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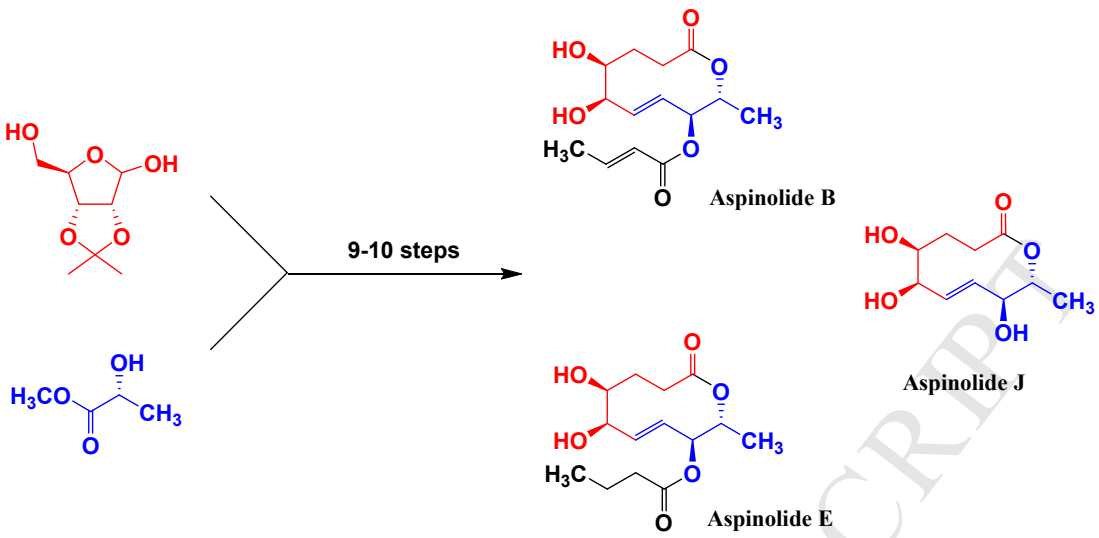

Divergent Total Synthesis of Aspinolides B, E and J

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Abstract

Stereoselective total synthesis of aspinolides B, E and J, naturally occurring 10-membered lactones, were accomplished by divergent strategies starting from the commercially available 2,3-O-isopropylidene-D-ribose and methyl D-lactate. The synthesis features rapid access to the both key fragments from chiral pool and the formation of 10-membered ring lactones containing *trans* double bond employing cross-metathesis reaction (CM) and intramolecular Shiina macrolactonization.

Introduction

Naturally occurring 10-membered lactones exhibit various important biological activities such as antibacterial, antimalarial, cytotoxic, antitumor, antifungal, antifeedant, phytotoxic, anti-microfilament, etc.[1] Within this family, the 10-membered macrolide, aspinolide B, was isolated from the cultures of *Aspergillus ochraceus* by Zeeck group, along with other aspinolides in 1997 (Fig. 1).[2] Subsequent exploration of the secondary metabolome of *trichoderma arundinaceum* (Ta37) and TaΔTri5 (harzianum A non-producer mutant) led to a second isolation of aspinolides B (**1**), C (**2**) and characterization of new aspinolides D-J.[3, 4] Architecturally, aspinolides B (**1**), E (**3**) and J (**4**) have the same 10-membered lactone backbone and stereochemistry, except for the ester on the side chain which attaches to C-8, respectively (**Fig. 1**). The relative stereochemistry of aspinolide B was established by using X-ray crystallographic diffraction analysis and the absolute configuration (*4S,5R,8S,9R*) was further established on the basis of Helmchen's method.[2, 5] Preliminary biological studies on aspinolides indicated that aspinolide B slightly repressed SA-related genes, while aspinolide C significantly induced the SA-related genes *PR1b1* and *PR-P2* when their expression of plant defence-related genes (50μg/ml) was analysed.[4]

