Total Synthesis of the *Z*-Isomers of the Proposed and Revised Structures of Aspergillide B via an Iodocyclization and Ring-Closing Metathesis Strategy

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Abstract: The synthesis of *Z*-isomers of both the proposed and revised structures of aspergillide B is described. A divergent route is employed that involves kinetically controlled ring-closing metathesis for the construction of a 14-membered macrocyclic ring, ester formation under Yamaguchi conditions, a Wacker-type oxidative cyclization for creation of the C4 stereogenic center and a previously reported diastereoselective isomerization–iodocyclization strategy for the construction of the 2,6-*trans*-disubstituted tetrahydropyran subunit.

Key words: aspergillides, ring-closing metathesis, Yamaguchi esterification, Wacker-type oxidation, iodocyclization, cytotoxic activity

Kusumi and co-workers isolated aspergillides A–C from the marine derived fungus, *Aspergillus ostianus* strain 01F313, cultured in a potato–dextrose (1/2PD) medium containing bromine-modified artificial sea water, and thereby launched an exciting chapter in natural product synthesis.[1] These novel macrolides exhibit significant cytotoxic activity against mouse lymphocytic leukemia cells with LD_{50} values ranging from 2–70 μg/mL. Structurally, the aspergillide macrolides bear a 14-membered lactone ring with 2,6-*cis*- or 2,6-*trans*-trisubstituted dihydro- or tetrahydropyran subunits and an *E*-alkene bond at C8–C9. Though the structures and stereochemistry were established on the basis of detailed NMR studies and by employing a modified Mosher's ester method, there were some discrepancies in the structures of aspergillides A and B. However, Kusumi and Uenishi assigned the corrected structures via X-ray crystallographic analysis of the benzoate ester derivatives, and by total synthesis.[2,3] The proposed and confirmed structures of aspergillides A and B are shown in Figure 1. Because of their potent cytotoxic activity and unique structural features, the aspergillides have attracted interest from the synthetic community.[2,4–6] Due to these structural ambiguities, we have focused our attention on the syntheses of the *Z*-isomers of both the enantiomers (revised and proposed) of aspergillide B.

Our group has previously developed an efficient and novel iodocyclization strategy for the synthesis of *trans*-2,6-dihydropyrans, which are building blocks of many complex bioactive natural products. The versatility of this methodology has resulted in the synthesis of complex natural products such as the bicyclic core of (+)-sorangicin A,[7a] the macrolactone core of leucascandrolide A,[7c] the total synthesis of polyrachitides[7b] and the formal total synthesis of cladosporin.[7d] In continuation of our efforts toward the synthesis of pyran-containing complex natural products, herein, we report a divergent synthesis of the proposed and revised structures of aspergillide B, with *cis*-alkene geometry at C8–C9, by employing an iodocyclization and ring-closing metathesis (RCM) based strategy.

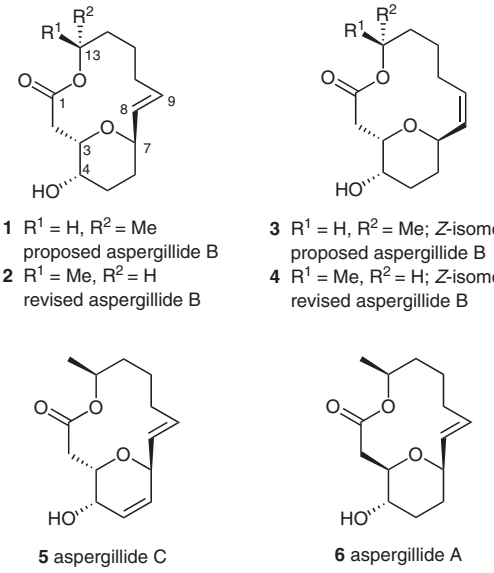

Figure 1 Structures of aspergillides A–C

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecules could be prepared from macrolactones **3** and **4**, which in turn could be synthesized from dienes **7a** and **7b**, respectively, following ring-closing metathesis[8] and *tert*-butyldimethylsilyl ether deprotection. Dienes **7a** or **7b** could be obtained by coupling of acid **10** with alcohols **8a** or **8b** under Yamaguchi conditions.[9] Alcohols **8a** and **8b** could in turn be obtained from enantiomerically pure epoxides **9a** and **9b**, respectively. Acid **10** could be prepared from pyran **11**, which itself could be easily accessible from enantiomerically pure epoxide **12**.

As per our retrosynthetic analysis, the synthesis of both (*R*)- and (*S*)-alkenols **8a** and **8b** was achieved from the regioselective ring-opening of chiral propylene oxides **9a** and **9b**, respectively, using 3-butenylmagnesium bromide

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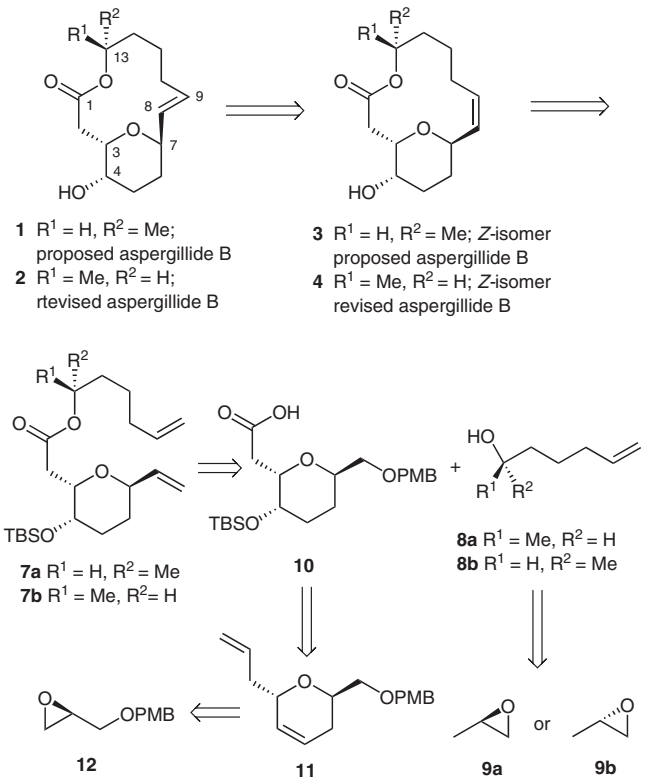
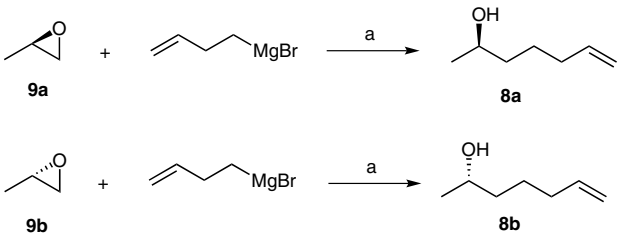


