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Synthesis of aspergillide A via proline-catalyzed *trans*-to-*cis* isomerization of a substituted tetrahydropyran

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ABSTRACT

The transformation of a common synthetic intermediate of aspergillides B and C into aspergillide A, a cytotoxin produced by a marine-derived fungus, has been accomplished in an eleven-step sequence involving an efficient proline-catalyzed isomerization of a 2,6-*trans*-substituted tetrahydropyran-2-acetaldehyde intermediate into the corresponding cis isomer and the Yamaguchi macrolactonization as the key steps.

1. Introduction

Aspergillides A–C are fourteen-membered macrolides isolated by Kusumi and co-workers from a bromine-modified 1/2PD culture medium of the marine-derived fungus Aspergillus ostianus strain 01F313 and shown to exhibit significant cytotoxicity against mouse lymphocytic leukemia cells (L1210).[1] The proposed structure of aspergillide C (**3**) (Fig. 1), including its absolute configuration, was soon confirmed by our total synthesis.[2] The structures of aspergillides A and B initially assigned by the Kusumi group were, however, found to need stereochemical revision through synthetic studies by Hande and Uenishi as well as X-ray crystallographic analyses by Ooi and co-workers, which concluded the genuine structures of aspergillides A and B to be **1** and **2**, respectively.[3,4] Their unique fourteen-membered macrolide structures embedded with a tetrahydro- or dihydropyran ring,[5,6] coupled with their interesting biological activity, prompted synthetic efforts toward **1**–**3** by quite a few research groups including us, which have so far culminated in five total/formal syntheses for **1**,[7] seven for **2**,[3,7c,e–g,8] and three for **3**.[2,9]

The latter half stage of our reported syntheses of aspergillides B (**2**) and C (**3**), both of which have a 3,7-*trans* stereochemical relationship, featured the Lewis-acid promoted Ferrier-type C-alkylation of cyclic acetal **4** to form a mixture **5** and **6** (Scheme 1), iodolactonization of the major 3,7-*trans* isomer **5** for the stereoselective installation of the 4-α-hydroxy group, and the Yamaguchi macrolactonization to construct the macrocyclic structures.[2,8c] In light of the previous syntheses shown in Scheme 1, we envisaged three possibilities of obtaining aspergillide A (**1**), the C3 epimer of aspergillide B with 3,7-*cis* stereochemistry, from a synthetic intermediate of **2** and **3**: (1) epimerization of the stereochemistry of macrocyclic intermediate **8** at the C3 position via a retro-oxy-Michael/oxy-Michael process (Route 1); (2) exploitation of the already existing 3,7-*cis* stereochemistry of **6** obtained as the minor isomer in the above-mentioned C-alkylation (Route 2); and (3) stereochemical inversion of the C3 position of the major isomer **5** via a retro-oxy-Michael/oxy-Michael sequence (Route 3). Our successful synthesis of aspergillide A (**1**) according to Route 3 was previously communicated together with some attempts in line with

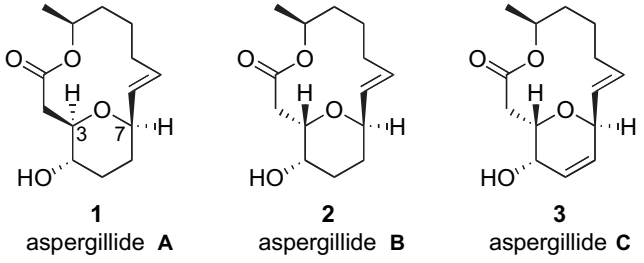

Fig. 1. Structures of aspergillides A, B, and C.

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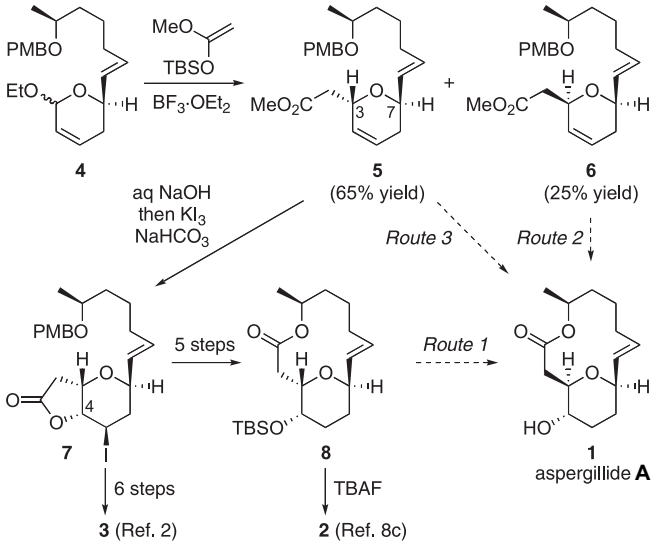


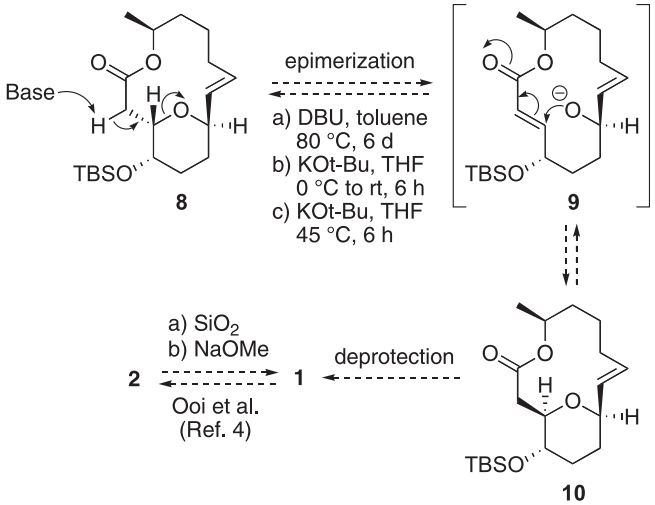
Scheme 1. The latter half stage of our reported synthesis of aspergillides B (**2**) and C (**3**), and three potential routes from their synthetic intermediates to aspergillide A (**1**).