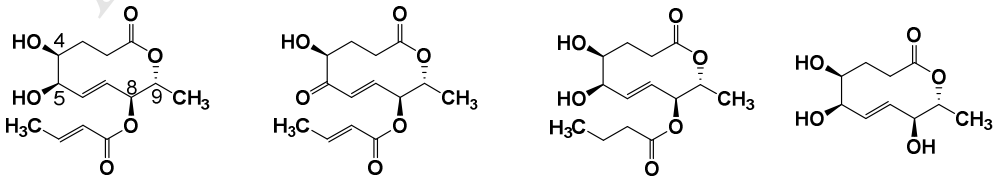
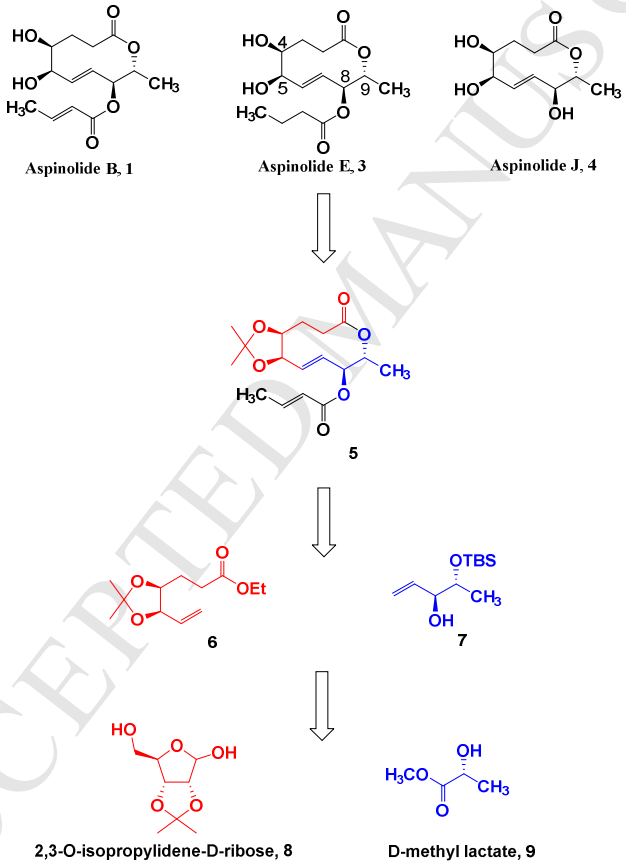


Fig. 1. Chemical structures of aspinolides (**1**-**4**).

Their interesting biological profile combined with structural features has aroused the interest of the synthetic community, and a few total syntheses of aspinolide have appeared accordingly.[6] Since the first synthesis of aspinolide B reported by Pilli and coworkers[6f] through Nozaki-Hiyama-Kishi reaction as the key step, many efforts have been made in the total synthesis of aspinolides. In view of the structural feature of aspinolides B, E and J, it is therefore highly desirable to develop an efficient synthetic approach, in which a readily accessible macrocyclic lactone skeleton bearing suitable functionality would serve as a key intermediate for the divergent total synthesis of these natural products as well their analogues. In particular, to the best of our knowledge, the total synthesis of aspinolides C-J have not been reported so far. As part of our interests in the total synthesis of various complex natural products based on carbohydrate skeletons, [7] herein we disclose the divergent and stereoselective synthesis of aspinolides B, E and J using readily available D-ribose as chiral pool.

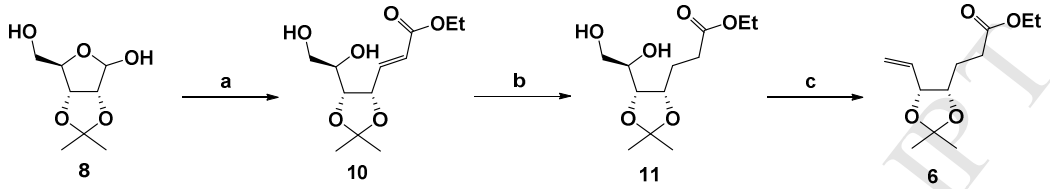
Results and discussion



Scheme 1. Retrosynthetic analysis of aspinolides B, E and J

Retrosynthetic analysis of the target aspinolides is shown in **Scheme 1**. Generally cyclizations of medium ring lactones are more difficult due to both enthalpic and entropic factors.[8] Several routes have been previously reported for synthesizing these 10-membered ring lactones containing *trans* double bond employing ring-closing metathesis (RCM) in the final step.[9] The major challenge in the macrocyclic formation using the RCM strategy is the necessary optimization of reaction conditions and controlling the double bond geometry.[10] Macrolactonization has proven to be particularly useful in the closing strained medium to large rings with the preservation of double bond geometry in the final stage.[11] Accordingly, we envisaged that aspinolides B, E and J could be