Scheme 1 Retrosynthetic analysis of both the isomers of aspergillide B

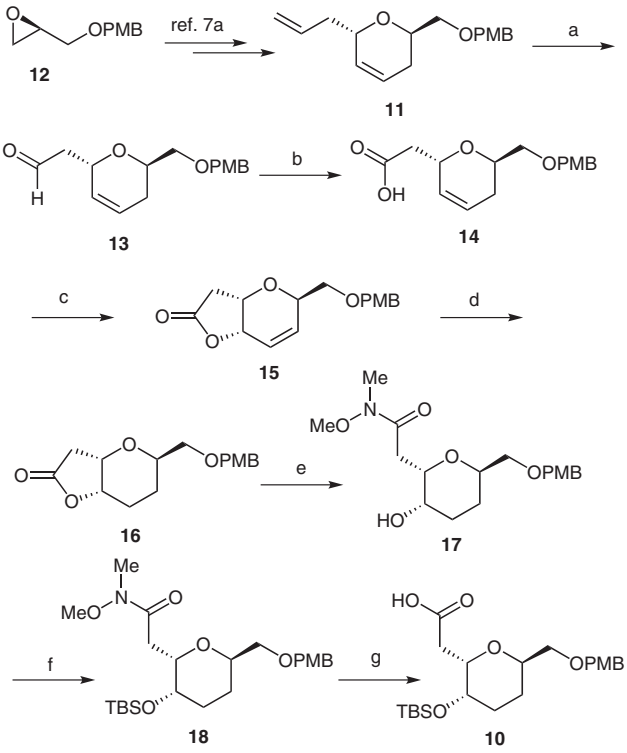
in the presence of 10 mol% of copper(I) cyanide (CuCN) (Scheme 2).[10]



Scheme 2 Synthesis of the alcohol intermediates **8a** and **8b**. *Reagents and conditions*: (a) CuCN (0.1 equiv), THF, –40 °C, 2 h (**8a** = 82%, **8b** = 84%).

The synthesis of the acid fragment **10** began from *p*-methoxybenzyl (PMB) protected glycidol **12**, which on transformation, following the sequence previously described by our group,[7b] furnished the 2,6-*trans*-disubstituted dihydropyran **11**. Compound **11** was subsequently converted into the trisubstituted pyran core by employing a Wacker-type oxidative lactonization sequence (Scheme 3).

Accordingly, the terminal double bond of compound **11** was transformed into an aldehyde via a selective, one-step dihydroxylation–oxidation sequence to give **13**.[11] Aldehyde **13** was easily converted into the corresponding acid **14** in 93% yield under Pinnick oxidation conditions.[12] Introduction of the requisite oxygen, with the correct stereo-



Scheme 3 Synthesis of the acid intermediate **10**. *Reagents and conditions*: (a) $NaIO_4$, OsO_4, 2,6-lutidine, 1,4-dioxane–H_2O (3:1), 0 °C, 3 h, 87%; (b) NaH_2PO_4, $NaClO_2$, 2-methylbut-2-ene, *t*-BuOH–H_2O (1:1), 3 h, 0 °C to r.t., 94%; (c) $Pd(OAc)_2$, $Cu(OAc)_2$, NaOAc·$3H_2O$, O_2, DMSO, 80 °C, 4 h, 74%; (d) Pd/C (10 wt%), Et_3N, H_2 (1 atm), toluene, 1 h, 97%; (e) Me(OMe)NH·HCl, Me_3Al, 0 °C to r.t., CH_2Cl_2, 2 h, 85%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to r.t., 30 min, 96%; (g) (i) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, (ii) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH–H_2O (1:1), 0 °C to r.t., 3 h, 68% over 2 steps.

chemistry at C4 of the macrolide, was achieved by palladium(II)-catalyzed oxidative lactonization of γ,δ-unsaturated acid **14** in a completely *syn*-selective manner involving double bond migration.[6b,13] Hydrogenation of unsaturated lactone **15** using palladium on carbon (10 wt%) in toluene gave lactone **16**, which was converted into the corresponding hydroxy-amide **17** in 85% yield using the Weinreb amine salt, *N*,*O*-dimethylhydroxylamine hydrochloride, and trimethylaluminum as the base.[14] The secondary hydroxy group in compound **17** was protected as its *tert*-butyldimethylsilyl ether (TBSOTf, 2,6-lutidine) to afford compound **18**. Controlled reduction of amide **18** with diisobutylaluminum hydride (DIBAL-H) afforded the corresponding aldehyde, which on subsequent oxidation under Pinnick conditions provided the advanced intermediate **10**.

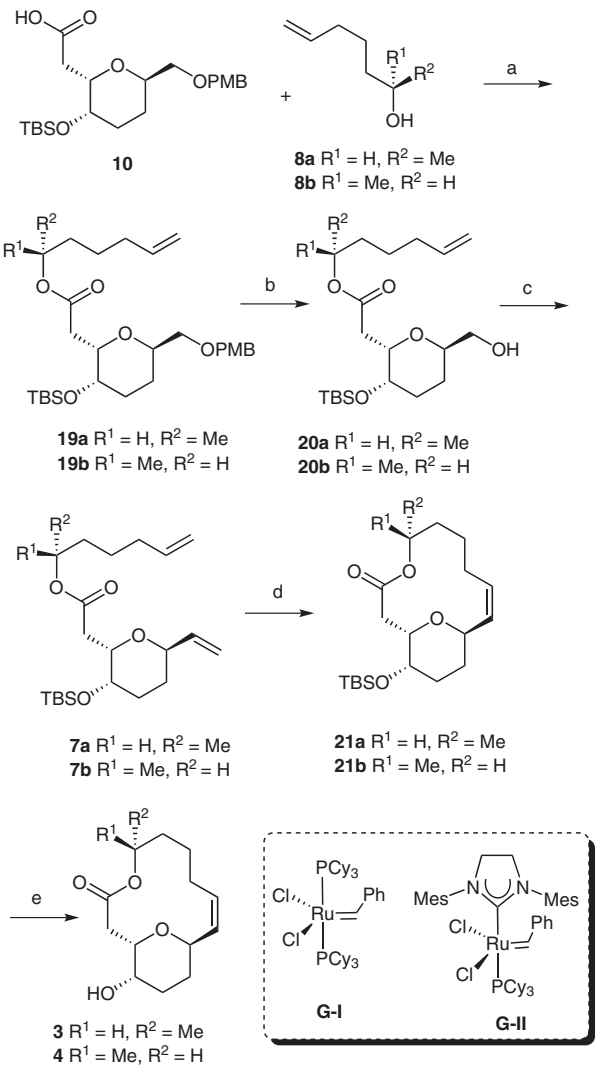
Having successfully synthesized the fragments **8a**, **8b** and **10** in convenient and highly stereoselective manners, we next focused on their coupling under different lactonization conditions. Initially, the coupling was carried out using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP).[15] Unfortunately, the reaction was very sluggish and afforded the product in poor yield. Changing the coupling reagent to *N*-ethyl-*N*′-