Route 1.[7a] In this article, we describe a full account of our synthetic efforts toward **1** including those along Route 2.

2. Results and discussion

2.1. Epimerization of macrocyclic intermediate 8 (Route 1)

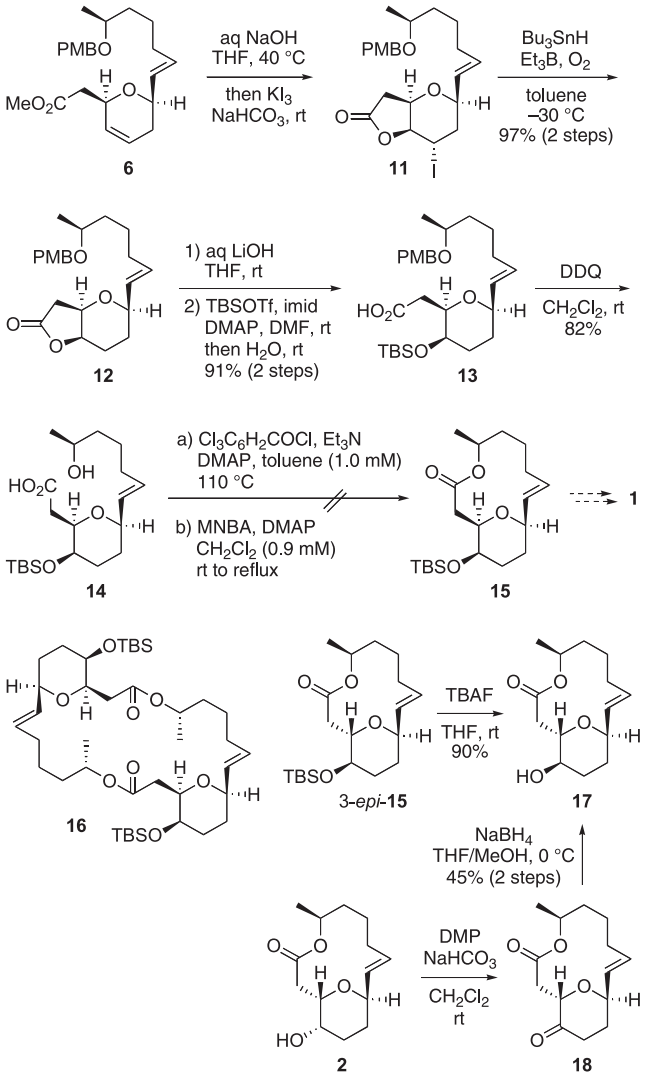
Since aspergillides A (**1**) and B (**2**) are epimeric to each other at the alkoxy-bearing C3 position β to the lactone carbonyl, it would be most convenient if the direct epimerization of **2** to **1** via a retro-oxy-Michael/oxy-Michael process could be effected. This possibility was previously examined by Ooi et al.[4] Their treatment of **2** with either SiO_2 or NaOMe, however, afforded no desired product **1**, giving only a methanolysis product in the latter case (Scheme 2). These results as well as our concern about the possible formation of a γ-lactone through the intramolecular attack of the C4 hydroxy group to the lactone carbonyl during basic or acidic treatment of **2** made us choose the TBS-protected form of **2** (compound **8**) as a suitable epimerization substrate. Thus, the 3,7-*trans* isomer **8** was first exposed to DBU in toluene, hoping to obtain the corresponding 3,7-*cis* isomer **10** via alkoxy unsaturated ester **9**. This treatment was, however, unsuccessful, resulting only in the recovery of the starting material **8** even at elevated temperatures. The use of KO*t*-Bu as a stronger base also brought no fruitful outcome, giving only the starting material at room temperature or a complex mixture at 45 °C.[10]



Scheme 2. Attempted epimerization of 3,7-*trans* isomer **8** to 3,7-*cis* isomer **10**.

2.2. Exploitation of the 3,7-*cis* stereochemistry of minor isomer 6 (Route 2)

2.2.1. Macrolactonization of a 3,4-cis/3,7-cis seco acid. Faced with the difficulty to epimerize the 3,7-*trans* macrolactone **8** into the corresponding cis isomer **10**, we next attempted to take advantage of the 3,7-*cis* stereochemistry existing in the minor C-alkylation product **6**, the same stereochemistry as that present in aspergillide A (**1**) (see Scheme 1). In line with our previous procedures employed for the syntheses of aspergillides A and B,[2,8c] the olefinic ester **6** was hydrolyzed with an aq NaOH solution, and the resulting carboxylate intermediate was directly treated with $KI_3/NaHCO_3$ to give iodolactone **11** (Scheme 3). Reductive removal of the iodine atom from **11** proceeded smoothly, affording **12** in 97% overall yield from **6**. Hydrolysis of the lactone moiety of **12** with LiOH in aq THF gave a mixture containing a hydroxy carboxylate intermediate. The mixture was concentrated to dryness, dissolved in DMF, and then treated with an excess amount of TBSOTf in the presence of imidazole and DMAP to give a bis-TBS-protected intermediate, the TBS

