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Total synthesis of peumusolide A, NES non-antagonistic inhibitor for nuclear export of MEK

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ABSTRACT

The first total synthesis of peumusolide A (**1**) has been achieved by combination of regio- and stereo-selective aluminum-mediated hydroiodination to 2-yn-1-ol and enantioselective reduction of 4-en-1-yn-3-one with the chiral oxazaborolidine as the key reactions. This total synthesis has unequivocally established our proposed absolute structure of **1**.

1. Introduction

In many kinds of tumor cells, the mitogen-activated protein kinase (MAPK) cascade, one of the important signal pathways for cell proliferation, was reported to be significantly activated as compared with that in normal cells. Export of MAPK/ERK kinase (MEK) from the nucleus to the cytoplasm was established as an essential process for the cell proliferation by this cascade.[1] Hence, inhibitors for nuclear export of MEK have been intensively anticipated to be attractive scaffolds toward new antitumor agents.[2] Previously, we disclosed peumusolide A (**1**) as the first MAPK/ERK kinase (MEK)-export inhibitor with nuclear export signal (NES)[3] non-antagonistic mode from the Southern American medicinal plant *Peumus boldus* Molina. Furthermore, peumusolide A (**1**) was verified to be the promising anti-tumor scaffold by demonstrating selective growth-inhibition for the MEK-activated tumor cells.[4]

In addition to peumusolide A (**1**), several congenic polyketides with interesting biological activities have been revealed very recently.[5,6] Despite such attractive biological properties, the asymmetric synthesis of the core structure, α-alkylidene-β-hydroxy-γ-methylenebutyrolactone, in these polyketides was only achieved by using the sulfoxide as a chiral auxiliary.[7] However, the synthetic route involved strict geometrical limitation giving rise to only (2*E*)-isomers. To examine structure–activity relationship of peumusolide A (**1**) in detail, we developed the stereo-controlled construction of the core structure of **1** by utilizing regio- and stereo-selective hydroiodination to 2-yn-1-ol and enantioselective reduction of 4-en-1-yn-3-one as the key reactions.[8] By application of this protocol, we have accomplished the total synthesis of (*S*)-peumusolide A (**1**). This paper describes the first total synthesis of **1** leading to impregnable confirmation of our proposed absolute structure for **1** isolated from the medicinal plant (Fig. 1).

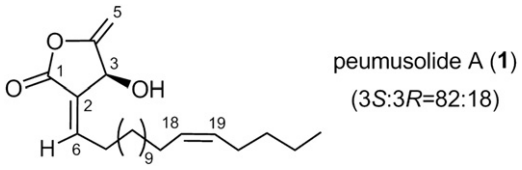

Figure 1. Chemical structures of peumusolide A (**1**).

2. Results and discussion

2.1. Retrosynthetic analysis

Our retrosynthetic approach to peumusolide A (**1**) is illustrated in Figure 2. Namely, the lactone moiety in **1** would be furnished by silver-mediated alkyne-lactonization of optically active 4-carboxy-1-yn-3-ol **2** in the last stage. The carboxylic acid **2** will be provided by asymmetric reduction of 4-en-1-yn-3-one **3**. The conjugated

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ketone **3** was envisioned to be obtained by C3-elongation of (*Z*)-iodoalkene **4** using protected 2-propyn-1-al. The (*Z*)-iodoalkene **4** will be accessible from 2-yn-1-ol **5** by regio- and *trans*-selective hydroiodination. The 2-yn-1-ol **5** was planned to be prepared by coupling of phenyl alkenyl sulfone and protected 4-bromo-2-butyn-1-ol.

