **19**.* To a solution of ester **5** (16.3 mg, 0.0405 mmol) in CH_2Cl_2 (38 mL) was added **G-II** (3.4 mg, 0.0040 mmol) in CH_2Cl_2 (2 mL), and the resultant solution was stirred at 40 °C for 20 h. After being cooled to room temperature, the resultant solution was exposed to air with stirring at room temperature for a while and then concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (4–10% EtOAc/hexanes) gave (*Z*)-olefin **19** (8.3 mg, 69%) as a colorless oil: $[\alpha]_D^{26}$ +63.4 (*c* 0.74 in benzene); IR (film) 2930, 1726, 1452, 1373, 1334, 1301, 1245, 1220, 1190, 1137, 1104, 1071, 1038, 916 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 (ddd, *J*=10.7, 5.9, 2.5 Hz, 1H), 5.16 (dd, *J*=10.7, 2.8 Hz, 1H), 5.01 (m, 1H), 4.70 (d, *J*=6.5 Hz, 1H), 4.55 (d, *J*=6.5 Hz, 1H), 4.06 (m, 1H), 3.66 (ddd, *J*=11.3, 9.3, 2.4 Hz, 1H), 3.33 (s, 3H), 3.28 (ddd, *J*=10.3, 9.7, 4.4 Hz, 1H), 2.81 (dd, *J*=12.1, 2.8 Hz, 1H), 2.31 (dd, *J*=12.1, 11.3 Hz, 1H), 2.28–2.17 (m, 2H), 1.77 (m, 1H), 1.68–1.45 (m, 6H), 1.40 (m, 1H), 1.23 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.3, 135.5, 128.1, 95.0, 79.8, 75.04, 74.97, 69.7, 55.5, 39.2, 34.5, 31.7, 30.3, 28.0, 25.9, 20.9; HRMS (ESI) calcd for $C_{16}H_{26}O_5Na$ [(M+Na)$^+$] 321.1672, found 321.1662.

*4.1.14. Ester **6**.* To a solution of 2,6-*trans*-tetrahydropyran *trans*-**7** (19.3 mg, 0.0602 mmol) in diethyl ether (1.5 mL) was added TMSOK (23.2 mg, 0.181 mmol). The resultant mixture was stirred at room temperature for 3 h before being quenched with H_2O and acidified with 1 M aqueous HCl solution (pH=ca. 2). The resultant mixture was extracted with $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a pad of silica gel (eluted with 40% EtOAc/hexanes) to give a carboxylic acid (17.8 mg), which was used in the next reaction without further purification.

To a solution of the above material (17.8 mg) in THF (1.3 mL) cooled to 0 °C were added Et_3N (0.040 mL, 0.29 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.018 mL, 0.12 mmol). The resultant mixture was stirred at room temperature for 80 min. The solvent was removed under reduced pressure, and the residue was taken up in toluene (0.8 mL). To this mixture was added a solution of alcohol **18** (21.2 mg, 0.186 mmol) and DMAP (21.3 mg, 0.174 mmol) in toluene (0.8 mL), and the resultant mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl solution and brine, dried over

Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–10% EtOAc/hexanes) gave ester **6** (19.3 mg, 81% yield for the two steps) as a colorless oil: $[\alpha]_D^{26}$ +7.5 (*c* 1.29 in benzene); IR (film) 2937, 1730, 1446, 1377, 1281, 1148, 1105, 1037, 966, 915, 748, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J*=7.2 Hz, 2H), 7.29 (dd, *J*=7.9, 7.2 Hz, 2H), 7.22 (dd, *J*=7.9, 7.9 Hz, 1H), 6.60 (dd, *J*=16.1, 1.7 Hz, 1H), 6.22 (dd, *J*=16.1, 5.2 Hz, 1H), 5.75 (m, 1H), 4.99–4.89 (m, 3H), 4.70 (d, *J*=6.9 Hz, 1H), 4.63 (d, *J*=6.9 Hz, 1H), 4.48 (m, 1H), 4.39 (ddd, *J*=9.3, 4.8, 4.1 Hz, 1H), 3.73 (m, 1H), 3.37 (s, 3H), 2.76 (dd, *J*=15.1, 9.3 Hz, 1H), 2.57 (dd, *J*=15.1, 4.8 Hz, 1H), 2.09–1.98 (m, 3H), 1.90–1.77 (m, 2H), 1.62–1.33 (m, 5H), 1.20 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 138.4, 136.8, 131.2, 129.1, 128.5 (×2), 127.5, 126.4 (×2), 114.7, 95.3, 72.0, 71.2, 71.0, 70.7, 55.7, 35.3, 35.0, 33.4, 26.5, 24.6, 24.1, 20.0; HRMS (ESI) calcd for $C_{24}H_{34}O_5Na$ [$(M+Na)^+$] 425.2298, found 425.2313.