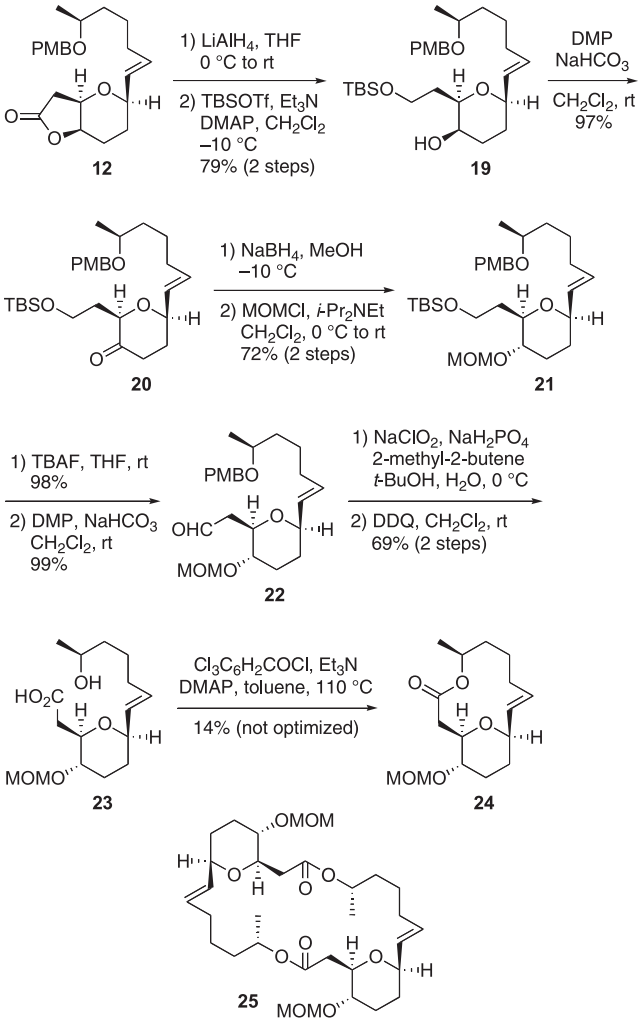


Scheme 3. Attempt for the conversion of **6** into aspergillide A (**1**).

ester group of which was then selectively hydrolyzed by directly adding water to the reaction mixture to afford hydroxy-protected carboxylic acid **13** in 91% yield for the two steps. Oxidative deprotection of the PMB group of **13** with DDQ furnished seco acid **14** in 82% yield, which set the stage for the pivotal macrolactonization step.

The macrolactonization of **14** was attempted by using Yamaguchi's[11] and Shiina's[12] protocols. Unfortunately, however, subjection of **14** to the Yamaguchi lactonization conditions ($Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene, 110 °C, 13 h) gave a complex mixture. Despite our careful chromatographic separation, no desired product **15** was detected from the mixture, but instead dimeric macrodiolide **16** and 3-*epi*-**15** were obtained in yields of 19% and 34%, respectively. The structure of 3-*epi*-**15** was confirmed by its deprotection into alcohol **17** whose spectral (^1H and ^{13}C NMR) and TLC data were identical with those of a sample derived from aspergillide B (**2**) in two steps via ketone **18**.[13] The formation of 3-*epi*-**15** in 34% yield came as a surprise to us. From the facts that no desired product **15** was isolated and that the macrolactonization of analogous 3,7-*trans*-substituted seco acids proceeded smoothly to give precursors of aspergillides B and C in high yields,[2,3,7–9] we are speculating that 3-*epi*-**15** would have been produced via *cis*-to-*trans* epimerization at the stage of an activated ester derivative of **14** prior to macrolactonization.[7e,14] Exposure of **14** to the Shiina macrolactonization conditions [MNBA (2-methyl-6-nitrobenzoic anhydride), DMAP, CH_2Cl_2], on the other hand, gave only the macrodiolide **16** in 20% yield at room temperature (20 h) and in 16% yield at reflux (18 h) along with some unidentified products.

2.2.2. Macrolactonization of a 3,4-trans/3,7-cis seco acid.- Considering the possibility that the presence of the TBSO group at the C4 position of **14** oriented *cis* to the C3 substituent might have encumbered its macrolactonization into **15** (see Scheme 3), we next planned to macrolactonize a seco acid possessing a 3,4-*trans*/3,7-*cis* stereochemical relationship, exactly the same stereochemistry as that of natural aspergillide A (**1**). The preparation of the desired seco acid (compound **23** in Scheme 4) began with reductive opening of the lactone ring of **12** to give a diol intermediate. Selective protection of its primary hydroxy group with TBSOTf in CH_2Cl_2 in the presence of Et_3N and DMAP afforded **19** in 79% yield from **12**. Oxidation of the alcohol **19** with Dess–Martin's periodinane (DMP) proceeded smoothly to provide ketone **20** (97% yield),[15] which was then subjected to stereoselective reduction with $NaBH_4$ in MeOH to give an alcohol. The product was then protected as its MOM ether **21** bearing an α-oriented oxygen functionality at the C4 position with a 3,4-*trans* relationship (72% from **20**). Unmasking of the TBS-protected alcohol and subsequent DMP oxidation gave 3,7-*cis* aldehyde **22** (97% for the two steps), which was then converted into the seco acid **23** by the Pinnick oxidation followed by PMB-deprotection with DDQ (69% for the two steps). For the macrolactonization of **23** we attempted three methodologies. The Shiina protocol [MNBA, DMAP, CH_2Cl_2 (0.7 mM), rt, 22 h] only gave the corresponding dimeric macrodiolide **25** in low yields and Gerlach's modification of the Corey–Nicolaou method [PySSPy, Ph_3P, $AgClO_4$, toluene (0.7 mM), 120 °C, 23 h][16] resulted in the formation of a complex mixture. To our delight, however, we could finally obtain the target macrocycle **24**, albeit in low yield (14%, not optimized), by use of the Yamaguchi macrolactonization conditions [$Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene (0.9 mM), 110 °C, 8 h].[17] Although the chemical yield of **24** was not satisfactory and the formation of the undesired dimeric product **25** was unavoidable, it was suggested that a 3,4-*trans*/3,7-*cis* seco acid like **23** would likely macrocyclize. At this point, we decided to review the synthetic route to the seco acid **23**, which commenced with the minor C-alkylation product **6** (see Scheme 1), seeking for a more efficient approach to **23** (or its equivalent) using the major