(dimethylaminopropyl)carbodiimide (EDCI)[16] did not improve the yield substantially. Furthermore, changing the solvent from dichloromethane to *N*,*N*-dimethylformamide was not successful. We then turned our attention to the Yamaguchi esterification where 2,4,6-trichlorobenzoyl chloride and 4-(*N*,*N*-dimethylamino)pyridine were used as the coupling reagents. Under these conditions, the coupled products **19a** and **19b** were obtained in very good yields. Compounds **19a** and **19b** were next subjected to selective deprotection of the *p*-methoxybenzyl ether in the presence of the silyl ether using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (buffered at pH 7) in CH_2Cl_2 to afford the primary alcohols **20a** and **20b** in good yields. The primary alcohol was oxidized into an aldehyde with 2-iodoxybenzoic acid (IBX) in acetonitrile at reflux temperature,[17] and subsequent one-carbon Wittig homologation with methyltriphenylphosphonium iodide furnished the corresponding dienes **7a** and **7b**.

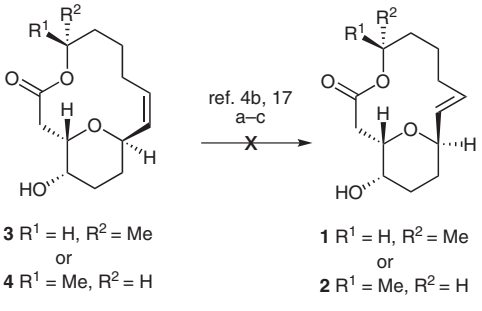
With both the ring-closing metathesis precursors in hand, we focused our attention on the crucial macrocyclization by following the method reported by Diaz-Oltra and coworkers during their synthesis of aspergillide A.[4b,18] Their prediction of the stereochemical outcome of the ring-closing metathesis reaction was that a relatively flexible 14-membered macrolide containing a tetrahydropyran would form in a *cis*-selective manner under kinetically controlled conditions. Thus, treatment of dienes **7a** and **7b** with 10 mol% of Grubbs' first- or second-generation catalysts (**G-I** or **G-II**), in dichloromethane at reflux temperature, furnished the macrocyclization products **21a** and **21b** with the desired *cis*-geometry (confirmed from the coupling constants, $J = 10.9$ Hz for **21a** and $J = 10.5$ Hz for **21b**) (Scheme 4). The above observation from the ring-closing metathesis suggested that even for a flexible lactone, the presence of a tetrahydropyran ring switches the stereochemical outcome of the reaction from a thermodynamically stable *trans* product to that of a kinetically favored *cis* product. Compounds **21a** and **21b** were subjected to desilylation by treatment with tetra-*n*-butylammonium fluoride (TBAF) to furnish the products **3** and **4** in 90% and 92% yields, respectively.

We next focused our attention on the isomerization of the *cis* double bond. However, by following the earlier reported conditions for *cis–trans* isomerization,[18] we did not obtain the desired isomerized products even after reacting for two days (Scheme 5).

In summary, we have accomplished the synthesis of the *Z*-isomers of both the proposed and revised structures of aspergillide B, by a divergent route that involves kinetically controlled ring-closing metathesis for the construction of a 14-membered macrocyclic ring, Yamaguchi esterification, a Wacker-type oxidative cyclization for the creation of the C4 stereogenic center, and a diastereoselective isomerization–iodocyclization strategy for the construction of the 2,6-*trans*-disubstituted tetrahydropyran subunit. Further application of the iodocyclization strategy to the synthesis of other aspergillides is underway in our laboratory and the results will be reported in due course.



Scheme 4 Synthesis of macrolactones **3** and **4**. *Reagents and conditions*: (a) Et_3N, 2,4,6-trichlorobenzoyl chloride, DMAP, 3 h, 0 °C to r.t. (**19a** = 85%, **19b** = 83%); (b) DDQ, CH_2Cl_2–H_2O (9:1), r.t. (**20a** = 90%, **20b** = 87%); (c) (i) IBX, MeCN, 85 °C, 1 h; (ii) $Me^+PPh_3I^-$, *n*-BuLi, 30 min, aldehyde, –78 °C to 0 °C (**7a** = 52%, **7b** = 55%, over 2 steps); (d) **G-II**, CH_2Cl_2, reflux, 4 h (**21a** = 82%, **21b** = 79%); (e) TBAF, THF, r.t., 2 h (**3** = 90%, **4** = 92%).



Scheme 5 Toward the synthesis of aspergillides B (**1**) and (**2**). *Reagents and conditions*: (a) *hν* (>280 μm), 25 °C, 48 h, no reaction; (b) I_2 (cat.), CH_2Cl_2, sunlight, 36 h, no reaction; (c) *hν* (250–280 μm), quartz tube, toluene, 24–36 h, no reaction.

Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an Ar atmosphere in oven- or flame-dried glassware. Experiments which required an inert atmosphere were carried out under dry N_2 in flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, toluene and Et_2O from Na and benzophenone; CH_2Cl_2, DMSO, DMF and hexane from CaH_2; MeOH and EtOH from Mg cake. Commercial reagents were used without purification. Thin-layer chromatography was performed on precoated silica gel-60 F_{254} (0.5 mm) glass plates (Merck). Flash column chromatography was carried out on 60–120 mesh or 100–200 mesh silica gel (Merck). Optical rotations $[\alpha]_D$ were obtained using a Perkin Elmer model 343 apparatus and are given in 10^{-1} deg·cm^2·g^{-1}. IR spectra were recorded using a Perkin-Elmer Infrared-683 spectrophotometer and are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded using Bruker Avance 300, Avance 500, and Varian 400 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. HRMS spectra were obtained using a CEC-21-11013 double focussing mass spectrometer operating at 70 eV.