*4.1.15. (Z)-Olefin **20**.* To a solution of ester **6** (8.1 mg, 0.020 mmol) in CH_2Cl_2 (3.5 mL) was added a solution of **G-II** (1.7 mg, 0.0020 mmol) in CH_2Cl_2 (0.5 mL), and the resultant solution was stirred at 40 °C for 9 h. The reaction mixture was exposed to air with stirring at room temperature for 1.5 h, treated with Et_3N (0.8 mL), and stirred further at room temperature for 1 h. The resultant solution was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–15% EtOAc/hexanes) gave (*Z*)-olefin **20** (1.0 mg, 17%) as a colorless oil: $[\alpha]_D^{26}$ −49.6 (*c* 0.16 in benzene); IR (film) 2926, 1730, 1449, 1371, 1277, 1192, 1148, 1098, 1035, 917 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.69 (m, 1H), 5.46 (m, 1H), 4.86 (m, 1H), 4.74 (d, *J*=6.9 Hz, 1H), 4.63 (m, 1H), 4.59 (d, *J*=6.9 Hz, 1H), 4.19 (ddd, *J*=11.7, 2.8, 1.7 Hz, 1H), 3.51 (m, 1H), 3.37 (s, 3H), 2.78 (dd, *J*=15.5, 11.7 Hz, 1H), 2.30 (dd, *J*=15.5, 2.8 Hz, 1H), 2.12 (m, 1H), 1.95–1.87 (m, 2H), 1.78 (m, 1H), 1.75–1.51 (m, 5H), 1.33 (m, 1H), 1.18 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 138.7, 128.0, 95.0, 72.4, 71.2, 69.5, 69.2, 55.8, 38.7, 32.6, 27.3, 24.5, 24.3, 23.2, 21.8; HRMS (ESI) calcd for $C_{16}H_{26}O_5Na$ [$(M+Na)^+$] 321.1672, found 321.1669.

*4.1.16. Dimer **21**.* To a solution of ester **6** (11.0 mg, 0.0273 mmol) in CH_2Cl_2 (5.0 mL) was added a solution of **G-I** (2.3 mg, 0.0027 mmol) in CH_2Cl_2 (0.5 mL), and the resultant solution was stirred at 40 °C for 18 h. The reaction mixture was exposed to air with stirring at room temperature for 1 h, treated with Et_3N (0.3 mL), and stirred further at room temperature for 30 min. The resultant solution was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–20% EtOAc/hexanes) gave dimer **21** (4.9 mg, 23% yield) as a mixture of *E*/*Z* isomers along with recovered **6** (4.4 mg). Data for **21**: $[\alpha]_D^{26}$ +3.9 (*c* 0.60 in benzene); IR (film) 2932, 1729, 1452, 1376, 1281, 1186, 1148, 1104, 1036, 966, 918, 748, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, signals for major isomer) δ 7.37 (d, *J*=7.2 Hz, 4H), 7.28 (dd, *J*=7.6, 7.2 Hz, 4H), 7.21 (dd, *J*=7.6, 7.6 Hz, 2H), 6.60 (d, *J*=16.1 Hz, 2H), 6.22 (dd, *J*=16.1, 4.8 Hz, 2H), 5.34–5.25 (m, 2H), 4.92 (m, 2H), 4.69 (d, *J*=6.8 Hz, 2H), 4.63 (d, *J*=6.8 Hz, 2H), 4.47 (m, 2H), 4.39 (m, 2H), 3.72 (m, 2H), 3.37 (s, 6H), 2.76 (dd, *J*=15.1, 8.9 Hz, 2H), 2.56 (dd, *J*=15.1, 4.8 Hz, 2H), 2.09–1.77 (m, 10H), 1.62–1.22 (m, 10H), 1.19 (d, *J*=6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, signals for major isomer) δ 171.2 (×2), 136.8 (×2), 131.2 (×2), 130.2 (×2), 129.1 (×2), 128.5 (×4), 127.6 (×2), 126.4 (×4), 95.3 (×2), 72.0 (×2), 71.2 (×2), 71.1 (×2), 70.8 (×2), 55.7 (×2), 35.4 (×2), 35.1 (×2), 32.3 (×2), 26.9 (×2), 25.3 (×2), 24.1 (×2), 20.0 (×2); HRMS (ESI) calcd for $C_{46}H_{64}O_{10}Na$ [$(M+Na)^+$] 799.4392, found 799.4413.