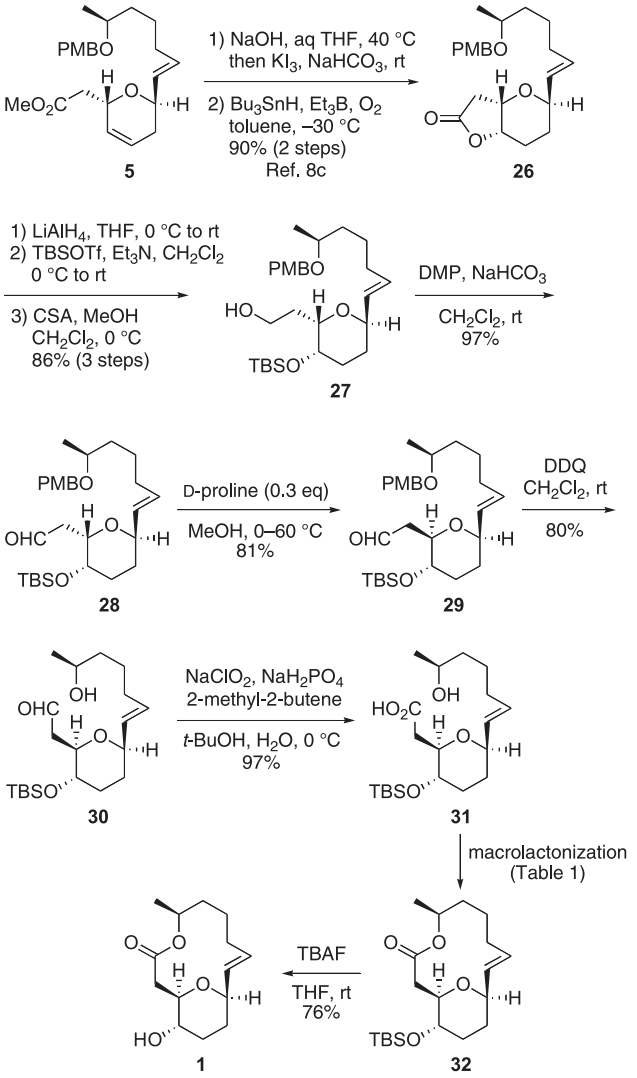


Scheme 4. Preparation of 3,4-*trans*/3,7-*cis* seco acid **23** and its macrolactonization.

C-alkylation product **5** with 3,7-*trans* stereochemistry as the starting material.

2.3. Preparation of a 3,4-*trans*/3,7-*cis* seco acid from 3,7-*trans* intermediate 5 and its transformation to aspergillide A (1) (Route 3)

For the preparation of an appropriate macrocyclization precursor with a 3,4-*trans*/3,7-*cis* stereochemical relationship from the major isomer **5** in the Ferrier-type C-alkylation of **4** (see Scheme 1), the unsaturated ester **5** bearing a 3,7-*trans* stereochemical relationship was first exposed to a one-pot hydrolysis/iodolactonization sequence, the product of which was then reduced with Bu_3SnH in toluene in the presence of Et_3B and O_2 to give lactone **26** in 90% yield for the two steps (Scheme 5).[8c] $LiAlH_4$ reduction of **26** and subsequent treatment of the resulting diol afforded a bis-TBS-protected intermediate. Selective removal of the TBS group on the primary hydroxy function with camphorsulfonic acid in MeOH/CH_2Cl_2 gave alcohol **27** in 86% yield from **26**. Exposure of **27** to DMP/$NaHCO_3$ in CH_2Cl_2 cleanly afforded aldehyde **28**, the substrate we chose for the epimerization at its C3 position. Gratifyingly, on treatment with a catalytic amount of D-proline in MeOH, the 3α-substituted aldehyde **28** underwent smooth equilibration to give a 95:5 epimeric mixture of **29** and **28**, favoring the desired 3β-epimer **29** with 3,7-*cis* stereochemistry.[18,19] After chromatographic isolation in 81% yield, the aldehyde **29** was subjected to oxidative

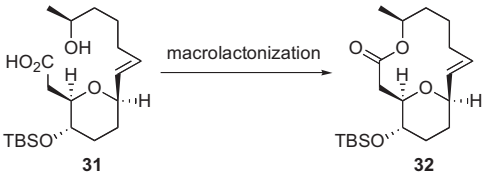


Scheme 5. Preparsation of 3,4-*trans*/3,7-*cis* seco acid **31** via proline-catalyzed epimerization and its transformation to aspergillide A (**1**).

deprotection of the PMB group to provide hydroxy aldehyde **30** (80% yield), which was then oxidized by the Pinnick method to give macrocyclization precursor **31** (97% yield).

Having secured the seco acid **31** possessing the same 3,4-*trans*/3,7-*cis* stereochemistry as **23**, we proceeded to its macrolactonization into **32**. As shown in Table 1, besides the three methods employed in this study so far (the Yamaguchi, Shiina, and Gerlach protocols), we also examined macrolactonization conditions using the Mukaiyama reagent, 2-bromo-1-ethylpyridinium tetrafluoroborate.[20] Exposure of **31** to the Mukaiyama, Gerlach, and Shiina conditions (at 50 °C) resulted in the formation of complex mixtures (entries 1–3), while the implementation of the Shiina macrolactonization at room temperature afforded dimeric macrodiolide **33** in 22% yield along with minor products that were not characterized (entry 4). Fortunately, however, treatment of the seco acid **31** under Yamaguchi's conditions at 110 °C gave rise to the desired lactone **32** in 25% yield together with dimeric byproduct **33** (14%) and a trace amount of 3-*epi*-**32** (entry 5). The structure of 3-*epi*-**32** was confirmed by comparing its ^{1}H and ^{13}C NMR spectra with those of an authentic sample (compound **8** in Scheme 1) previously prepared in our total synthesis of aspergillide B (**2**).[8c] Lowering the reaction temperature to 80 °C brought some desirable effect, giving **32** in an improved yield of 30% (entry 6). Some

Table 1
Macrolactonization of **31**



Entry	Reagents and conditions	Isolated yield (%)		
		32	**33**[a]	3-*epi*-**32**[a]
1	$BrC_5H_4NEt\cdot BF_4$, Et_3N MeCN, 90 °C, 6 h	complex mixture		
2	PySSPy, Ph_3P, $AgBF_4$ Toluene, 110 °C, 54 h	complex mixture		
3	MNBA, DMAP CH_2Cl_2/THF, 50 °C, 17 h	complex mixture		
4	MNBA, DMAP CH_2Cl_2, rt, 28 h	—	22	—
5	$Cl_3C_6H_2COCl$, Et_3N, DMAP Toluene, 110 °C, 5 h	25	14	trace
6	$Cl_3C_6H_2COCl$, Et_3N, DMAP Toluene, 80 °C, 8 h	30	19	trace

[a] See Fig. 2 for the structure.