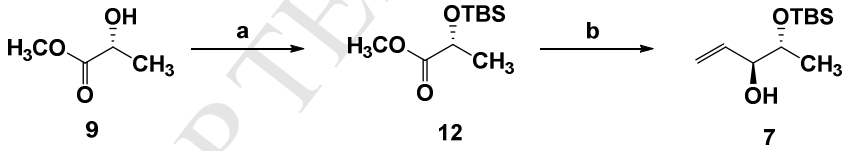
elaborated from well functionalized macrocyclic lactone **5**. The key intermediate **5** could be obtained from building blocks **6** and **7**, as the precursors of cross metathesis (CM) followed by Shiina macrolactonization of the resulting CM product containing *trans* double bond. The ester **6** would be readily accessible obtained from 2,3-O-isopropylidene-D-ribose whereas the fragment **7** could be accessed from D-methyl lactate through reduction and Grignard addition by a one-pot sequence.



Scheme 2. Synthesis of ester **6.** *Reagents and conditions:* (a) $Ph_3P{=}CHCO_2Et$, PhCOOH(cat.), DCM, reflux, 92%; (b) Pd-C, MeOH-EtOAc, H_2; (c) I_2, PPh_3, imidazole, toluene, reflux, 67% for 2 steps;

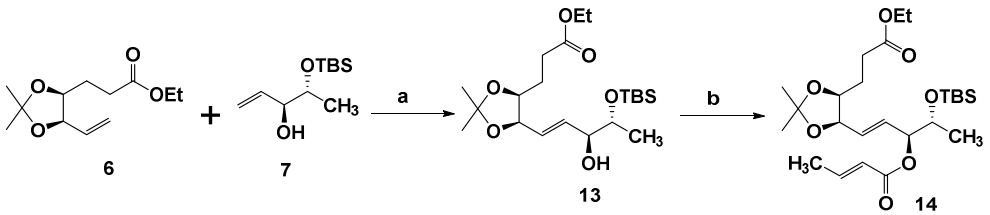
As depicted in Scheme **2**, the synthesis of fragment **6** was commenced with commercially available 2,3-O-isopropylidene-D-ribose (**8**) which was subjected to chain extension with Wittig olefination to afford *α,β*-unsaturated ester **10** according to the reported procedure.[12a,b] Hydrogenation of **10** over 5% Pd-C in methanol and EtOAc gave the diol **11** in excellent yield. According to the methodology developed by Garegg and Samuelsson,[13] **11** was then converted into the teminal alkene **6** [14] by using I_2/TPP/imidazole in refluxing toluene.

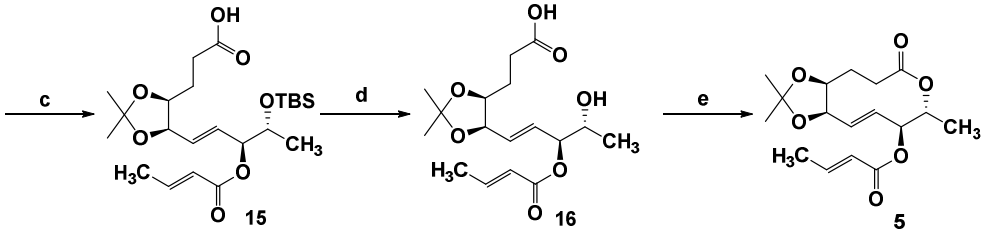
The synthesis of fragment **7** was accessible from D-methyl lactate in 70% yield over two steps as shown in Scheme **3**. Protection of lactate with silyl group afforded the known compound **12** in 96% yield. [15a] Reduction of ester **12** by DIBAL-H and subsequent treatment of the resulting aldehyde with vinylmagnesium chloride in one-pot furnished the desired *anti* allylic alchol **7** (5.8:1 mixture of diastereoisomers from crude ^{1}H NMR analysis). [15b-c]



Scheme 3. Synthesis of compound **7.** *Reagents and conditions:* (a) TBSCl, imidazole, DCM, rt, 96%; (b) DIBAL-H, Et_2O, then vinylmagnesium chloride, -98 °C-rt, 73%;