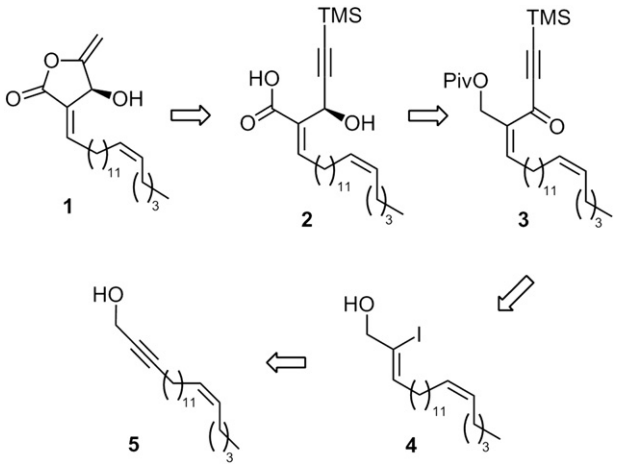


Figure 2. Retrosynthetic analysis of peumusolide A (**1**).

2.2. Construction of 4-en-1-yn-3-one framework

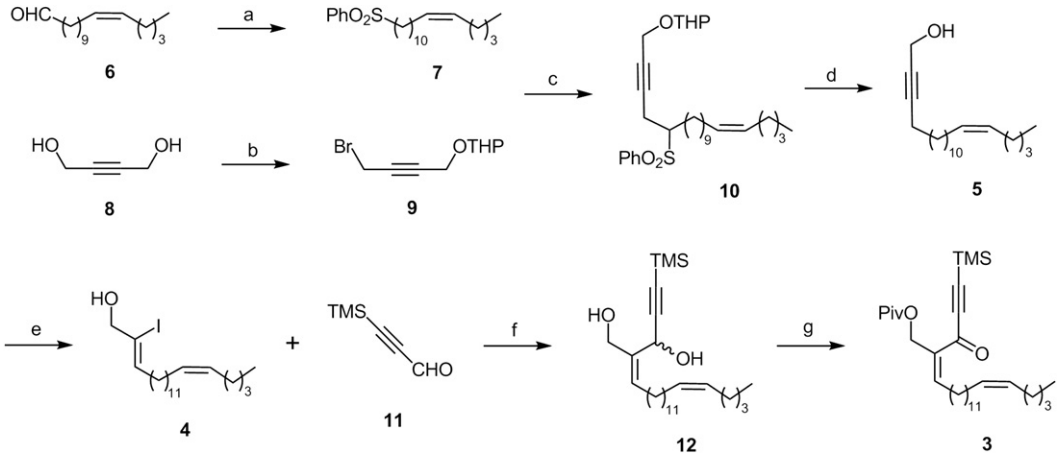
In the first instance, construction of 4-en-1-yn-3-one framework was executed as shown in Scheme 1. Reduction of commercially available (*Z*)-11-hexadecen-1-al (**6**) with $NaBH_4$ followed by treatment with diphenyldisulfide and tri-*n*-butylphosphine afforded phenylsulfide in 98% yield for two steps. The resulting phenylsulfide was subjected to oxidation with Oxone to give phenyl sulfone **7** in 92% yield. On the other hand, preparation of the counterpart bromoalkyne **9** commenced with purchased 2-butyne-1,4-diol (**8**). In brief, protection of either hydroxyl group in **8** was conducted with dihydropyran (DHP) and pyridinium *p*-toluenesulfonate (PPTS) to provide tetrahydropyranyl (THP) ether in 67% yield. Treatment of the THP ether with CBr_4 and triphenylphosphine afforded the bromoalkyne **9** in 71% yield. Coupling of **7** and **9** proceeded with *t*-BuLi in the presence of hexamethylphosphoramide (HMPA) to afford alkynyl sulfone **10** in 56% yield. Successive desulfonation with 5% sodium-amalgam and removal of the THP group in **10** with *p*-toluenesulfonic acid (*p*-TsOH) provided primary alcohol **5** bearing an en-yne functionality in 55% yield for two steps.