*4.1.17. (E)-Vinyl iodide **25**.* Ozone was bubbled through a solution of tetrahydropyran *trans*-**7** (139.1 mg, 0.4342 mmol) in CH_2Cl_2 (10 mL) cooled to −78 °C until pale blue color persisted (ca. 15 min). After O_2 gas was bubbled through the reaction mixture to remove excess ozone, triphenylphosphine (227.8 mg, 0.8684 mmol) was added. The resultant mixture was allowed to warm to room temperature overnight and then concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–30% EtOAc/hexanes) gave an aldehyde (99.8 mg, 93%) as a colorless oil: $[\alpha]_D^{18}$ −16.5 (*c* 1.0 in $CHCl_3$); IR (film) 2951, 1734, 1149, 1106, 1034 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.65 (br s, 1H), 4.32 (d, *J*=7.0 Hz, 1H), 4.25 (d, *J*=7.0 Hz, 1H), 4.14 (m, 1H), 3.63 (m, 1H), 3.34 (s, 3H), 3.26 (m, 1H), 3.04 (s, 3H), 2.77 (dd, *J*=16.0, 9.0 Hz, 1H), 2.41 (dd, *J*=16.0, 5.0 Hz, 1H), 1.67 (m, 1H), 1.48–1.36 (m, 2H), 1.18 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.1, 171.2, 95.4, 77.6, 73.0, 71.2, 55.3, 51.2, 35.8, 24.1, 19.5; HRMS (ESI) calcd for $C_{11}H_{18}O_6Na$ [$(M+Na)^+$] 269.0996, found 269.1006.

To a mixture of $CrCl_2$ (470.6 mg, 3.829 mmol) and CHI_3 (452.4 mg, 1.149 mmol) in THF (1 mL) cooled to 0 °C was added a solution of the above aldehyde (94.3 mg) in 1,4-dioxane (6 mL). The resultant mixture was stirred at room temperature for 2 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution. The resultant mixture was extracted with diethyl ether, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–10% EtOAc/hexanes) gave an approximately 5:1 mixture of (*E*)-vinyl iodide **25** and the corresponding (*Z*)-isomer (98.6 mg, 70%). Further purification by flash chromatography on silica gel (1% diethyl ether/benzene) gave pure (*E*)-vinyl iodide **25** (70.8 mg, 50%) along with a 1.5:1 mixture of *E*/*Z* isomers (11.7 mg, 8%). Data for **25**: $[\alpha]_D^{29}$ +18.9 (*c* 1.00 in $CHCl_3$); IR (film) 2948, 1737, 1148, 1103, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (dd, *J*=14.5, 4.5 Hz, 1H), 6.42 (dd, *J*=14.5, 2.0 Hz, 1H), 4.67 (d, *J*=7.0 Hz, 1H), 4.59 (d, *J*=6.5 Hz, 1H), 4.33–4.25 (m, 2H), 3.70–3.64 (m, 4H), 3.36 (s, 3H), 2.72 (dd, *J*=15.5, 8.5 Hz, 1H), 2.54 (dd, *J*=16.0, 5.0 Hz, 1H), 2.00 (m, 1H), 1.83–1.72 (m, 2H), 1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 144.9, 95.3, 78.7, 73.4, 71.5, 70.3, 55.7, 51.8, 35.0, 25.0, 23.6; HRMS (ESI) calcd for $C_{12}H_{19}O_5INa$ [$(M+Na)^+$] 393.0169, found 393.0157.

*4.1.18. Olefin **26**.* To a suspension of CuI (327.6 mg, 1.72 mmol) in THF (30 mL) cooled to −20 °C were added vinylmagnesium bromide (1.0 M solution in THF, 34.4 mL, 34.4 mmol) and (*S*)-propylene oxide (1.20 mL, 17.2 mmol). The resultant mixture was stirred at −20 °C overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude (*S*)-4-penten-2-ol was used in the next reaction without further purification.

To a solution of the above (*S*)-4-penten-2-ol in diethyl ether (35 mL) cooled to 0 °C were added pyridine (2.09 mL, 25.8 mmol) and benzoyl chloride (2.97 mL, 25.8 mmol). The resultant mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *N*,*N*′-dimethylethylenediamine at 0 °C, and the mixture was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (20–30% CH_2Cl_2/hexanes) gave olefin **26** (2.83 g, 87% for the two steps) as a pale yellow oil: $[\alpha]_D^{29}$ +18.9 (*c* 1.00 in $CHCl_3$); IR (film) 2979, 2933, 1717, 1273, 1112, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05–8.00 (m, 2H), 7.53 (m, 1H), 7.44–7.39 (m, 2H), 5.82 (m, 1H), 5.20 (m, 1H), 5.15–5.04 (m, 2H), 2.51–2.36 (m, 2H), 1.34 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 133.6, 132.7, 130.7, 129.5 (×2), 128.3 (×2), 117.8, 70.7, 40.3, 19.5; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ [$(M+H)^+$] 191.1067, found 191.1068.