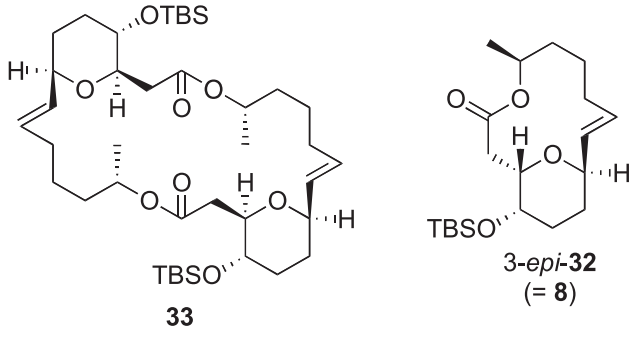


Fig. 2. Undesired products formed in the macrolactonization of **31**.

additional attempts to further improve the chemical yield, mainly by varying the reaction temperature and concentration, were unsuccessful. The modest yields of this macrolactonization could be rationalized by considering that the seco acid **31**, which would surely adopt a stable chair conformation with its C3-, C4-, and C7-substituents equatorially oriented, would need to change its conformation into an energetically unfavorable one with all the substituents axially arranged to macrocyclize into **32**,[21] as discussed by Fuwa and co-workers in their macrolactonization of **23**.[7e,17] Finally, deprotection of the TBS group furnished in 76% yield aspergillide A (**1**) as a white crystalline solid (mp 64.5–65.5 °C), the ^{1}H and ^{13}C NMR spectra as well as the specific rotation of which showed good agreement with those of natural aspergillide A.

3. Conclusion

The conversion of our synthetic intermediate **26** of aspergillide B (**2**) into aspergillide A (**1**) was accomplished in nine steps by using the efficient proline-mediated epimerization of the 3,7-*trans*-substituted intermediate **28** into the corresponding cis isomer **29** and the Yamaguchi macrolactonization as the key steps. This synthesis constitutes the first synthesis of aspergillide A (**1**) and represents the successful completion of our efforts toward the total synthesis of all the three aspergillides (A, B, and C) from the common intermediate **5**.

4. Experimental

4.1. General

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian MR-400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) or a Varian UNITY plus-500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Optical rotation values were measured with a Jasco DIP-371 polarimeter, and the mass spectra were obtained with Jeol JMS-700 spectrometer operated in the EI or FAB mode. Melting points were determined with a Yanaco MP-J3 apparatus and are uncorrected. Merck silica gel 60 (7–230 mesh) was used for column chromatography. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and CH_3CN from CaH_2; MeOH from $Mg(OMe)_2$; toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

*4.1.1. 2-{(2S,3S,6S)-3-tert-Butyldimethylsilyloxy-6-[(S)-6-(4-methoxybenzyloxy)-1-heptenyl]tetrahydropyran-2-yl}ethanol (**27**).* To a stirred suspension of $LiAlH_4$ (11.9 mg, 0.314 mmol) in THF (1 mL) was added dropwise a solution of **26** (91.1 mg, 0.243 mmol) in THF (2 mL) at 0 °C. After being stirred at room temperature for 1 h, the mixture was quenched by successively addition of water (10 μL), 15% NaOH aq (10 μL), and water (30 μL). The mixture was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to give a diol intermediate as a pale yellow oil (98.3 mg), which was then taken up in CH_2Cl_2 (3 mL). To the solution was successively added Et_3N (110 μL, 0.789 mmol) and TBSOTf (160 μL, 0.683 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min and at room temperature for an additional 30 min. The mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=20:1) to give a bis-TBS-protected intermediate (155 mg) as a colorless oil, which was then dissolved in a mixture of CH_2Cl_2 and MeOH (1:1, 2 mL). To the solution was added camphorsulfonic acid (12.4 mg, 52.8 μmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h before being quenched with satd $NaHCO_3$ aq and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1–3:1) to give 103 mg (86%) of **27** as a pale yellow oil. $[\alpha]_{D^{15}}$ −5.69 (*c* 1.37, $CHCl_3$); IR: ν_{max} 3453 (br m), 1513 (m), 1248 (s), 1088 (s), 834 (s); ^1H NMR (400 MHz): δ 0.057 (3H, s), 0.064 (3H, s), 0.89 (9H, s), 1.17 (3H, d, *J*=6.1 Hz), 1.34–1.62 (5H, m), 1.62–1.80 (3H, m), 1.89 (1H, ddt, *J*=13.5, 6.5, 3.7 Hz), 1.98–2.12 (3H, m), 2.70 (1H, br t, *J*=5.1 Hz, OH), 3.48 (1H, sex, *J*=6.1 Hz), 3.71–3.83 (3H, m), 3.80 (3H, s), 3.93 (1H, ddd, *J*=10.2, 4.1, 4.1 Hz), 4.14–4.21 (1H, m), 4.37 (1H, d, *J*=11.3 Hz), 4.49 (1H, d, *J*=11.3 Hz), 5.43 (1H, dd, *J*=15.7, 5.9 Hz), 5.65 (1H, dtd, *J*=15.7, 6.5, 0.8 Hz), 6.85–6.89 (2H, m), 7.24–7.28 (2H, m); ^{13}C NMR (100 MHz): δ −4.9, −4.7, 18.1, 19.6, 25.0, 25.8 (3C), 27.5, 28.1, 29.2, 32.3, 36.1, 55.2, 61.8, 68.6, 69.9, 70.2, 74.3, 75.9, 113.7 (2C), 129.2 (2C), 129.8, 131.1, 132.9, 158.9; HRMS (EI): *m*/*z* calcd for $C_{28}H_{48}O_5Si$, 492.3271; found, 492.3273 (M^+).