Sequential treatment of **5** with *n*-BuLi, *i*-Bu_2AlH (DIBAL), and iodine induced *trans*-selective hydroiodination to give (*Z*)-iodoalkene **4** in 50% yield for three steps.[9] Coupling of the iodoalkene **4** and 3-trimethylsilyl-2-propyn-1-al (**11**) using MeLi and *t*-BuLi[10] provided en-yne-diol **12** in 80% yield. After protection of the primary hydroxyl group in **12** as pivaloyl ester, the resulting ester was converted to conjugated ketone **3** by MnO_2 oxidation in 74% yield for two steps. The *Z*-configuration of the trisubstituted olefin in **3** was unequivocally confirmed by the NOE correlations between the olefinic proton and the methylene protons adjacent to the pivaloyloxy function in the NOESY spectrum.

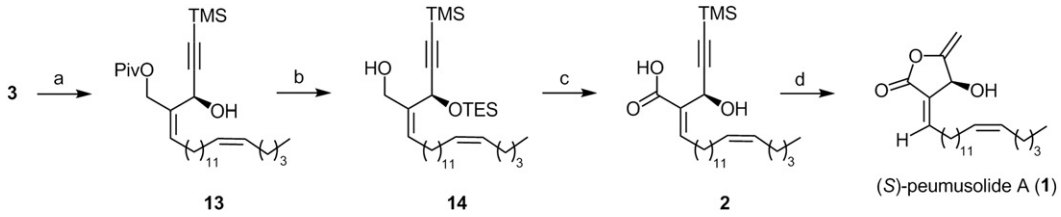
2.3. Transformation from 4-en-1-yn-3-one into peumusolide A (1)

Subsequently, transformation from the conjugated ketone **3** into peumusolide A (**1**) was conducted as illustrated in Scheme 2. Previously, McDonald et al. presented that optical active 2-methyl-CBS-oxazaborolidine[11] enabled to distinguish from the ene and yne function in reduction of 3-en-1-yn-2-one to furnish an optically active 3-en-1-yn-2-ol in high enantiomeric excess.[12] Furthermore, we demonstrated that application of this asymmetric reduction to unprecedented 4-substituted 4-en-1-yn-3-one also afforded an optical alcohol with predicted stereochemical outcome in high enantioselectivity.[8] Thus, asymmetric center at C-3 was introduced by reduction with the CBS catalyst. Asymmetric reduction of the ketone **3** with the complex of (*S*)-2-methyl-CBS-oxazaborolidine and BH_3 provided optical active secondary alcohol **13** in 82% yield with 94% ee.

Introduction of triethylsilyl (TES) protection to the secondary hydroxyl group in **13** using triethylsilyl chloride (TESCl) and imidazole followed by reductive removal of the pivaloyl protection with $LiBH_4$ gave primary alcohol **14** quantitatively. The alcohol **14** was treated with MnO_2 to provide aldehyde, which was submitted to $NaClO_2$ oxidation to generate carboxylic acid **2** concomitant with removal of the TES group in 71% yield for two steps. Removal of the TMS group in **2** with K_2CO_3 and subsequent Ag(I)-mediated alkyne-lactonization furnished the desired γ-lactone in 78% yield for two steps. After chiral HPLC separation of the resulting lactone, the total synthesis of (*S*)-peumusolide A (**1**) has been accomplished. The absolute configuration of **1** was unambiguously confirmed by the CD



Scheme 1. Construction of 4-en-1-yn-3-one framework. Reagents and conditions: (a) (i) $NaBH_4$, MeOH, rt; (ii) PhSSPh, *n*-Bu_3P, benzene, rt, 98% for two steps; (iii) Oxone, THF/MeOH/H_2O, rt, 92%; (b) (i) DHP, PPTS, CH_2Cl_2, rt, 67%; (ii) PPh_3, CBr_4, THF, rt, 71%; (c) *t*-BuLi, HMPA, THF, −78 °C→−50 °C, 56%; (d) (i) 5% Na/Hg, Na_2HPO_4, MeOH, −10 °C, 61%; (ii) *p*-TsOH, MeOH, rt, 90%; (e) (i) *t*-BuLi, THF, −20 °C; (ii) DIBAL, THF, reflux; (iii) I_2, rt, 50% for three steps; (f) MeLi, *t*-BuLi, Et_2O, −78 °C, 80%; (g) (i) PivCl, pyridine, $(CH_2Cl)_2$, reflux, 81%; (ii) MnO_2, $(CH_2Cl)_2$, rt, 91%.