*4.1.19. (E)-Olefin **27**.* To a solution of olefin **26** (55.3 mg, 0.291 mmol) in THF (2 mL) cooled to 0 °C was added a solution of 9-BBN-H dimer (85.1 mg, 0.349 mmol) in THF (1 mL). After being

stirred at room temperature for 105 min, the reaction mixture was treated with 3 M aqueous Cs_2CO_3 solution (0.180 mL, 0.520 mmol) and stirred at room temperature for 35 min. To this mixture were added $PdCl_2(dppf)\cdot CH_2Cl_2$ (14.1 mg, 0.0173 mmol), Ph_3As (21.2 mg, 0.0693 mmol), and a solution of (*E*)-vinyl iodide **25** (64.1 mg, 0.173 mmol) in DMF (1 mL). After being stirred at room temperature for 11.5 h, the reaction mixture was diluted with diethyl ether and H_2O. The aqueous layer was extracted with diethyl ether, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–30% EtOAc/hexanes) gave (*E*)-olefin **27** (53.0 mg, 73%) as a pale yellow oil: $[\alpha]_D^{27}$ −7.5 (*c* 1.0 in benzene); IR (film) 2938, 1740, 1715, 1276, 1110, 1036, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04–7.99 (m, 2H), 7.52 (m, 1H), 7.44–7.38 (m, 2H), 5.64 (m, 1H), 5.47 (dd, *J*=15.5, 4.5 Hz, 1H), 5.14 (m, 1H), 4.66 (d, *J*=7.0 Hz, 1H), 4.59 (d, *J*=7.0 Hz, 1H), 4.30 (ddd, *J*=9.0, 5.5, 4.0 Hz, 1H), 4.24 (m, 1H), 3.70–3.62 (m, 4H), 3.35 (s, 3H), 2.71 (dd, *J*=15.5, 9.0 Hz, 1H), 2.57 (dd, *J*=15.0, 5.0 Hz, 1H), 2.12–2.03 (m, 2H), 1.93 (m, 1H), 1.82–1.56 (m, 4H), 1.55–1.38 (m, 3H), 1.31 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 166.1, 132.7, 132.5, 130.8, 129.5 (×2), 129.5, 128.2 (×2), 95.2, 71.8, 71.4, 71.2, 70.2, 55.6, 51.6, 35.5, 34.6, 32.2, 26.1, 24.9, 23.8, 20.0; HRMS (ESI) calcd for $C_{24}H_{34}O_7Na$ [$(M+Na)^+$] 457.2197, found 457.2193.

*4.1.20. Hydroxy acid **23**.* To a solution of (*E*)-olefin **27** (23.3 mg, 0.0557 mmol) in MeOH (5.0 mL) was added a solution of NaOH (79.1 mg) in H_2O (0.5 mL). After being stirred at room temperature overnight, the reaction mixture was cooled to 0 °C and acidified with 1 M aqueous HCl solution (pH=ca. 2). The resultant mixture was extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (0.5% MeOH/$CHCl_3$) gave hydroxy acid **23** (15.5 mg, 88%) as a colorless oil: $[\alpha]_D^{17}$ −21.1 (*c* 0.570 in $CHCl_3$); IR (film) 3422, 2933, 1716, 1148, 1104, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.53 (dd, *J*=15.5, 5.5 Hz, 1H), 4.70 (d, *J*=7.0 Hz, 1H), 4.60 (d, *J*=7.5 Hz, 1H), 4.35 (m, 1H), 4.23 (ddd, *J*=12.0, 4.0, 4.0 Hz, 1H), 3.78 (m, 1H), 3.65 (m, 1H), 3.37 (s, 3H), 2.75 (dd, *J*=16.0, 9.0 Hz, 1H), 2.54 (dd, *J*=16.0, 4.0 Hz, 1H), 2.10 (m, 1H), 2.06–1.97 (m, 2H), 1.84–1.76 (m, 2H), 1.56–1.34 (m, 4H), 1.17 (s, 3H), 1.6 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 175.4, 133.7, 128.8, 95.2, 71.9, 71.8, 69.8, 68.1, 55.7, 38.2, 35.3, 32.1, 24.8, 23.6, 23.1; HRMS (ESI) calcd for $C_{16}H_{27}O_7$ [$(M-H)^-$] 315.1813, found 315.1814.