*4.1.2. {(2S,3S,6R)-3-tert-Butyldimethylsilyloxy-6-[(S)-6-(4-methoxybenzyloxy)-1-heptenyl]tetrahydropyran-2-yl}acetaldehyde (**28**).* To a stirred suspension of **27** (95.5 mg, 0.194 mmol) and $NaHCO_3$ (66.4 mg, 0.790 mmol) in CH_2Cl_2 (2 mL) was added Dess–Martin's periodinane (167 mg, 0.394 mmol) at room temperature. After 5 h, the mixture was quenched with $Na_2S_2O_3$ aq and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give 91.8 mg (97%) of **28** as a pale yellow oil. $[\alpha]_{D^{17}}$ +4.53 (*c* 1.18, $CHCl_3$); IR: ν_{max} 2720 (w), 1726 (s), 1247 (s), 1087 (s), 836 (s); ^1H NMR (400 MHz): δ 0.047 (3H, s), 0.062 (3H, s), 0.88 (9H, s), 1.17 (3H, d, *J*=6.1 Hz), 1.32–1.69 (6H, m), 1.74–1.89 (2H, m), 1.96–2.06 (2H, m), 2.69 (1H, ddd, *J*=16.2, 6.3, 2.3 Hz), 2.73 (1H, ddd, *J*=16.2, 7.8, 2.6 Hz), 3.43–3.52 (1H, m), 3.79 (3H, s), 3.85 (1H, ddd, *J*=9.0, 4.3, 4.3 Hz), 4.01–4.08 (1H, m), 4.37 (1H, d, *J*=11.4 Hz), 4.37–4.44 (1H, m), 4.49 (1H, d, *J*=11.4 Hz), 5.41 (1H, dd, *J*=15.5, 5.7 Hz), 5.63 (1H, dtd, *J*=15.5, 6.6, 0.8 Hz), 6.84–6.89 (2H, m), 7.23–7.28 (2H, m), 9.77 (1H, dd, *J*=2.6, 2.3 Hz); ^{13}C NMR (100 MHz): δ −4.9, −4.7, 18.0, 19.6, 24.9, 25.7 (3C), 27.4, 28.2, 32.3, 36.1, 42.1, 55.2, 67.8, 69.9, 70.4, 71.4, 74.2, 113.6 (2C), 129.1 (2C), 129.5, 131.1, 132.9, 158.9, 201.2; HRMS (EI): *m*/*z* calcd for $C_{28}H_{46}O_5Si$, 490.3115; found, 490.3113 (M^+).

*4.1.3. {(2R,3S,6R)-3-tert-Butyldimethylsilyloxy-6-[(S)-6-(4-methoxybenzyloxy)-1-heptenyl]tetrahydropyran-2-yl}acetaldehyde (**29**).* To a stirred solution of **28** (71.0 mg, 0.145 mmol) in MeOH (0.6 mL) was added D-proline (5.2 mg, 44 μmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, warmed to 60 °C, and then stirred for an additional 3 h. The mixture was diluted with EtOAc and successively washed with satd $NaHCO_3$ aq and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give 57.4 mg (81%) of **29** as a pale yellow oil. $[\alpha]_{D^{21}}$ +45.6 (*c* 1.13, $CHCl_3$); IR: ν_{max} 2733 (w), 1728 (s), 1247 (s), 1092 (vs), 836 (s); ^1H NMR (400 MHz): δ 0.050 (3H, s), 0.064 (3H, s), 0.87 (9H, s), 1.16 (3H, d, *J*=6.2 Hz), 1.32–1.61 (6H, m), 1.69–1.77 (1H, m), 1.94–2.09 (3H, m), 2.48 (1H, ddd, *J*=16.2, 8.6, 3.0 Hz), 2.76 (1H, ddd, *J*=16.2, 3.9, 2.0 Hz), 3.35 (1H, ddd, *J*=10.0, 9.0, 4.5 Hz), 3.43–3.52 (1H, m), 3.71 (1H, ddd, *J*=8.6, 8.6, 3.9 Hz), 3.80 (3H, s), 3.78–3.86 (1H, m), 4.37 (1H, d, *J*=11.3 Hz), 4.48 (1H, d, *J*=11.3 Hz), 5.40 (1H, dd, *J*=15.5, 5.8 Hz), 5.63 (1H, dtd, *J*=15.5, 6.7, 0.8 Hz), 6.84–6.89 (2H, m), 7.23–7.28 (2H, m), 9.78 (1H, dd, *J*=3.0, 2.0 Hz); ^{13}C NMR (100 MHz): δ −4.8, −4.0, 17.9, 19.6, 24.9, 25.7 (3C), 31.3, 32.3, 33.2, 36.1, 46.6, 55.2, 69.9, 70.8, 74.3, 77.8, 77.8, 113.7 (2C), 129.1 (2C), 130.0, 131.1, 132.1, 159.0, 201.8; HRMS (EI): *m*/*z* calcd for $C_{28}H_{46}O_5Si$, 490.3115; found, 490.3118 (M^+).