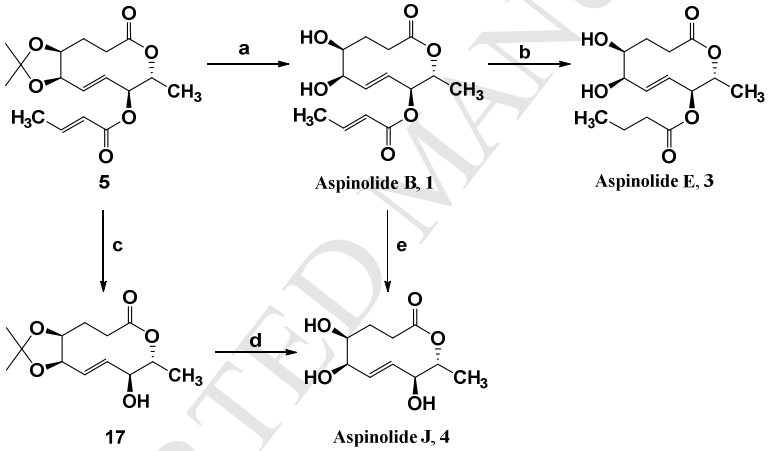
With the required building blocks in hand, we then turned our attention to the construction of the macrocyclic lactone skeleton following our retrosynthetic analysis (**Scheme 4**). The olefin cross-metathesis between fragments **6** and **7** carried out smoothly using a catalytic amount of Hoveyda-Grubbs Catalyst (2nd Generation)[16] generated the desired olefin **13** in a satisfactory yield of 75%. A small amount of homodimer of **7** (11%) was also observed.





Scheme 4. Syntheses of aspinolide J. *Reagents and conditions:* (a) Hoveyda-Grubbs Catalyst 2nd Generation, dry DCM, reflux, 8 h, 75%; (b) crtonic anhydride, cat. DMAP, Py, rt, 5 h, 88%; (c) LiOH, THF/H_2O=3:2, 0^{o}C to rt, 24 h; (d) HF-pyridine complex, THF/Py (10:1), rt, 24 h, 67% for two steps; (e) MNBA, DMAP, toluene, 80^{o}C, 18 h, 90%;

Esterification of **13** with crtonic anhydride in pyridine in the presence of DMAP to generate **14** in 88% yield. Regioselective hydrolysis of the ethyl ester of **14** with aqueous lithium hydroxide afforded acid **15**. Cleavage of the TBS group with weakly acidic HF-pyridine complex and macrolactonization in the presence of MNBA and DMAP (Shiina's protcol)[11b,17] furnished the key intermediate **5** in excellent yield.



Scheme 5. *Reagents and conditions:* (a) 4N HCl, MeOH, rt, 2 h, 89%; (b) $NaBH_4$, CuCl, THF-EtOH (3:7), -40^{o}C, 1 h, 76%; (c) 5% K_2CO_3, acetone, rt, 24 h; (d) 1N HCl, MeOH, rt, 3 h, 65% for two steps; (e) 5% K_2CO_3, acetone, rt. 40%;

With the key macrocyclic lactone **5** in hand, the stage was set for completion of the divergent total synthesis of aspinolides B, E and J. Deprotection of the acetonide group in the lactone **5** with 4N HCl afforded aspinolide B (**1**) in 89% yield. After considerable experimentation, selective reduction of the crotonate to afford the corresponding butyrate ester, aspinolides E (**3**), was accomplished by application of Narisada's Cu(I)/ $NaBH_4$ protocol.[18] The crotonate ester in **5** was selective hydrolyzed smoothly to afford **17** under 5% K_2CO_3 in acetone.[4] The resulting alcohol **17**, without further purification, was subjected to 1N HCl underwent acetonide deprotection at ambient temperature to deliver the desired macrolactone aspinolides J (**4**) in 65% overall yield (Scheme **5**). Alternatively, hydrolysis of the natural product aspinolide B (**1**) with 5% K_2CO_3 in acetone also resulted in aspinolides J (**4**). The physical and spectroscopic data of aspinolides B, E

and J were in good agreement with the data previously reported for the natural products. [2,3,4,19]

Conclusions

In summary, we have successfully developed an efficient approach for the divergent total synthesis of aspinolides B, E and J. In particular, aspinolides E and J, which are the first total synthesis so far, were achieved in 10 linear steps with a 16.6% overall yield and with a 13.8% overall yields, respectively. Further optimization of this strategy and the synthesis of other aspinolides as well as the bioactivity evaluations are currently underway in our laboratory.

Experimental section

General Experimental

Unless noted otherwise, commercially available materials were used without further purification. All solvents were dried according to the established procedures ahead of use. Flash chromatography (FC) was performed using silica gel (200-300 meshes) according to the standard protocol. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F_{254} plates. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 20 ^{o}C. Melting points were recorded in open capillary tubes with a melting point apparatus (Buchi Melting Point M-560) and are uncorrected. IR(FT-IR) spectra were recorded on a Perkin-Elmer BXII spectrometer with KBr pellets. High-resolution mass spectrometry data (HRMS) were acquired using a Q-TOF analyzer in acetone or methanol as solvent. ^{1}H NMR, ^{13}C NMR were measured on 400 MHz or 100 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform; δ 7.26 for ^{1}H NMR or 77.0 for proton decoupled ^{13}C NMR), and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet.