Scheme 2. Transformation from 4-en-1-yn-3-one into peumusolide A (**1**). Reagents and conditions: (a) (*S*)-2-methyl-CBS-oxazaborolidine, BH_3·THF, THF, −40 °C, 82%, 94% ee; (b) (i) TESCl, imidazole, CH_2Cl_2, rt; (ii) $LiBH_4$, THF, reflux, quant. for two steps; (c) (i) MnO_2, $(CH_2Cl)_2$, reflux; (ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, 40 °C, 71% for two steps; (d) (i) K_2CO_3, MeOH/THF, rt; (ii) Ag_2CO_3, benzene, 80 °C, 78% for two steps; (iii) chiral HPLC separation, 90%.

spectra described in our previous report.[8] In addition, the physicochemical data as well as the biological potency of **1** are in entire accordance with those of the isolated peumusolide A from the medicinal plant, this verifying our proposed absolute structure of **1**.

3. Conclusion

In summary, the first total synthesis of peumusolide A (**1**) has been achieved by combination of regio- and stereo-selective aluminum-mediated hydroiodination to 2-yn-1-ol and enantioselective reduction of 4-en-1-yn-3-one with the chiral oxazaborolidine as the key reactions. This synthesis has unequivocally established our proposed absolute structure of **1**. Additionally, it is noteworthy that the present study opens an avenue to synthesize naturally occurring congeneric α-(*E*)-alkylidene-β-hydroxy-γ-methylenebutyrolactones bearing olefin moieties in the side chains.[13,14]

4. Experimental

4.1. General procedures

^{1}H NMR spectra were recorded on a JEOL JNM LA-500 (500 MHz) and NOESY spectra were recorded on a Varian Unity Inova 600 (600 MHz) spectrometer. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale, and signal patterns are indicated as follows. All ^{1}H NMR data were referenced to the residual solvent signal (δ_H 7.26 ppm) as an internal standard. Optical rotations were obtained on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-5300 infrared spectrometer. FABMS and HR FABMS data were acquired on a JEOL JMS SX-102 mass spectrometer. HPLC was performed on a JASCO PU2080 pump equipped with a JASCO UV2070 UV detector. Silica gel (Fuji Silysia Chemical, BW-200) and pre-coated thin-layer chromatography (TLC) plates (Merck, Kiesel gel 60 F_{254}) were used for column chromatography and TLC, respectively. Spots on TLC plates were detected by spraying $Ce(SO_4)_2/H_2SO_4$ [$Ce(SO_4)_2 \cdot nH_2O$ 10 g in 6.3% aqueous H_2SO_4 1.0 L] or acidic *para*-anisaldehyde solution (*para*-anisaldehyde 25 mL, *c*-H_2SO_4 25 mL, AcOH 5 mL, EtOH 425 mL) with subsequent heating. Tetrahydrofuran (THF), diethyl ether, and benzene were freshly distilled from sodium–benzophenon ketyl. Dichloromethane and dichloroethane were freshly distilled from CaH_2. Hexamethylphosphoramide (HMPA) was distilled in vacuo from CaH_2 and stored with 4 Å molecular sieves. Pyridine was dried over KOH pellets.