2-{(2*S*,6*R*)-6-[(4-Methoxybenzyloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl}acetaldehyde (13)

To a stirred solution of alkene **11** (3.0 g, 10.948 mmol) in 1,4-dioxane (40 mL) was added 2,6- lutidine (2.4 mL, 21.897 mmol). $NaIO_4$ (9.4 g, 43.795 mmol) was dissolved in distilled H_2O (12 mL) and then added to the above reaction mixture at 0 °C. Next, OsO_4 (0.11 mL, 0.219 mmol, 2 M solution in toluene) was added at the same temperature and stirring was continued in the dark. After completion of the reaction (as indicated by TLC), the mixture was quenched with sat. aq $NaHSO_3$ solution (30 mL). The organic solvent was removed under reduced pressure and the aq layer was extracted with MTBE (3 × 75 mL). The combined organic layer was washed with HCl (1 M, 3 × 30 mL) to remove excess 2,6-lutidine and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified over silica gel (EtOAc–hexane, 1:4) to furnish the desired aldehyde **13** as a pale yellow liquid (2.6 g, 87%).

$[\alpha]_D^{25}$ +37.8 (*c* 2.1, $CHCl_3$).

IR (neat): 2926, 2857, 1723, 1610, 1512, 1248, 1097, 823 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.82 (t, *J* = 2.3 Hz, 1 H), 7.24 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 9.1 Hz, 2 H), 5.89 (dddd, *J* = 2.3, 5.3, 9.8, 14.4 Hz, 1 H), 5.70 (dddd, *J* = 2.3, 4.5, 9.8, 14.4 Hz, 1 H), 4.81 (m, 1 H), 4.50 (s, 2 H), 3.97–3.85 (m, 1 H), 3.80 (s, 3 H), 3.49 (dddd, *J* = 6.0, 9.8, 15.8, 17.4 Hz, 2 H), 2.79 (dddd, *J* = 3.0, 9.1, 13.6, 15.6 Hz, 1 H), 2.57 (dddd, *J* = 1.5, 4.5, 15.9, 16.6 Hz, 1 H), 2.12–1.98 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.9, 159.0, 130.1, 129.2, 127.7, 124.8, 113.6, 72.9, 71.7, 67.8, 67.4, 55.1, 47.7, 26.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}O_4Na$: 299.1238; found: 299.1243.

2-{(2*S*,6*R*)-6-[(4-Methoxybenzyloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl}acetic Acid (14)

To a solution of aldehyde **13** (2.2 g, 7.971 mmol) in *t*-BuOH (35 mL) was added 2-methyl-2-butene (8.0 mL, 7.971 mmol, 1 M solution in THF) at r.t. A solution of NaH_2PO_4 (3.7 g, 23.913 mmol) and $NaClO_2$ (1.1 g, 11.95 mmol) in H_2O (35 mL) was added to the reaction mixture at 0 °C, which was then allowed to stir for 3 h at r.t. After completion of the reaction (monitored by TLC), the mixture was extracted with EtOAc (3 × 75 mL), and the combined organic layer washed with brine (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc–hexane, 2:3) to afford acid **14** (2.18 g, 94%) as a colorless oil.

$[\alpha]_D^{25}$ +27.0 (*c* 1.5, $CHCl_3$).

IR (neat): 3036, 2923, 1729, 1712, 1612, 1513, 1248, 1092, 1035, 824, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 5.88 (m, 1 H), 5.71 (m, 1 H), 4.66 (m, 1 H), 4.48 (s, 2 H), 3.90 (m, 1 H), 3.79 (s, 3 H), 3.51 (dd, *J* = 6.4, 10.2 Hz, 1 H), 3.43 (dd, *J* = 4.5, 10.2 Hz, 1 H), 2.71 (dd, *J* = 9.2, 15.3 Hz, 1 H), 2.50 (dd, *J* = 4.9, 15.3 Hz, 1 H), 2.07–1.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 159.2, 130.0, 129.4, 127.5, 125.1, 113.7, 73.0, 71.7, 69.1, 67.5, 55.2, 38.7, 26.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}O_5Na$: 315.1187; found: 315.1202.

(3*S*,5*R*,7*S*)-5-[(4-Methoxybenzyloxy)methyl]-3,3a,5,7a-tetrahydro-2*H*-furo[3,2-*b*]pyran-2-one (15)

A solution of acid **14** (1.8 g, 6.164 mmol), $NaOAc·3H_2O$ (1.67 g, 12.328 mmol), $Cu(OAc)_2$ (2.2 g, 12.328 mmol) and $Pd(OAc)_2$ (0.138 g, 0.616 mmol) in DMSO (30 mL) was stirred at 80 °C under an O_2 atm for 8 h. After dilution with sat. NH_4Cl solution (50 mL) and extraction with CH_2Cl_2 (4 × 50 mL), the combined organic layers were washed with brine (2 × 75 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc–hexane, 1:2) afforded the lactone **15** (1.32 g, 74%) as a colorless oil.

$[\alpha]_D^{25}$ –12.5 (*c* 0.8, $CHCl_3$).

IR (neat): 2932, 2859, 1788, 1771, 1611, 1513, 1249, 1155, 1036, 835 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.89 (d, *J* = 8.3 Hz, 2 H), 6.17–6.13 (m, 2 H), 4.63 (m, 1 H), 4.54 (m, 1 H), 4.50 (d, *J* = 1.5 Hz, 2 H), 4.40 (m, 1 H), 3.81 (s, 3 H), 3.56 (d, *J* = 4.5 Hz, 2 H), 2.78 (dd, *J* = 6.0, 18.1 Hz, 1 H), 2.66 (d, *J* = 18.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 159.3, 133.4, 129.6, 129.3, 121.2, 113.8, 72.9, 72.1, 71.2, 69.6, 67.8, 55.2, 36.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_5Na$: 313.1037; found: 313.1046.