*4.1.21. Macrolactone **28**.* To a solution of hydroxy acid **23** (14.6 mg, 0.0462 mmol) in THF (2 mL) cooled to 0 °C were added Et_3N (0.039 mL, 0.28 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.029 mL, 0.18 mmol). After being stirred at room temperature for 3.5 h, the reaction mixture was diluted with toluene (15 mL) and added dropwise to a solution of DMAP (169.2 mg, 1.385 mmol) in toluene (32 mL) at 100 °C over a period of 6.5 h. The reaction mixture was cooled to room temperature, washed successively with 0.5 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–10% EtOAc/CH_2Cl_2) gave macrolactone **28** (10.0 mg, 73%) as a colorless clear oil: $[\alpha]_D^{28}$ −57.2 (*c* 1.00 in $CHCl_3$); IR (film) 2931, 1733, 1248, 1148, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.17 (dddd, *J*=15.5, 10.5, 4.5, 1.5 Hz, 1H), 5.63 (dd, *J*=16.0, 4.5 Hz, 1H), 5.06 (m, 1H), 4.73 (d, *J*=7.5 Hz, 1H), 4.59 (d, *J*=7.0 Hz, 1H), 4.47 (br s, 1H), 4.23 (d, *J*=11.0 Hz, 1H), 3.56 (br s, 1H), 3.36 (s, 3H), 2.58 (dd, *J*=14.5, 11.5 Hz, 1H), 2.27 (dd, *J*=14.0, 1.5 Hz, 1H), 2.19 (m, 1H), 2.12 (m, 1H), 1.99–1.88 (m, 2H), 1.88–1.77 (m, 2H), 1.72 (m, 1H), 1.66–1.54 (m, 1H), 1.48–1.34 (m, 2H), 1.17 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 138.0, 128.6, 95.0, 72.1, 71.2, 70.0, 68.8, 55.6, 39.9, 31.7, 30.6, 24.7, 24.1, 23.0, 19.0; HRMS (ESI) calcd for $C_{16}H_{26}O_5Na$ [$(M+Na)^+$] 321.1672, found 321.1668.

*4.1.22. Aspergillide B (**1**).* A mixture of macrolactone **28** (2.0 mg, 0.0067 mmol) and $LiBF_4$ (65.4 mg, 0.698 mmol) in CH_3CN (2.0 mL) and H_2O (0.04 mL) was heated at 72 °C for 9.25 h. After being cooled to room temperature, the reaction mixture was poured into H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–50% EtOAc/hexanes) gave aspergillide B (**1**) (1.6 mg, 94%) as a colorless clear oil: $[\alpha]_D^{26}$ −88.1 (*c* 0.10 in MeOH); IR (film) 3420, 2929, 2854, 1732, 1277, 1193, 1086, 1025, 970 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.14 (dddd, *J*=15.6, 10.7, 4.4, 1.5 Hz, 1H), 5.33 (dd, *J*=15.6 4.4 Hz, 1H), 5.04 (m, 1H), 4.25 (br s, 1H), 4.03 (br d, *J*=11.2 Hz, 1H), 3.16 (br s, 1H), 2.66 (dd, *J*=13.7, 11.7 Hz, 1H), 2.07 (dd, *J*=13.7, 2.0 Hz, 1H), 1.99 (dddd, *J*=13.2, 10.8, 4.9, 2.4 Hz, 1H), 1.78–1.66 (m, 2H), 1.62–1.44 (m, 3H), 1.36–1.22 (m, 4H), 1.01 (d, *J*=6.4 Hz, 3H), 0.93 (dddd, *J*=13.7, 4.9, 2.4, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.8, 138.2, 129.0, 71.5, 69.8, 69.6, 67.2, 39.9, 32.0, 30.7, 27.8, 25.3, 22.6, 19.1; HRMS (ESI) calcd for $C_{14}H_{22}O_4Na$ [$(M+Na)^+$] 277.1410, found 277.1404.