4.2. Construction of 4-en-1-yn-3-one framework

*4.2.1. (Z)-11-Hexadecenyl phenyl sulfone (**7**).* A solution of **6** (500 mg, 2.10 mmol) in MeOH (12.5 mL) was treated with $NaBH_4$ (95.3 mg, 2.53 mmol) at rt for 1 h. After the reaction mixture was poured into aq satd NaCl, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave alcohol. To a solution of the alcohol in benzene (30.4 mL) were successively added PhSSPh (1.38 g, 6.31 mmol) and *n*-Bu_3P (1.56 mL, 6.31 mmol), then the reaction mixture was stirred at rt for 2 h. Removal of the solvent from the reaction mixture under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 70 g, *n*-hexane/EtOAc=15:1) to afford sulfide (681.3 mg, 98% for two steps). A solution of the sulfide (681.3 mg, 2.05 mmol) in THF/MeOH/H_2O (3:1:1, 37.5 mL) was treated with Oxone (3.78 g, 6.15 mmol) at rt for 2 h. After the reaction mixture was treated with aq satd Na_2SO_3 for 10 min, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 20 g, *n*-hexane/EtOAc=7:1) to afford **7** (687.5 mg, 92%) as colorless oil: IR ν_{max} (KBr) 1654, 1305, 1145, 1113 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (2H, d, *J*=7.5 Hz), 7.60 (3H, m), 5.34 (2H, m), 3.07 (2H, t, *J*=8.1 Hz), 2.01 (4H, m), 1.70 (2H, tt, *J*=7.5, 7.5 Hz), 1.23–1.33 (18H, m), 0.89 (3H, t, *J*=7.0 Hz); MS (FAB) *m*/*z* 365 $[M+H]^+$; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{37}O_2S$: 365.2514, found: 365.2508.

*4.2.2. 4-Bromo-1-O-(2-tetrahydropyranyl)-2-butyn-1-ol (**9**).* To a solution of the alcohol **8** (500 mg, 5.80 mmol) in CH_2Cl_2 (11.6 mL) were successively added dihydropyran (0.53 mL, 6.30 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (146.0 mg, 0.63 mmol), then the reaction mixture was stirred at 40 °C for 1 h. After the reaction mixture was poured into aq satd NaCl, the whole was extracted with EtOAc. The EtOAc extract was successively washed with aq satd $NaHCO_3$ and aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 20 g, *n*-hexane/EtOAc=5:1) to afford THP ether (661.2 mg, 67%). A solution of the THP ether (450.7 mg, 2.65 mmol) in THF (13.3 mL) was treated with CBr_4 (1.76 g, 5.30 mmol) and Ph_3P (1.39 g, 5.30 mmol) at rt for 1 h. After the reaction mixture was poured into H_2O, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 50 g, *n*-hexane/EtOAc=10:1) to afford **9** (438.2 mg, 71%) as colorless oil. The chemical structure of **9** was confirmed by comparison of the spectral data with those reported in the literature.[15]

*4.2.3. (Z)-5-Phenylsulfonyl-1-O-(2-tetrahydropyranyl)-15-icosen-2-yn-1-ol (**10**).* To a solution of the alcohol **7** (502.4 mg, 1.38 mmol) in THF (13.8 mL) and HMPA (1.38 mL) was added *t*-BuLi (1.73 mL, 2.76 mmol, 1.6 M in *n*-pentane) at −78 °C, then the reaction mixture was stirred at −78 °C for 15 min. After a solution of **9** (385.8 mg, 1.66 mmol) in THF/HMPA (10:1, 2.76 mL) was added to the mixture at −78 °C, the whole was stirred at −50 °C for 1 h. The reaction mixture was poured into aq satd NH_4Cl, then the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified

by column chromatography (SiO_2 15 g, *n*-hexane/EtOAc=15:1) to afford **10** (400.7 mg, 56%) as colorless oil: IR ν_{max} (KBr) 2238, 1660, 1305, 1148, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (2H, d, *J*=7.5 Hz), 7.64 (3H, m), 5.37 (2H, m), 4.70 (1H, br s), 4.04 (2H, m), 3.79 (1H, ddd, *J*=18.7, 7.9, 3.0 Hz), 3.52 (1H, ddd, *J*=18.7, 4.0, 2.5), 3.09 (1H, quint-like, *J*=ca. 8 Hz), 2.73 (1H, dd, *J*=17.8, 7.8 Hz), 2.64 (1H, dd, *J*=17.8, 10.5 Hz), 2.02 (4H, m), 1.25–1.33 (26H, m), 0.90 (3H, t, *J*=6.8 Hz); MS (FAB) *m*/*z* 517 $[M+H]^+$; HRMS (FAB) *m*/*z* calcd for $C_{31}H_{49}O_4S$: 517.3352, found: 517.3340.