(3a*S*,5*R*,7a*S*)-5-[(4-Methoxybenzyloxy)methyl]hexahydro-2*H*-furo[3,2-*b*]pyran-2-one (16)

Pd/C (10 wt%) (350 mg) was added to a stirred solution of compound **15** (1.2 g, 3.448 mmol) in toluene (25 mL), followed by a catalytic amount of Et_3N at r.t. under a H_2 atm. The mixture was stirred for 1 h at r.t. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite and then washed thoroughly with EtOAc (3 × 25 mL). The filtrate was concentrated under reduced pressure and purification of the crude residue by silica gel column chromatography (EtOAc–hexane, 1:2) furnished the desired product **16** (0.976 g, 97%) as a colorless liquid.

$[\alpha]_D^{25}$ –31.8 (*c* 0.8, $CHCl_3$).

IR (neat): 2929, 2857, 1730, 1712, 1612, 1513, 1248, 1095, 1037, 821 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 4.46 (s, 2 H), 4.43–4.36 (m, 2 H), 3.94 (quin, 1 H), 3.80 (s, 3 H), 3.56–3.46 (m, 2 H), 2.65–2.49 (m, 2 H), 2.11–1.84 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 159.2, 131.7, 129.3, 113.8, 77.0, 72.9, 70.4, 69.6, 68.3, 55.2, 37.1, 21.5, 19.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}O_5Na$: 315.1192; found: 315.1202.

2-{(2*S*,3*S*,6*R*)-3-Hydroxy-6-[(4-methoxybenzyloxy)methyl]tetrahydro-2*H*-pyran-2-yl}-*N*-methoxy-*N*-methylacetamide (17)

To a stirred solution of Me(OMe)NH·HCl (0.8 g, 8.219 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise Me_3Al (4.1 mL, 8.219

mmol, 2 M solution in CH_2Cl_2) a period of 5 min at 0 °C, under an N_2 atm. The mixture was stirred at the same temperature for 45 min to form a clear solution. To this mixture was added dropwise a solution of lactone **16** (1.2 g, 4.109 mmol) in CH_2Cl_2 (25 mL) over a period of 20 min. After being stirred for another 1 h, the mixture was quenched with HCl (1 M, 20 mL) and the aq layer extracted with CH_2Cl_2 (3 × 40 mL). The resulting extract was washed with brine (2 × 60 mL), dried over Na_2SO_4 and concentrated in vacuo to give a yellow oily liquid, which following silica gel column chromatography (EtOAc–hexane, 7:3), furnished the desired γ-hydroxy amide **17** (1.23 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$ –10.8 (*c* 1.6, $CHCl_3$).

IR (neat): 3450, 2926, 2856, 1770, 1512, 1249, 1156, 1034, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.48 (AB_q, *J* = 11.7, 19.8 Hz, 2 H), 4.38 (m, 1 H), 3.87 (m, 2 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.58–3.50 (m, 1 H), 3.49–3.42 (m, 1 H), 3.19 (s, 3 H), 3.07 (s, 1 H), 2.96–2.75 (m, 2 H), 1.97–1.79 (m, 2 H), 1.74–1.60 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 159.1, 130.2, 129.2, 113.7, 72.9, 71.3, 71.0, 70.3, 68.2, 66.8, 61.3, 55.2, 32.1, 31.5, 26.2, 23.9, 21.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{27}NO_6Na$: 376.1714; found: 376.1720.

2{(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(4-methoxybenzyloxy)methyl]tetrahydro-2*H*-pyran-2-yl}-*N*-methoxy-*N*-methylacetamide (18)

To a stirred solution of hydroxy compound **17** (0.75 g, 2.124 mmol) in CH_2Cl_2 (30 mL) under an N_2 atm was added 2,6-lutidine (0.49 mL, 4.249 mmol) followed by TBSOTf (0.6 mL, 2.549 mmol) at 0 °C, and the resulting mixture stirred for 30 min. After completion of the reaction (monitored by TLC), the mixture was quenched with H_2O (20 mL) and diluted with CH_2Cl_2 (30 mL). The organic layer was separated and quickly washed with HCl (1 M, 2 × 20 mL) to remove excess 2,6-lutidine. The organic layer was then washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under vacuum. The crude residue was purified by silica gel column chromatography (EtOAc–hexane, 2:3) to furnish the desired silyl ether **18** (0.952 g, 96%) as a pale yellow oil.

$[\alpha]_D^{25}$ –12.8 (*c* 1.3, $CHCl_3$).

IR (neat): 2929, 2856, 1734, 1612, 1513, 1251, 1101, 1052, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.47 (s, 2 H), 4.42 (m, 1 H), 3.88 (m, 2 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 3.45 (dddd, *J* = 5.3, 10.0, 15.5, 16.1 Hz, 2 H), 3.17 (s, 3 H), 2.92–2.80 (m, 1 H), 2.69 (m, 1 H), 1.86–1.72 (m, 2 H), 1.66–1.38 (m, 2 H), 0.88 (s, 9 H), 0.05 (d, *J* = 5.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 159.0, 130.5, 129.2, 113.6, 72.9, 72.8, 71.7, 68.9, 68.1, 61.2, 55.2, 32.0, 29.3, 27.4, 25.8, 25.6, 18.0, –4.8, –5.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{41}NO_6SiNa$: 490.2560; found: 490.2565.

2-{(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(4-methoxybenzyloxy)methyl]-tetrahydro-2*H*-pyran-2-yl}acetic Acid (10)

To a stirred solution of the amide **18** (0.5 g, 1.071 mmol) in CH_2Cl_2 (25 mL), DIBAL-H (1.38 mL, 1.606 mmol, 1.2 M in toluene) was slowly added over a period of 5 min at –78 °C under an N_2 atm. After stirring for 30 min at the same temperature, TLC showed complete consumption of the starting material. The mixture was quenched by the slow addition of a sat. solution of sodium potassium tartrate (25 mL), then diluted with CH_2Cl_2 (30 mL) and allowed to stir at r.t. for another 2 h to afford two distinct layers. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under vacuum to give the crude aldehyde (0.31 g, 73%) as a colorless liquid, which was immediately used in the next step without further characterization.

To a solution of the crude aldehyde (0.31 g, 0.759 mmol) in *t*-BuOH (10 mL) was added 2-methyl-2-butene (0.76 mL, 0.759 mmol, 1 M solution in THF) at r.t. NaH_2PO_4 (0.315 g, 2.279 mmol) and $NaClO_2$ (0.103 g, 1.139 mmol) were dissolved in H_2O (10 mL) to form a clear solution, which was subsequently added to the above mentioned reaction mixture at 0 °C. The mixture was allowed to stir for a further 2 h at r.t. and then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc–hexane, 1:4) to afford the acid **10** (0.3 g, 93%) as a colorless oil.