Synthesis of ethyl 3-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propanoate (6)

A catalytic amount of 10% Pd/C (10 mg) was added to a solution of **10** (195 mg, 0.75 mmol) in MeOH/EtOAc (1:1, 12 mL). The mixture was stirred at room temperature for 1 h under H_2 atmosphere. After completion of reaction (TLC), the catalyst was removed by filtration, washed twice with ethyl acetate and the combined filtrate was concentrated to afford **11** as a colorless oil which was used for the next step without further purification.

To a solution of the crude **11** in dry toluene (7 mL) was added triphenylphosphine (786 mg, 3.0 mmol) followed by imidazole (204 mg, 3.0 mmol) and stirred vigorously. To the resulting solution was added iodine (571 mg, 2.25 mmol) portion wise and the mixture was refluxed for 3 h. After completion of reaction, the mixture was cooled to room temperature and poured into saturated aqueous $Na_2S_2O_3$ (20 mL), and then was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash column chromatography (petroleum ether/EtOAc 20:1) to give **6** as a colorless

oil (114 mg, 67% for two steps). $[\alpha]_D^{20}$ -4.6 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (ddd, *J* = 17.5, 10.3, 7.6 Hz, 1H), 5.35 - 5.24 (m, 2H), 4.53 (t, *J* = 6.9 Hz, 1H), 4.17 - 4.10 (m, 3H), 2.51 - 2.32 (m, 2H), 1.77 - 1.71 (m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.3, 133.8, 118.6, 108.4, 79.5, 77.2, 60.4, 30.9, 28.1, 26.1, 25.6, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$Calcd for C12H20O4Na 251.1259; Found 251.1273; IR (KBr) 2893, 2933, 1738, 1370, 1255, 1211, 1159, 1065, 1044, 932, 867 cm^{-1}.

Synthesis of (3*S*,4*R*)-4-((tert-butyldimethylsilyl)oxy)pent-1-en-3-ol (7)

To a solution of TBS-protected lactate **12** (2.6 g, 11.9 mmol) in dry ether (60 mL) was added slowly DIBAL-H (1.0 M, 13.1 mL, 13.1 mmol) via syringe at −98 °C under N_2 atmosphere and stirred for 15 min. After completion of reaction (TLC), vinylmagnesium chloride (1.0 M, 29.7 mL, 29.7 mmol) was added dropwise into the mixture via syringe. The solution was then warmed to room temperature and stirred for 2 h. After completion, the reaction was quenched with saturated sodium potassium tartarate (30 mL) and stirred overnight. The aqueous layer was extracted with ether (3 × 80 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate 80: 1) to give **7** (1.87 g, 73%) as a colorless oil; $[\alpha]_D^{20}$ - 19.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H), 5.31 - 5.17 (m, 2H), 4.02 (ddt, *J* = 6.3, 3.6, 1.4 Hz, 1H), 3.84 (qd, *J* = 6.3, 3.6 Hz, 1H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.5, 116.5, 76.6, 71.2, 25.8, 18.0, 17.6, -4.4, -4.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for C18H28O3SiNa 343.1705; Found 343.1711; IR (KBr) 2956, 2930, 2886, 2857, 1472, 1381, 1256, 1096, 1007, 935, 836, 773 cm^{-1}.

Synthesis of ethyl 3-((4*R*,5*R*)-5-((3*S*,4*R*,*E*)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxypent-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (13)