*4.1.23. (E)-Vinyl iodide **24**.* Ozone was bubbled through a solution of tetrahydropyran *cis*-**7** (43.3 mg, 0.135 mmol) in CH_2Cl_2 (8 mL) cooled to −78 °C until pale blue color persisted. The excess ozone was removed by bubbling O_2 gas through the reaction mixture. The reaction mixture was treated with triphenylphosphine (71 mg, 0.27 mmol), and the resultant solution was allowed to warm to room temperature over a period of 2 h. The resultant mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (20–30% EtOAc/hexanes) gave an aldehyde (27.2 mg, 82%): $[\alpha]_D^{18}$ +114.9 (*c* 1.0 in C_6H_6); IR (film) 2952, 2891, 1739, 1105, 1038 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.38 (s, 1H), 4.38 (d, *J*=6.5 Hz, 1H), 4.28 (d, *J*=6.5 Hz, 1H), 3.77 (ddd, *J*=9.0, 9.0, 3.0 Hz, 1H), 3.37 (s, 3H), 3.22 (dd, *J*=11.5, 2.5 Hz, 1H), 3.10–2.97 (m, 4H), 2.83 (dd, *J*=15.5, 3.0 Hz, 1H), 2.49 (dd, *J*=15.5, 9.0 Hz, 1H), 1.82 (m, 1H), 1.46 (m, 1H), 1.09–0.93 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.0, 171.2, 95.2, 80.8, 77.6, 74.6, 55.2, 51.2, 37.9, 29.2, 25.4; HRMS (ESI) calcd for $C_{11}H_{18}O_6Na$ [$(M+Na)^+$] 269.0996, found 269.0994.

To a mixture of $CrCl_2$ (135.0 mg, 1.098 mmol) in THF (0.5 mL) cooled to 0 °C was added a solution of the above aldehyde (27.2 mg) and CHI_3 (130.0 mg, 0.3315 mmol) in 1,4-dioxane (3.0 mL), and the resultant mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with diethyl ether and quenched with saturated aqueous $Na_2S_2O_3$ solution. The resultant mixture was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–20% EtOAc/hexanes) gave an approximately 3:1 mixture of (*E*)-vinyl iodide **24** and the corresponding (*Z*)-isomer (35.4 mg, 87%). Further purification of the mixture by flash chromatography on silica gel (1% diethyl ether/benzene) gave **24** (23.4 mg, 57%) as a yellow oil: $[\alpha]_D^{16}$ +115.6 (*c* 0.66 in benzene); IR (film) 2946, 1740, 1108, 1037 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.30 (dd, *J*=15.0, 5.5 Hz, 1H), 6.13 (dd, *J*=15.0, 1.0 Hz, 1H), 4.43 (d, *J*=6.5 Hz, 1H), 4.32 (d, *J*=6.5 Hz, 1H), 3.81 (ddd, *J*=8.5, 8.5, 3.5 Hz, 1H), 3.35–3.29 (m, 4H), 3.10–3.03 (m, 4H), 2.83 (dd, *J*=15.0, 3.5 Hz, 1H), 2.47 (dd, *J*=15.0, 8.5 Hz, 1H), 1.83 (dddd, *J*=12.0, 4.0, 4.0, 4.0 Hz, 1H), 1.17–1.02 (m, 2H), 0.95 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.4, 145.9, 95.2, 78.8, 77.7, 77.4, 74.9, 55.2, 51.2, 38.1, 30.3, 29.7; HRMS (ESI) calcd for $C_{12}H_{19}O_5Na$ [$(M+Na)^+$] 393.0169, found 393.0176.

*4.1.24. (E)-Olefin **29**.* To a solution of **26** (19.2 mg, 0.101 mmol) in THF (0.9 mL) cooled to 0 °C was added a solution of 9-BBN-H dimer (29.6 mg, 0.121 mmol) in THF (0.5 mL), and the resultant solution