$[\alpha]_D^{25}$ –20.8 (*c* 1.0, $CHCl_3$).

IR (neat): 2935, 2858, 1712, 1612, 1513, 1250, 1104, 1038, 838, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 4.42 (s, 2 H), 4.30 (m, 1 H), 3.88–3.78 (m, 2 H), 3.75 (s, 3 H), 3.42 (dd, *J* = 5.8, 10.2 Hz, 1 H), 3.33 (dd, *J* = 4.3, 10.0 Hz, 1 H), 2.74–2.59 (m, 2 H), 1.78–1.68 (m, 2 H), 1.58–1.34 (m, 2 H), 0.82 (s, 9 H), 0.01 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.9, 159.1, 130.1, 129.3, 113.7, 73.1, 72.9, 71.6, 68.7, 67.8, 55.2, 32.0, 27.2, 25.7, 17.9, –4.8, –5.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{36}O_6SiNa$: 447.2142; found: 447.2143.

(*R*)-Hept-6-en-2-yl 2-{(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(4-methoxybenzyloxy)methyl]tetrahydro-2*H*-pyran-2-yl)acetate (19a)

To a stirred solution of acid **10** (125 mg, 0.295 mmol) in dry toluene (5 mL) at 0 °C was added Et_3N (0.13 mL, 0.884 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.07 mL, 0.442 mmol), and the mixture was stirred for 30 min at r.t. A solution of DMAP (35 mg, 0.295 mmol) and (*R*)-alkenol **8a** (30 mg, 0.265 mmol) in dry toluene (10 mL) was added at 0 °C and the mixture was allowed to stir at r.t. for 6 h. After completion of the reaction (monitored by TLC), the mixture was diluted with EtOAc (25 mL) and H_2O (20 mL). The organic layer was separated and the aq layer extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to give a colorless oil. Purification by silica gel column chromatography (EtOAc–hexane, 1:14) furnished the desired coupled product **19a** (130 mg, 85% based on the starting acid) as a colorless liquid.

$[\alpha]_D^{25}$ –42.7 (*c* 0.9, $CHCl_3$).

IR (neat): 2930, 2857, 1731, 1612, 1513, 1251, 1099, 1057, 836, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.3 Hz, 2 H), 6.81 (d, *J* = 9.1 Hz, 2 H), 5.85–5.64 (m, 1 H), 5.08 (m, 1 H), 4.98–4.85 (m, 2 H), 4.42 (s, 2 H), 4.29 (quin, *J* = 5.2 Hz, 1 H), 3.92–3.81 (m, 1 H), 3.79 (s, 3 H), 3.74 (m, 1 H), 3.43–3.27 (m, 2 H), 2.66 (dddd, *J* = 4.5, 9.8, 15.1, 19.6 Hz, 1 H), 2.52 (dddd, *J* = 3.0, 7.5, 15.1, 19.6 Hz, 1 H), 2.10–1.97 (m, 2 H), 1.82–1.69 (m, 2 H), 1.65–1.38 (m, 6 H), 1.19 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 159.1, 138.5, 130.4, 129.2, 128.2, 114.7, 113.7, 73.8, 72.9, 72.0, 70.8, 68.2, 68.0, 55.2, 35.3, 33.5, 32.0, 27.4, 26.3, 25.8, 24.6, 19.9, 18.0, –4.7, –4.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{48}O_6SiNa$: 543.2749; found: 543.2756.

(*R*)-Hept-6-en-2-yl 2-[(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-(hydroxylmethyl)tetrahydro-2*H*-pyran-2-yl]acetate (20a)

To a solution of PMB-ether **19a** (0.12 g, 0.231 mmol) in CH_2Cl_2 (25 mL) and pH 7 buffer (3 mL) at r.t. was added DDQ (2.6 g, 11.60 mmol), and the mixture allowed to stir for 2 h at the same temperature. The mixture was quenched with sat. $NaHCO_3$ solution (25 mL) and the aq layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4 and evaporated to give a red-colored crude residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:4) to afford the desired primary alcohol **20a** (83 mg, 90%) as a colorless liquid.

$[\alpha]_D^{25}$ –38.7 (*c* 1.1, $CHCl_3$).

IR (neat): 3465, 2937, 2860, 1732, 1642, 1463, 1286, 1255, 1187, 1106, 837, 777 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.84–5.73 (m, 1 H), 5.01 (m, 1 H), 4.98–4.92 (m, 2 H), 4.27 (dt, *J* = 3.8, 10.7 Hz, 1 H), 3.85–3.73 (m, 2 H), 3.63 (dd, *J* = 7.9, 11.4 Hz, 1 H), 3.49 (m, 1 H), 2.71 (dd, *J* = 10.5, 15.9 Hz, 1 H), 2.51 (dd, *J* = 3.4, 15.7 Hz, 1 H), 2.23 (br s, 1 H), 2.05 (q, *J* = 7.6 Hz, 2 H), 1.80–1.72 (m, 2 H), 1.61–1.55 (m, 2 H), 1.51 (m, 1 H), 1.44–1.36 (m, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 138.4, 114.7, 72.3, 71.2, 70.1, 67.8, 63.9, 35.3, 33.5, 32.9, 27.4, 25.8, 24.6, 24.0, 19.9, –4.7, –4.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{40}O_5SiNa$: 423.2537; found: 423.2532.

(*R*)-Hept-6-en-2-yl 2-[(2*S*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]acetate (7a)

To a stirred solution of primary alcohol **20a** (70 mg, 0.175 mmol) in dry MeCN (8 mL) was added IBX (74 mg, 0.262 mmol) at r.t. under an Ar atm. The mixture was heated at 85 °C for 1 h. After completion of reaction (monitored by TLC), the mixture was diluted with Et_2O (15 mL) and then filtered through a pad of Celite. The filtrate was washed with sat. $NaHCO_3$ solution (20 mL) and the aq layer extracted with Et_2O (3 × 20 mL). The combined organic fraction was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (EtOAc–hexane, 1:9) to afford the pure aldehyde (56 mg, 81%) as a pale yellow liquid, which was immediately used in the next step.