Hoveyda-Grubbs Catalyst 2nd Generation (4 mg, 0.006 mmol) was added to a mixture of **6** (50 mg, 0.22 mmol) and **7** (95 mg, 0.44 mmol) in dry DCM (15 mL). The mixture was refluxed for 8 h. After completion of reaction (TLC), the solution was concentrated and purified by flash column chromatography (petroleum ether/EtOAc 8:1) to give **13** as a colorless oil (68 mg, 75%). $[\alpha]_D^{20}$ -4.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-d) δ 5.75 - 5.73 (m, 2H), 4.58 - 4.55 (m, 1H), 4.17 - 4.07 (m, 4H), 3.86 (qd, J = 6.3, 3.4 Hz, 1H), 2.50 -2.32 (m, 2H), 1.77 - 1.72 (m, 2H), 1.46 (s, 3H), 1.35 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.07 (d, J = 1.1 Hz, 6H); ^{13}C NMR (100 MHz, Chloroform-d) δ 173.2, 132.8, 127.7, 108.4, 78.7, 77.4, 75.5, 71.2, 60.4, 30.9, 28.2, 26.1, 25.8, 25.7, 18.0, 17.6, 14.2, -4.5, -4.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{40}O_6SiNa$ 439.2492; Found 439.2482; IR (KBr) 3473, 2956, 2930, 2855, 1735, 1469, 1373, 1258, 1216, 1154, 1094, 1008, 976, 833, 776, 736 cm^{-1}.

Synthesis of (3*S*,4*R*,*E*)-4-((tert-butyldimethylsilyl)oxy)-1-((4*R*,5*R*)-5-(3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-1-en-3-yl (*E*)-but-2-enoate (14)

To a solution of **13** (400 mg, 0.96 mmol) in pyridine (10 mL), crtonic anhydride (0.5 mL, 3.36 mmol) and catalytic amount of DMAP was added, and the mixture kept at room temperature for 5 h. The reaction was quenched by the addition of MeOH (1 mL). The solution was concentrated with toluene and poured into saturated aqueous $NaHCO_3$ (20 mL) and then extracted with EtOAc

(2 × 20 mL). The combined organic phase was washed with saturated aqueous $CuSO_4$, water, and dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash column chromatography (petroleum ether/EtOAc 10:1) to give **14** as a colorless oil (408 mg, 88%). $[\alpha]_D^{20}$ -9.0 (*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.97 (dq, *J* = 15.6, 6.9 Hz, 1H), 5.90 - 5.80 (m, 2H), 5.71 (dd, *J* = 15.6, 7.0 Hz, 1H), 5.17 (dd, *J* = 7.3, 3.3 Hz, 1H), 4.57 (t, *J* = 6.6 Hz, 1H), 4.17 - 4.09 (m, 3H), 3.97 (qd, *J* = 6.4, 3.3 Hz, 1H), 2.48 - 2.32 (m, 2H), 1.88 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.74 - 1.68 (m, 2H), 1.46 (s, 3H), 1.34 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 3.8 Hz, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.2, 165.5, 144.8, 130.5, 128.5, 122.8, 108.4, 78.3, 77.4, 77.3, 69.5, 60.3, 30.8, 28.1, 26.0, 25.7 (3C), 25.6, 19.9, 18.02, 19.78, 14.2, -4.7, -4.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{44}O_7SiNa$ 507.2749; Found 507.2741; IR (KBr) 2959, 2933, 2857, 1733, 1652, 1446, 1373, 1258,1216, 1180, 1102, 1003, 966, 836, 773, 739 cm^{-1}.

Synthesis of 3-((4*R*,5*R*)-5-((3*S*,4*R*,*E*)-3-(((*E*)-but-2-enoyl)oxy)-4-hydroxypent-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoic acid (16)

A cooled (0 ^{o}C) solution of ester **14** (100 mg, 0.21 mmol) in THF/H_2O (3:2, 8mL) was treated with LiOH (13 mg, 0.31 mmol). The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was acidified with 1N HCl until pH = 3 and was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude acid **15** was used for the next step without further purification.

To a cooled (0 ^{o}C) solution of the above crude **15** in THF/pyridine (10:1, 11 mL) was added HF-pyridine complex (0.43 ml，3.15 mmol) dropwise and stirred at room temperature for 24 h. After completion of reaction (TLC), it was quenched with saturated NH_4Cl solution, extracted with EtOAc (3 × 10 mL), washed with saturated aqueous $CuSO_4$, brine and dried over Na_2SO_4. The combined organic phase was evaporated under reduced pressure and purified by flash column chromatography (dichloromethane/MeOH 30:1) to give **16** as a colorless oil (47 mg, 67% for two steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (dq, *J* = 14.1, 6.8 Hz, 1H), 5.90 - 5.80 (m, 3H), 5.27 (dd, *J* = 5.6, 3.5 Hz, 1H), 4.60 (t, *J* = 5.9 Hz, 1H), 4.18 (dt, *J* = 8.7, 5.6 Hz, 1H), 3.98 (qd, *J* = 6.5, 3.6 Hz, 1H), 2.54 - 2.38 (m, 2H), 1.89 (dd, *J* = 7.0, 1.7 Hz, 3H), 1.77 - 1.67 (m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.4, 165.6, 145.7, 131.0, 127.9, 122.3, 108.6, 78.0, 77.2, 77.0, 69.0, 30.4, 28.0, 25.8, 25.5, 18.04, 18.01; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{26}O_7Na$ 365.1576; Found 365.1568; IR (KBr) 3447, 2925, 1717, 1655, 1443, 1378, 1263, 1180, 1101, 1063, 974, 867, 736 cm^{-1}.