was stirred at room temperature for 70 min. In a separate flask, a solution of (*E*)-vinyl iodide **24** (21.3 mg, 0.0575 mmol) in DMF (0.7 mL) was prepared. To this solution were added $PdCl_2(dppf)\cdot CH_2Cl_2$ (4.7 mg, 0.0058 mmol), Ph_3As (7.0 mg, 0.023 mmol), and 3 M aqueous Cs_2CO_3 solution (0.060 mL, 0.18 mmol). The resultant mixture was stirred at room temperature for 15 min before it was treated with the above alkylborane solution. After being stirred at room temperature overnight, the resultant mixture was diluted with diethyl ether and washed with H_2O. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–20% EtOAc/hexanes) gave (*E*)-olefin **29** (22.7 mg, 94%) as a yellow oil: $[\alpha]_D^{16}$ +55.8 (*c* 0.80 in $CHCl_3$); IR (film) 2937, 1741, 1715, 1276, 1111, 1037, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J*=7.5 Hz, 2H), 7.52 (dd, *J*=7.5, 7.5 Hz, 1H), 7.41 (dd, *J*=7.5, 7.5 Hz, 2H), 5.60 (ddd, *J*=15.5, 6.5, 6.5 Hz, 1H), 5.41 (dd, *J*=15.5, 6.5 Hz, 1H), 5.13 (m, 1H), 4.68 (d, *J*=6.5 Hz, 1H), 4.57 (d, *J*=6.5 Hz, 1H), 3.80 (m, 1H), 3.70 (ddd, *J*=8.0, 8.0, 4.0 Hz, 1H), 3.64 (s, 3H), 3.34 (s, 3H), 3.26 (ddd, *J*=8.0, 8.0, 4.0 Hz, 1H), 2.77 (dd, *J*=15.0, 4.0 Hz, 1H), 2.46 (dd, *J*=15.0, 8.0 Hz, 1H), 2.21 (m, 1H), 2.02 (dt, *J*=7.5, 7.5 Hz, 2H), 1.76–1.64 (m, 2H), 1.64–1.54 (m, 2H), 1.54–1.36 (m, 3H), 1.31 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 166.2, 132.7, 131.7, 130.8, 130.4, 129.5 (×2), 128.3 (×2), 95.2, 77.7, 77.2, 75.4, 71.5, 55.6, 51.6, 38.1, 35.5, 32.1, 31.0, 29.9, 24.8, 20.0; HRMS (ESI) calcd for $C_{24}H_{34}O_7Na$ [$(M+Na)^+$] 457.2197, found 457.2197.

*4.1.25. Carboxylic acid **22**.* To a solution of (*E*)-olefin **29** (17.3 mg, 0.0413 mmol) in MeOH (3 mL) was added 4 M aqueous NaOH solution (0.3 mL, 1.2 mmol), and the resultant solution was stirred at room temperature for 19 h. The reaction mixture was cooled to 0 °C and acidified with 1 M aqueous HCl solution. The resultant mixture was extracted with $CHCl_3$, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (1–3% MeOH/$CHCl_3$) gave carboxylic acid **22** (11.9 mg, 91%) as a colorless oil: $[\alpha]_D^{28}$ +59.8 (*c* 1.00 in $CHCl_3$); IR (film) 3420, 2934, 1715, 1107, 1036 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.64 (ddd, *J*=15.0, 7.0, 7.0 Hz, 1H), 5.42 (dd, *J*=15.0, 6.5 Hz, 1H), 4.70 (d, *J*=7.0 Hz, 1H), 4.57 (d, *J*=7.0 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.68 (ddd, *J*=9.0, 9.0, 3.5 Hz, 1H), 3.34 (s, 3H), 3.28 (m, 1H), 2.84 (dd, *J*=15.5, 3.5 Hz, 1H), 2.51 (dd, *J*=15.5, 8.0 Hz, 1H), 2.22 (m, 1H), 2.06–1.96 (m, 2H), 1.74 (m, 1H), 1.54–1.32 (m, 6H), 1.16 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 132.6, 129.9, 95.1, 78.1, 76.9, 74.9, 68.0, 55.7, 38.6, 37.8, 32.1, 30.8, 29.7, 25.0, 23.4; HRMS (ESI) calcd for $C_{16}H_{27}O_6$ [$(M-H)^-$] 315.1813, found 315.1811.

*4.1.26. Macrolactone **30**.* To a solution of carboxylic acid **22** (13.3 mg, 0.0420 mmol) in THF (5.0 mL) cooled to 0 °C were added Et_3N (0.045 mL, 0.32 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.035 mL, 0.22 mmol), and the reaction mixture was stirred at room temperature for 1.5 h. The resultant mixture was diluted with toluene (70 mL) and added to a solution of DMAP (770 mg, 6.30 mmol) in toluene (140 mL) over a period of 13 h. The reaction mixture was cooled to room temperature and washed with 0.5 M aqueous HCl solution, saturated $NaHCO_3$ solution, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–20% diethyl ether/benzene) gave macrolactone **30** (2.5 mg, 20%) as a colorless clear oil: $[\alpha]_D^{28}$ −58.7 (*c* 0.20 in $CHCl_3$); IR (film) 2929, 1732, 1717, 1148, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (dd, *J*=15.0, 8.0 Hz, 1H), 5.71 (ddd, *J*=15.0, 9.0, 3.0 Hz, 1H), 4.96 (m, 1H), 4.70 (s, 2H), 4.35 (dd, *J*=13.0, 4.5 Hz, 1H), 4.26 (dd, *J*=6.5, 6.5 Hz, 1H), 3.47 (m, 1H), 3.37 (s, 3H), 2.63 (dd, *J*=15.0, 13.0 Hz, 1H), 2.36 (dd, *J*=15.0, 4.5 Hz, 1H), 2.33–2.18 (m, 2H), 2.11 (m, 1H), 1.97–1.85 (m, 2H), 1.85–1.70 (m, 2H), 1.58–1.46 (m, 2H), 1.37 (m, 1H), 1.20 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 136.7, 132.5, 94.6, 71.6, 71.4, 71.3, 71.1, 55.5, 40.8, 32.3, 31.1, 23.7, 22.7, 19.9, 18.6; HRMS (ESI) calcd for $C_{16}H_{26}O_5Na$ [$(M+Na)^+$] 321.1672, found 321.1667.