The aldehyde (56 mg, 0.141 mmol) was dissolved in dry THF (5 mL) under N_2. In another round-bottomed flask, methyltriphenylphosphonium iodide (227 mg, 0.563 mmol) was taken up in dry THF (10 mL) under an N_2 atm, and cooled to 0 °C. *n*-BuLi (0.3 mL, 1.6 M in hexane) was slowly added and the mixture stirred for 30 min. During this time the mixture turned yellow, which was indicative of formation of the ylide. This yellow solution was cooled to –78 °C and then the aldehyde was added. The resulting solution was slowly warmed to 0 °C and stirred at the same temperature for 3 h. The mixture was quenched with sat. NH_4Cl solution (20 mL) and the organic compound was extracted into Et_2O (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc–hexane, 1:49) afforded the desired diene **7a** (35 mg, 64%).

$[\alpha]_D^{25}$ –14.2 (*c* 1.2, $CHCl_3$).

IR (neat): 3077, 2928, 2856, 2125, 1732, 1462, 1378, 1286, 1186, 1106, 1035, 837, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.68 (m, 2 H), 5.29–5.09 (m, 2 H), 5.05–4.90 (m, 3 H), 4.35–4.17 (m, 2 H), 3.82 (m, 1 H), 2.69 (dd, *J* = 9.6, 15.1 Hz, 1 H), 2.53 (dd, *J* = 8.3, 14.2 Hz, 1 H), 2.10–1.90 (m, 2 H), 1.97–1.87 (m, 1 H), 1.80–1.69 (m, 1 H), 1.66–1.54 (m, 3 H), 1.51–1.35 (m, 3 H), 1.20 (d, *J* = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 138.5, 138.1, 115.6, 114.7, 72.7, 70.9, 70.5, 67.7, 35.3, 33.8, 33.5, 27.4, 27.1, 25.84, 25.80, 24.6, 19.9, 18.1, –4.7, –4.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{40}O_4SiNa$: 419.2588; found: 419.2582.

(1*S*,5*R*,11*R*,14*S*,*Z*)-14-(*tert*-Butyldimethylsilyloxy)-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (21a)

Ar gas was bubbled through a stirred solution of diene **7a** (25 mg, 0.063 mmol) in CH_2Cl_2 (60 mL) for 15 min. **G-II** (5 mg, 10 mol%) was added and the mixture heated at reflux temperature for 3 h. At this point, TLC showed complete disappearance of the starting material. The solvent was evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:9) to furnish the *cis*-alkene **21a** (19 mg, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ –31.5 (*c* 0.8, $CHCl_3$).

IR (neat): 3008, 2923, 2851, 1724, 1446, 1368, 1219, 1176, 1059, 772 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.59 (td, *J* = 5.0, 10.9 Hz, 1 H), 5.36 (t, *J* = 9.8 Hz, 1 H), 5.27–5.16 (m, 1 H), 4.53 (t, *J* = 9.6 Hz, 1 H), 4.33 (m, 1 H), 3.93 (m, 1 H), 2.96 (t, *J* = 12.8 Hz, 1 H), 2.65–2.53 (m, 1 H), 2.48 (dd, *J* = 3.4, 13.3 Hz, 1 H), 1.93 (m, 1 H), 1.87–1.71 (m, 2 H), 1.68–1.52 (m, 4 H), 1.48–1.37 (m, 1 H), 1.32 (m, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 135.2, 129.7, 76.0, 71.3, 68.1, 63.9, 32.2, 31.9, 30.4, 28.2, 27.8, 25.8, 24.6, 19.4, –4.7, –4.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{36}O_4SiNa$: 391.2280; found: 391.2269.

(1*S*,5*R*,11*R*,14*S*,*Z*)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (*Z*-Aspergillide B) (3)

A solution of the TBS-ether **21a** (15 mg, 0.040 mmol) in THF (2 mL) was treated with TBAF (0.06 ml, 0.061 mmol) at 0 °C under an N_2 atm, and stirred for 2 h at r.t. After completion of the reaction (monitored by TLC), the mixture was quenched with sat. NH_4Cl solution (5 mL). The aq layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc–hexane, 1:4) afforded *Z*-aspergillide B (**3**) (9 mg, 90%).

$[\alpha]_D^{25}$ –26.7 (*c* 0.7, $CHCl_3$).

IR (neat): 3496, 2928, 2857, 1732, 1640, 1459, 1275, 1174, 1106, 1061, 861, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.63 (td, *J* = 5.0, 11.1 Hz, 1 H), 5.39 (t, *J* = 9.5 Hz, 1 H), 5.22 (m, 1 H), 4.57 (t, *J* = 10.2 Hz, 1 H), 4.37 (dt, *J* = 4.4, 12.0 Hz, 1 H), 3.96 (m, 1 H), 2.92 (t, *J* = 12.8 Hz, 1 H), 2.64 (m, 1 H), 2.49 (dd, *J* = 3.1, 13.3 Hz, 1 H), 2.31 (m, 1 H), 1.99–1.87 (m, 2 H),1.87–1.73 (m, 2 H), 1.70–1.51 (m, 3 H), 1.44 (m, 1 H), 1.24 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 136.1, 129.1, 74.8, 71.6, 67.6, 64.7, 32.8, 32.1, 29.2, 27.7, 27.3, 24.3, 19.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{22}O_4Na$: 277.1410; found: 277.1404.

(*S*)-Hept-6-en-2-yl 2-{(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(4-methoxybenzyloxy)methyl]tetrahydro-2*H*-pyran-2-yl}acetate (19b)

Starting from compounds **10** and **8b** and following a similar procedure to that employed for the Yamaguchi esterification to give **19a**, compound **19b** (0.150 g, 83%) was obtained as a pale yellow oil.

R_f = 0.6 (EtOAc–hexane, 1:14); $[\alpha]_D^{25}$ –34.0 (*c* 1.6, $CHCl_3$).

IR (neat): 2930, 2856, 1731, 1615, 1513, 1248, 1099, 1052, 836, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 5.84–5.66 (m, 1 H), 5.02–4.86 (m, 3 H), 4.42 (s, 2 H), 4.29 (quin, *J* = 5.2 Hz, 1 H), 3.86 (m, 1 H), 3.79 (s, 3 H), 3.74 (m, 1 H), 3.38 (m, 1 H), 3.30 (m, 1 H), 2.66 (m, 1 H), 2.52 (m, 1 H), 2.07–1.99 (m, 2 H), 1.80–1.71 (m, 2 H), 1.62–1.33 (m, 6 H), 1.18 (d, *J* = 5.9 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 159.1, 138.4, 130.4, 129.2, 114.6, 113.6, 73.8, 72.9, 72.0, 70.8, 68.2, 67.9, 55.2, 35.3, 33.5, 32.0, 27.4, 26.3, 25.7, 24.6, 19.9, 18.0, –4.7, –4.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{48}O_6SiNa$: 543.2749; found: 543.2758.