Synthesis of (3a*S*,8*R*,9*S*,11a*R*,*E*)-2,2,8-trimethyl-6-oxo-3a,5,6,8,9,11a-hexahydro-4*H*-[1,3]di-oxolo-[4,5-*e*]oxecin-9-yl (*E*)-but-2-enoate (5)

To a solution of the seco acid **16** (50 mg, 0.146 mmol) in toluene (35 mL) was slowly added a solution of MNBA (65 mg, 0.19 mmol) and DMAP (107 mg, 0.876 mmol) in toluene (35 mL) at 80 ^{o}C with a mechanically driven syringe over a 18 h period under a nitrogen atmosphere. After completion of reaction (TLC), the mixture cooled to room temperature and concentrated under reduced pressure. The crude was purified by flash column chromatography (petroleum ether/EtOAc 5:1) to give **5** as a colorless oil (42 mg, 90%). $[\alpha]_D^{20}$ -41.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.99 (dq, *J* = 15.5, 6.7 Hz, 1H), 5.86 - 5.80 (m, 1H), 5.71 - 5.61 (m,

2H), 5.11 - 5.02 (m, 2H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.38 - 4.34 (m, 1H), 2.56 - 2.49 (m, 1H), 2.15 - 2.07 (m, 2H), 2.06 - 2.00 (m, 1H), 1.88 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.57 (s, 3H), 1.34 (d, *J* = 5.4 Hz, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*) *δ* 173.4, 165.5, 145.7, 129.7, 126.0, 122.2, 108.6, 79.4, 76.8, 74.9, 70.1, 29.7, 26.7, 26.4, 24.8, 18.1, 17.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{24}O_6Na$ 347.1471; Found 347.1463; IR (KBr) 2988, 2938, 1728, 1655, 1446, 1383, 1258, 1174, 1109, 1062, 1018 cm^{-1}.

Synthesis of Aspinolide B (1)

To a solution of **5** (40 mg，0.123 mmol) in MeOH (4 mL) was added a drop of 4N HCl. The reaction mixture was stirred at 30 ^{o}C for 2 h, then the reaction was neutralized with triethylamine and concentrated under reduced pressure. The crude was purified by flash column chromatography (hexane/EtOAc/ dichloromethane 1:1:1) to give Aspinolide B (**1**) as a white solid (31 mg, 89%). m.p.: 99-101 ^{o}C, lit. 102-103 [6f]; $[\alpha]_D^{20}$ -44.4 (*c* 1.0, MeOH), lit. $[\alpha]_D^{20}$ -44.0 (*c* 1.0, MeOH) [6f]; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (dq, *J* = 15.5, 6.9 Hz, 1H), 5.85 (dq, *J* = 15.6, 1.7 Hz, 1H), 5.67 (dd, *J* = 15.9, 1.9 Hz, 1H), 5.57 (ddd, *J* = 15.9, 8.1, 2.3 Hz, 1H), 5.09 (dq, *J* = 9.2, 6.3 Hz, 1H), 4.95 (t, *J* = 8.7 Hz, 1H), 4.53 - 4.52 (m, 1H), 3.65 (dt, *J* = 11.2, 2.7 Hz, 1H), 2.47 (ddd, *J* = 15.6, 9.9, 1.3 Hz, 1H), 2.29 (dtd, *J* = 14.8, 11.4, 1.3 Hz, 1H), 2.11 - 2.04 (m, 1H), 1.90 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.80 - 1.74 (m, 1H), 1.33 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 175.4, 165.6, 146.0, 131.4, 127.5, 122.0, 78.6, 75.2, 72.7, 71.8, 32.5, 27.1, 18.1, 16.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{21}O_6$ 285.1338; Found 285.1331; IR (KBr) 3447, 2980, 2938, 1723, 1655, 1446, 1360, 1180, 1151, 1065, 1018 cm^{-1}.