*4.1.4. {(2R,3S,6R)-3-tert-Butyldimethylsilyloxy-6-[(S)-6-hydroxy-1-heptenyl]tetrahydropyran-2-yl}acetaldehyde (**30**).* To a stirred mixture of **29** (70.0 mg, 0.143 mmol) in CH_2Cl_2 (0.75 mL)/1 M phosphate buffer (pH 7.0, 0.25 mL) was added DDQ (67.5 mg, 0.288 mol) at room temperature. After 5 h, additional DDQ (66.7 mg, 0.285 mmol) was added, and the mixture was stirred for 3 h. The mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=5:1–3:1) to give 42.2 mg (80%) of **30** as a yellow oil. $[\alpha]_{D^{18}}$ +49.1 (*c* 1.02, $CHCl_3$); IR: ν_{max} 3414 (br m), 2734 (w), 1728 (s), 1253 (s), 1091 (vs); ^1H NMR (400 MHz): δ 0.050 (3H, s), 0.064 (3H, s), 0.87 (9H, s), 1.18 (3H, d, *J*=6.1 Hz), 1.35–1.62 (7H, m), 1.71–1.78 (1H, m), 1.96–2.08 (3H, m), 2.48 (1H, ddd, *J*=16.2, 8.6, 3.1 Hz), 2.77 (1H, ddd, *J*=16.2, 3.9, 1.8 Hz), 3.35 (1H, ddd, *J*=10.0, 9.0, 4.5 Hz), 3.71 (1H, ddd, *J*=8.8, 8.8, 3.9 Hz), 3.75–3.87 (2H, m), 5.43 (1H, dd, *J*=15.5, 5.8 Hz), 5.64 (1H, dtd, *J*=15.5, 6.6, 0.8 Hz), 9.77–9.80 (1H, m); ^{13}C NMR (100 MHz): δ −4.8, −4.0, 17.9, 23.5, 25.1, 25.7 (3C), 31.3, 32.2, 33.2, 38.7, 46.6, 67.9, 70.8, 77.8, 77.8, 130.1, 131.9, 201.9; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{39}O_4Si$, 371.2618; found, 371.2619 ($[M+H]^+$).

*4.1.5. {(2R,3S,6R)-3-tert-Butyldimethylsilyloxy-6-[(S)-6-hydroxy-1-heptenyl]tetrahydropyran-2-yl}acetic acid (**31**).* To a stirred solution of **30** (41.6 mg, 0.112 mmol) and 2-methyl-2-butene (1.5 mL) in *t*-BuOH (1.5 mL) was added to a freshly prepared mixture of $NaClO_2$ (55.8 mg, 0.494 mmol) and 20% NaH_2PO_4 aq (2.7 mL) at 0 °C. After being stirred at 0 °C for 7 h in the dark, the mixture was quenched with satd NH_4Cl aq and extracted with EtOAc. The extract was

washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1–1:1) to give 41.9 mg (97%) of **31** as a white solid. Mp 82.5–83.5 °C; $[\alpha]_{D^{20}}$ +68 (*c* 0.92, $CHCl_3$); IR: ν_{max} 3375 (br w), 3293 (br w), 2666 (br w), 1703 (s), 1095 (s); ^{1}H NMR (400 MHz): δ 0.063 (6H, s), 0.87 (9H, s), 1.18 (3H, d, *J*=6.3 Hz), 1.36–1.60 (6H, m), 1.70–1.77 (1H, m), 1.98–2.09 (3H, m), 2.44 (1H, dd, *J*=15.7, 9.0 Hz), 2.85 (1H, dd, *J*=15.7, 3.1 Hz), 3.30–3.38 (1H, m), 3.61 (1H, ddd, *J*=8.9, 8.9, 3.2 Hz), 3.75–3.89 (2H, m), 5.44 (1H, dd, *J*=15.4, 5.9 Hz), 5.66 (1H, dt, *J*=15.4, 6.7 Hz); ^{13}C NMR (100 MHz): δ −4.8, −4.0, 17.9, 23.4, 25.0, 25.7 (3C), 31.1, 32.1, 33.1, 37.7, 38.6, 68.0, 70.6, 78.0, 78.7, 130.0, 132.4, 175.2; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{39}O_5Si$, 387.2567; found, 387.2564 ($[M+H]^+$).

*4.1.6. (1R,5S,11R,14S)-14-tert-Butyldimethylsilyloxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (**32**).* To a stirred solution of **31** (9.0 mg, 23 μmol) and Et_3N (20 μL, 144 μmol) in THF (0.5 mL) was added 2,4,6-trichlorobenzoyl chloride (19.0 μL, 118 μmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with toluene (3 mL) and stirred for an additional 0.5 h. The resulting mixture was added dropwise to a solution of DMAP (43.5 mg, 356 μmol) in toluene (25 mL) at 80 °C over 7 h. The mixture was cooled to room temperature and then diluted with EtOAc. The resulting solution was successively washed with 0.5 M HCl aq, satd $NaHCO_3$ aq, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative TLC (Merck silica gel 60 F_{254}, 0.25 mm thick, hexane/EtOAc=5:1) to give 2.6 mg (30%) of **32** and 3.2 mg (19%) of macrodiolide **33** as colorless oils. **32**: $[\alpha]_{D^{20}}$ −30 (*c* 0.20, $CHCl_3$); IR: ν_{max} 1733 (s), 1660 (w), 1065 (s), 1029 (s); ^{1}H NMR (400 MHz): δ 0.047 (3H, s), 0.053 (3H, s), 0.90 (9H, s), 1.21 (3H, d, *J*=6.7 Hz), 1.30–1.38 (1H, m), 1.46–1.61 (3H, m), 1.70–1.82 (1H, m), 1.86–1.97 (2H, m), 2.06–2.16 (1H, m), 2.21–2.31 (2H, m), 2.38 (1H, dd, *J*=14.5, 4.5 Hz), 2.53 (1H, dd, *J*=14.5, 12.7 Hz), 3.53 (1H, dt, *J*=4.7, 2.9 Hz), 4.08 (1H, dm, *J*=12.7 Hz), 4.14–4.20 (1H, m), 4.93–5.02 (1H, m), 5.73 (1H, ddd, *J*=15.3, 8.8, 3.3 Hz), 5.79 (1H, ddd, *J*=15.3, 7.7, 1.4 Hz); ^{13}C NMR (100 MHz): δ −4.8, −4.7, 18.1, 18.5, 23.2, 24.1, 24.2, 25.8 (3C), 30.9, 31.8, 40.8, 68.0, 71.4, 72.0, 74.9, 132.8, 136.9, 170.7; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{37}O_4Si$, 369.2461; found, 369.2465 ($[M+H]^+$). **33**: $[\alpha]_{D^{23}}$ +49 (*c* 0.39, $CHCl_3$); IR: ν_{max} 1731 (s), 1186 (m), 1130 (m), 1089 (s); ^{1}H NMR (400 MHz): δ 0.048 (6H, s), 0.059 (6H, s), 0.88 (18H, s), 1.20 (6H, d, *J*=6.3 Hz), 1.31–1.50 (8H, m), 1.51–1.62 (4H, m), 1.71–1.78 (2H, m), 1.83–1.95 (2H, m), 1.95–2.12 (4H, m), 2.27 (2H, dd, *J*=13.7, 10.8 Hz), 2.80 (2H, dd, *J*=13.7, 2.3 Hz), 3.31 (2H, ddd, *J*=10.2, 9.2, 4.7 Hz), 3.62 (2H, ddm, *J*=8.6, 2.3 Hz), 3.73–3.80 (2H, m), 5.01–5.11 (2H, m), 5.38 (2H, dd, *J*=15.5, 5.3 Hz), 5.57 (2H, dd, *J*=15.5, 6.5 Hz); ^{13}C NMR (100 MHz): δ −4.8 (2C), −4.0 (2C), 17.9 (2C), 20.3 (2C), 24.6 (2C), 25.7 (6C), 31.4 (2C), 32.2 (2C), 33.3 (2C), 35.9 (2C), 38.7 (2C), 70.2 (2C), 70.7 (2C), 77.3 (2C), 80.1 (2C), 130.0 (2C), 131.1 (2C), 172.3 (2C); HRMS (EI): *m*/*z* calcd for $C_{40}H_{72}O_8Si_2$, 736.4766; found, 736.4771 (M^+).