*4.2.4. (Z)-15-Icosen-2-yn-1-ol (**5**).* A solution of **10** (392.7 mg, 0.76 mmol) in MeOH (7.6 mL) was treated with sodium mercury amalgam (2.84 g, 30.4 mmol) and Na_2HPO_4 (1.08 g, 7.61 mmol) at rt for 10 h. After the reaction mixture was poured into H_2O, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 10 g, *n*-hexane/EtOAc=15:1) to afford desulfonated alkyne (174.5 mg, 61%). A solution of the alkyne (174.5 mg, 0.46 mmol) in MeOH (4.7 mL) was treated with *p*-TsOH·H_2O (17.4 mg, 0.093 mmol) at rt for 1 h. After the reaction mixture was poured into aq satd NaCl, the whole was extracted with EtOAc. The EtOAc extract was successively washed with aq satd $NaHCO_3$ and aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 10 g, *n*-hexane/EtOAc=15:1→7:1) to afford **5** (122.0 mg, 90%) as colorless oil: IR ν_{max} (KBr) 3372, 2208, 1654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40–5.33 (2H, m), 4.25 (2H, t, *J*=2.2 Hz), 2.21 (2H, tt, *J*=7.1, 2.2 Hz), 2.01 (4H, m), 1.26–1.53 (22H, m), 0.89 (3H, t, *J*=6.8 Hz); MS (FAB) *m*/*z* 293 $[M+H]^+$; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{37}O$: 293.2844, found: 293.2851.

*4.2.5. (2Z,15Z)-2-Iodo-2,15-icosadien-1-ol (**4**).* To a solution of **5** (117.5 mg, 0.40 mmol) in THF (1.33 mL) was added *t*-BuLi (0.30 mL, 0.47 mmol, 1.6 M in *n*-pentane) at −20 °C, then the reaction mixture was stirred at −20 °C for 10 min. After DIBAL (0.81 mL, 1.21 mmol, 1.5 M in toluene) was added to the mixture at −20 °C, the whole was heated under reflux for 20 h. The reaction mixture was cooled to rt, then dehydrated EtOAc (0.082 mL) and iodine (307.1 mg, 1.21 mmol) were successively added. After the whole was stirred at rt for 30 min, the mixture was treated with aq satd $Na_2S_2O_3$, aq satd K_2CO_3, and aq satd Rochelle salt at rt for 10 min. The whole was extracted with EtOAc, then the EtOAc extract was washed with H_2O and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 10 g, benzene/EtOAc=30:1) to afford **4** (84.8 mg, 50% for three steps) as colorless oil: IR ν_{max} (KBr) 3462, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (1H, t, *J*=6.7 Hz), 5.33–5.37 (2H, m), 4.24 (2H, d, *J*=6.0 Hz), 2.16 (2H, dt, *J*=7.5, 7.5 Hz), 2.01 (4H, m), 1.87 (1H, t, *J*=6.0 Hz, OH), 1.27–1.57 (22H, m), 0.89 (3H, t, *J*=6.8 Hz); MS (FAB) *m*/*z* 443 $[M+Na]^+$; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{37}IONa$: 443.1787, found: 443.1787.