*4.1.27. Dimer **31**.* To a solution of carboxylic acid **22** (11.9 mg, 0.0376 mmol) in THF (1.5 mL) cooled to 0 °C were added Et_3N (0.030 mL, 0.22 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.025 mL, 0.16 mmol). The resultant mixture was stirred at room temperature for 2.25 h before being diluted with toluene (12 mL). This mixed anhydride solution was added dropwise to a solution of DMAP (137.8 mg, 1.128 mmol) in toluene (23 mL) at 100 °C over a period of 5 h, and the resultant mixture was stirred at 100 °C for additional 1.25 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and washed successively with 0.5 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5% EtOAc/CH_2Cl_2) gave dimer **31** (6.5 mg, 29%) as a colorless oil: $[\alpha]_D^{26}$ +37.8 (*c* 0.68 in benzene); IR (film) 2935, 1730, 1453, 1377, 1294, 1191, 1105, 1037, 984, 917 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.56 (ddd, *J*=15.5, 8.2, 6.2 Hz, 2H), 5.39 (dd, *J*=15.5, 5.2 Hz, 2H), 5.03 (m, 2H), 4.71 (d, *J*=6.9 Hz, 2H), 4.57 (d, *J*=6.9 Hz, 2H), 3.77 (m, 2H), 3.69 (m, 2H), 3.34 (s, 6H), 3.25 (ddd, *J*=10.3, 10.0, 4.5 Hz, 2H), 2.84 (dd, *J*=14.0, 2.4 Hz, 2H), 2.33 (dd, *J*=14.0, 10.3 Hz, 2H), 2.21 (m, 2H), 2.04 (m, 2H), 1.88 (m, 2H), 1.76 (m, 2H), 1.59–1.31 (m, 12H), 1.18 (d, *J*=6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1 (×2), 131.3 (×2), 129.9 (×2), 95.0 (×2), 78.2 (×2), 77.4 (×2), 74.9 (×2), 70.4 (×2), 55.6 (×2), 38.5 (×2), 35.8 (×2), 32.2 (×2), 31.0 (×2), 29.9 (×2), 24.5 (×2), 20.3 (×2); HRMS (ESI) calcd for $C_{32}H_{52}O_{10}Na$ [$(M+Na)^+$] 619.3453, found 619.3447.

*4.1.28. Aspergillide A (**4**).* A stock solution of $LiBF_4$ in aqueous CH_3CN was prepared by mixing $LiBF_4$ (72.1 mg, 0.769 mmol), CH_3CN (2.0 mL), and H_2O (0.080 mL). A mixture of macrolactone **30** (1.0 mg, 0.0034 mmol) and 1.5 mL of the above stock solution was heated at 72 °C for 7 h. After being cooled to room temperature, the reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (30–50% EtOAc/hexanes) gave aspergillide A (**4**) (0.7 mg, 82%) as a colorless oil: $[\alpha]_D^{16}$ −66.7 (*c* 0.12 in $CHCl_3$); IR (film) 3365, 2927, 1733, 1717, 1558, 1541, 1507, 1457, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, *J*=15.0, 8.0, 2.0 Hz, 1H), 5.71 (ddd, *J*=15.0, 9.5, 3.0 Hz, 1H), 4.96 (m, 1H), 4.29–4.22 (m, 2H), 3.58 (m, 1H), 2.64 (dd, *J*=15.0, 12.5 Hz, 1H), 2.39 (dd, *J*=15.0, 4.5 Hz, 1H), 2.30 (m, 1H), 2.21 (m, 1H), 2.11 (m, 1H), 1.99–1.88 (m, 2H), 1.82 (m, 1H), 1.72 (m, 1H), 1.62–1.46 (m, 3H), 1.40 (m, 1H), 1.20 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 137.1, 132.1, 74.0, 71.5, 71.2, 66.8, 40.5, 32.1, 31.1, 23.7, 22.0, 21.7, 18.6; HRMS (ESI) calcd for $C_{14}H_{22}O_4Na$ [$(M+Na)^+$] 277.1410, found 277.1421.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.062.

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