*4.1.7. (1R,5S,11R,14S)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (**1**).* To a stirred solution of **32** (1.9 mg, 5.2 μmol) in THF (0.1 mL) was added TBAF (1 M solution in THF, 15 μL, 15 μmol) at room temperature, and the mixture was stirred for 2 h before being diluted with EtOAc. The resulting solution was successively washed with satd NH_4Cl aq and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=3:1–1:3) to give 1.0 mg (76%) of **1** as a white solid. Mp 64.5–65.5 °C; $[\alpha]_{D^{23}}$ −59 (*c* 0.13, $CHCl_3$) [lit.[1] $[\alpha]_{D^{27}}$ −59.5 (*c* 0.45, $CHCl_3$)]; IR: ν_{max} 3495 (m), 1735 (s), 1665 (w), 1011 (s), 976 (s); ^{1}H NMR: δ 1.21 (3H, d, *J*=6.8 Hz), 1.38–1.44 (1H, m), 1.48–1.57 (2H, m), 1.70–1.76 (1H, m), 1.79–1.87 (1H, m), 1.89–1.99 (2H, m), 2.08–2.17 (1H, m), 2.17–2.26 (2H, m), 2.28–2.34 (1H, m), 2.40 (1H, dd, *J*=15.6, 4.4 Hz), 2.65 (1H, dd, *J*=15.6, 13.2 Hz), 3.59 (1H, br s), 4.23–4.29 (1H, m), 4.27 (1H, br s), 4.93–5.00 (1H, m), 5.72 (1H, ddd, *J*=15.1, 9.3, 3.4 Hz), 5.81 (1H, ddd, *J*=15.1, 8.8, 2.0 Hz); ^{13}C NMR (125 MHz): δ 18.6, 21.7, 22.0, 23.7, 31.1, 32.2, 40.5, 66.8, 71.2, 71.5, 74.0, 132.1, 137.1, 170.0; HRMS (EI): *m*/*z* calcd for $C_{14}H_{22}O_4$, 252.1518; found, 252.1522 (M^+).

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Supplementary data

Supplementary data contains the ^{1}H and ^{13}C NMR spectral data of compounds **27**–**33**, and **1**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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17. The transformation (**23**→**24**) was effected in 20% yield by Fuwa and co-workers in their unified total synthesis of aspergillides A and B (Refs. 7c and 7e).
18. Massi, A.; Nuzzi, A.; Dondoni, A. *J. Org. Chem.* **2007**, *72*, 10279–10282 This method was originally developed for the epimerization of α-*C*-glycosylmethyl aldehydes with l-proline into the corresponding β-isomers. Taking into account the absolute stereochemistry of d-sugars employed as the substrates by Massi and co-workers, we employed d-proline as the first choice. The use of l-proline, however, gave almost the same result as that of d-proline..

19. For examples of related epimerization reactions using catalysts other than proline, see: (a) Tatsuta, K.; Suzuki, Y.; Toriumi, T.; Furuya, Y.; Hosokawa, S. *Tetrahedron Lett.* **2007**, *48*, 8018–8021; (b) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, *61*, 11679–11685; (c) Wang, Z.; Shao, H.; Lacroix, E.; Wu, S.-H.; Jennings, H. J.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105; (d) Shao, H.; Wang, Z.; Lacroix, E.; Wu, S.-H.; Jennings, H. J.; Zou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130–2131; (e) Michelet, V.; Adiey, K.; Bulic, B.; Genêt, J.-P.; Dujardin, G.; Rossignol, S.; Brown, E.; Toupet, L. *Eur. J. Org. Chem.* **1999**, 2885–2892.
20. (a) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707–721; (b) Smith, A. B., III; Dong, S.; Brenneman, J. B.; Fox, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 12109–12111.
21. The *m*-bromobenzoate of **1** analogous to **32** was revealed to exist in a conformation with the C3-, C4-, and C7-substituents axially oriented by its X-ray crystallographic analysis, and the MOM-protected congener (**24** in Scheme 4) of **32** was also shown to adopt essentially the same conformation as the *m*-bromobenzoate. For details, see Refs. 4 and 7e.