Synthesis of Aspinolide E (3)

To a stirred solution of Aspinolide B (**1**, 20 mg，0.07 mmol) and cuprous chloride (7 mg, 0.07 mmol) in the mixture of THF (1.2 mL) and EtOH (2.8 mL) was added $NaBH_4$ (26 mg, 0.7 mmol) portion wise at -40 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h. Then the reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (3 × 10 mL). The organic layer was separated, washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (petroleum ether/EtOAc/dichloromethane 1:1:1) to give Aspinolide E (**3**) as a white amorphous solid (15 mg, 76%). $[\alpha]_D^{20}$ -24.6 (*c* 0.24, $CHCl_3$); lit.[3] $[\alpha]_D^{20}$ -14.5 (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.65 (dd, *J* = 15.9, 1.9 Hz, 1H), 5.54 (ddd, *J* = 15.9, 8.3, 2.3 Hz, 1H), 5.07 (dq, *J* = 9.3, 6.3 Hz, 1H), 4.90 (t, *J* = 8.8 Hz, 1H), 4.52 (s, 1H), 3.65 (dt, *J* = 11.1, 2.6 Hz, 1H), 2.46 (dd, *J* = 15.5, 9.4 Hz, 1H), 2.33 - 2.24 (m, 3H), 2.07 ((dd, *J* = 15.6, 11.5 Hz, 1H), 1.74 - 1.81 (m, 1H), 1.65 (dq, *J* = 14.8, 7.4 Hz, 2H), 1.32 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 175.47, 172.78, 131.23, 127.74, 78.67, 75.13, 72.86, 71.84, 36.18, 32.44, 27.28, 18.37, 16.70, 13.64; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{22}O_6Na$ 309.1314; Found 309.1307; IR (KBr) 3457, 2959, 2928, 1728, 1438, 1373, 1180, 1157, 1070, 1000 cm^{-1}.

Synthesis of Aspinolide J (4)

Method A: Compound **5** (30 mg，0.093 mmol) was dissolved in acetone (5 mL) and treated with a aqueous solution of K_2CO_3 (5%) (3 mL). The reaction mixture was stirred at room temperature for 24 h. After completion of reaction (monitored by TLC), the mixture was neutralized with saturated

ammonium chloride solution and extracted with ethyl acetate. Evaporation of the solvent gave a crude extract. The crude was used for the next step without further purification.

To a solution of the above crude in MeOH (5 mL) was added a drop of 1N HCl. The reaction mixture was stirred at room temperature for 3 h, then the reaction was directly concentrated under reduced pressure. The crude was purified by flash column chromatography (hexane/EtOAc/MeOH, 5:5:1) to give Aspinolide J (**4**) as a white amorphous solid (13 mg, 65% for two steps).

Method B: Aspinolide B (**1**, 25 mg，0.088 mmol) was dissolved in acetone (5 mL) and treated with a aqueous solution of K_2CO_3 (5%) (2 mL). The reaction mixture was stirred at room temperature for 6 h. After completion of reaction (monitored by TLC), the mixture was neutralized with saturated ammonium chloride solution, extracted with ethyl acetate and dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and purified by flash column chromatography hexane/EtOAc/MeOH, 5:5:1) to give Aspinolide J (**4**) as a white amorphous solid (7.6 mg, 40%). $[\alpha]_D^{20}$ -16.7 (*c* 0.1, $CHCl_3$); lit.[4] $[\alpha]_D^{20}$ -14.9 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.69 (ddd, *J* = 15.9, 8.5, 2.2 Hz, 1H), 5.54 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.89 (dq, *J* = 8.8, 6.4 Hz, 1H), 4.54 (s, 1H), 3.87 (t, *J* = 8.6 Hz, 1H), 3.64 (d, *J* = 11.1 Hz, 1H), 2.45 (dd, *J* = 15.6, 9.7 Hz, 1H), 2.33 - 2.24 (m, 1H), 2.05 (dd, *J* = 15.5, 11.5 Hz, 1H), 1.80 - 1.74 (m, 1H), 1.42 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 176.2, 32.9, 27.5, 73.3, 79.2, 130.5, 131.3, 75.5, 74.7, 16.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{16}O_5Na$ 239.0895; Found 239.0890; IR (KBr) 3447, 2925, 1728, 1370, 1266, 1222, 1156, 1049, 1007, 969, 859, 737 cm^{-1}.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at

References and notes

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19. See *supplementary information* section II for the detailed comparisons of ^{1}H and ^{13}C NMR data of natural and synthetic aspinolides.