(*S*)-Hept-6-en-2-yl 2-[(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-(hydroxylmethyl)tetrahydro-2*H*-pyran-2-yl]acetate (20b)

Starting from **19b** and following a similar procedure to that employed for the PMB-ether cleavage of **19a**, primary alcohol **20b** (82 mg, 87%) was obtained as a colorless oil.

R_f = 0.4 (hexane–EtOAc, 1:4); $[\alpha]_D^{25}$ –14.0 (*c* 1.4, $CHCl_3$).

IR (neat): 3465, 2935, 2860, 1731, 1646, 1468, 1286, 1255, 1186, 1106, 837, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.79 (m, 1 H), 5.06–4.86 (m, 3 H), 4.27 (dt, *J* = 4.5, 10.5 Hz, 1 H), 3.87–3.71 (m, 2 H), 3.61 (dd, *J* = 7.5, 11.5 Hz, 1 H), 3.50 (m, 1 H), 2.72 (dd, *J* = 10.6, 15.7 Hz, 1 H), 2.50 (dd, *J* = 3.4, 15.9 Hz, 1 H), 2.23 (br s, 1 H), 2.06 (q, *J* = 7.5 Hz, 2 H), 1.83–1.71 (m, 2 H), 1.66–1.52 (m, 3 H), 1.48–1.31 (m, 3 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 138.4, 114.7, 72.2, 71.2, 70.1, 67.8, 63.8, 35.3, 33.4, 32.9, 29.7, 27.4, 25.8, 24.6, 23.9, 19.9, –4.7, –4.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{40}O_5SiNa$: 423.2537; found: 423.2532.

(*S*)-Hept-6-en-2-yl 2-[(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]acetate (7b)

Starting from **20b** and following a similar procedure to that employed for the IBX oxidation and one-carbon Wittig homologation of **20a**, diene **7b** (32 mg, 55% over two steps) was obtained as an oily liquid.

R_f = 0.7 (hexane–EtOAc, 1:19); $[\alpha]_D^{25}$ –18.2 (*c* 0.8, $CHCl_3$).

IR (neat): 3074, 2926, 2856, 2125, 1731, 1462, 1371, 1286, 1176, 1106, 1035, 837, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.90–5.69 (m, 2 H), 5.29–5.10 (m, 2 H), 5.05–4.90 (m, 3 H), 4.36–4.17 (m, 2 H), 3.82 (dt, *J* = 3.8, 8.3 Hz, 1 H), 2.69 (dd, *J* = 9.8, 15.1 Hz, 1 H), 2.52 (dd, *J* = 4.5, 15.1 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.93 (m, 1 H), 1.77 (m, 1 H), 1.69–1.55 (m, 3 H), 1.53–1.36 (m, 3 H), 1.21 (d, *J* = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 138.5, 138.1, 115.6, 114.7, 72.7, 70.9, 70.5, 67.7, 35.4, 33.9, 33.5, 27.4, 27.1, 25.8, 24.6, 20.0, 18.1, –4.7, –4.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{40}O_4SiNa$: 419.2588; found: 419.2582.

(1*S*,5*S*,11*R*,14*S*,*Z*)-14-(*tert*-Butyldimethylsilyloxy)-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (21b)

Starting from **7b** and following a similar procedure to that employed for the ring-closing metathesis of diene **7a**, macrocycle **21b** was obtained as a pale yellow viscous liquid (20 mg, 79%).

$[\alpha]_D^{25}$ –45.5 (*c* 0.8, $CHCl_3$).

IR (neat): 3010, 2923, 2856, 1724, 1456, 1368, 1224, 1176, 1059, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.57 (td, *J* = 4.7, 10.5 Hz, 1 H), 5.34 (t, *J* = 9.0 Hz, 1 H), 5.21 (m, 1 H), 4.51 (t, *J* = 9.8 Hz, 1 H), 4.30 (m, 1 H), 3.92 (m, 1 H), 2.94 (t, *J* = 12.8 Hz, 1 H), 2.68–2.52 (m, 1 H), 2.46 (dd, *J* = 3.2, 13.0 Hz, 1 H), 2.01–1.87 (m, 1 H), 1.84–1.73 (m, 2 H), 1.67 (m, 1 H), 1.61–1.48 (m, 5 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 135.2, 129.7, 75.9, 71.3, 68.0, 63.8, 32.1, 31.8, 30.4, 28.2, 27.7, 25.7, 24.5, 19.3, –4.8, –4.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{36}O_4SiNa$: 391.2280; found: 391.2279.

(1*S*,5*S*,11*R*,14*S*,*Z*)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (Aspergillide B) (4)

Starting from **21b** and following a similar procedure to that employed for the deprotection of silyl ether **21a**, aspergillide B (**4**) (7 mg, 92%) was obtained as a colorless oil.

$[\alpha]_D^{25}$ –53.4 (*c* 0.4, $CHCl_3$).

IR (neat): 3496, 2926, 2857, 1732, 1641, 1459, 1275, 1176, 1106, 1061, 861, 772 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.61 (td, *J* = 4.9, 10.8 Hz, 1 H), 5.37 (t, *J* = 9.8 Hz, 1 H), 5.20 (m, 1 H), 4.56 (t, *J* = 9.8 Hz, 1 H), 4.35 (dt, *J* = 2.9, 11.8 Hz, 1 H), 3.94 (m, 1 H), 2.91 (t, *J* = 12.8 Hz, 1 H), 2.62 (m, 1 H), 2.47 (dd, *J* = 2.9, 13.8 Hz, 1 H), 1.97–1.86 (m, 2 H), 1.85–1.74 (m, 3 H), 1.71–1.57 (m, 2 H), 1.53 (m, 1 H), 1.43 (m, 1 H), 1.23 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 136.0, 129.1, 74.8, 71.6, 67.6, 64.7, 32.8, 32.2, 29.3, 27.7, 27.3, 24.4, 19.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{22}O_4Na$: 277.1410; found: 277.1404.

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