*4.2.6. (4Z,17Z)-4-Hydroxymethyl-1-trimethylsilyl-4,17-docosadien-1-yn-3-ol (**12**).* To a solution of the alcohol **4** (79.8 mg, 0.19 mmol) in Et_2O (1.0 mL) was added MeLi (0.19 mL, 0.19 mmol, 1.0 M in Et_2O) at −30 °C, then the reaction mixture was stirred at −30 °C for 15 min. After *t*-BuLi (0.24 mL, 0.38 mmol, 1.6 M in *n*-pentane) was added to the mixture at −78 °C, the whole was stirred at −78 °C for 15 min. To the reaction mixture was added a solution of **11** (71.8 mg, 0.57 mmol) in Et_2O (3.7 mL) at −78 °C, then the whole was stirred at −78 °C for 1 h. After the reaction mixture was poured into aq satd NH_4Cl, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 8 g, *n*-hexane/EtOAc=5:1) to afford **12** (64.0 mg, 80%) as colorless oil: IR ν_{max} (KBr) 3314, 2172, 1668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (1H, t, *J*=7.4 Hz), 5.30–5.38 (3H, m), 4.57 (1H, dd, *J*=12.1, 5.7 Hz), 4.17 (1H, dd, *J*=12.1, 5.7 Hz), 2.88 (1H, d, *J*=5.7 Hz, CHO*H*), 2.11 (2H, dt, *J*=7.4, 7.7 Hz), 2.02 (5H, m, CH_2(CH=CH)CH_2, CH_2OH), 1.26–1.39 (22H, m), 0.89 (3H, t, *J*=6.8 Hz), 0.18 (9H, s); MS (FAB) *m*/*z* 443 $[M+H]^+$; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{48}O_2SiNa$: 443.3321, found: 443.3326.

*4.2.7. (4Z,17Z)-4-Pivaloyloxymethyl-1-trimethylsilyl-4,17-docosadien-1-yn-3-one (**3**).* A solution of **12** (59.6 mg, 0.14 mmol) was treated with pyridine (34.0 μL, 0.42 mmol) and pivaloyl chloride (19.2 μL, 0.31 mmol) in $(CH_2Cl)_2$ (6.3 mL) under reflux for 2 h. After the reaction mixture was poured into aq satd NaCl, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 8 g, *n*-hexane/EtOAc=8:1) to afford pivaloyl ester (57.9 mg, 81%) as colorless oil. A solution of the pivaloyl ester in $(CH_2Cl)_2$ (1.68 mL) was heated under reflux in the presence of MnO_2 (100.0 mg, 1.15 mmol) for 5 h. After the reaction mixture was filtered with Celite, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 6 g, *n*-hexane/EtOAc=25:1) to afford **3** (52.5 mg, 91%) as colorless oil: IR ν_{max} (KBr) 2172, 1734, 1662, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.37 (1H, t, *J*=7.6 Hz), 5.30–5.40 (2H, m), 4.82 (2H, s), 2.66 (2H, td, *J*=7.6, 7.6 Hz), 2.00 (4H, m), 1.23–1.53 (22H, m), 1.19 (9H, s), 0.91 (3H, t, *J*=6.8 Hz), 0.24 (9H, s); MS (FAB) *m*/*z* 503 $[M+H]^+$; HRMS (FAB) *m*/*z* calcd for $C_{31}H_{55}O_3Si$: 503.3921, found: 503.3930.

4.3. Transformation from 4-en-1-yn-3-one into peumusolide A (1)

*4.3.1. (S)-(4Z,17Z)-4-Pivaloyloxymethyl-1-trimethylsilyl-4,17-docosadien-1-yn-3-ol (**13**).* To a solution of **3** (48.7 mg, 0.097 mmol) in THF (1.50 mL) were successively (*S*)-2-methyl-CBS-oxazaborolidine (0.58 mL, 0.58 mmol, 1.0 M in toluene) and BH_3·THF (0.49 mL, 0.49 mmol, 1.0 M in THF) at −78 °C, then the reaction mixture was stirred at −40 °C for 3 h. After gradual addition of MeOH and aq satd Rochelle salt, the whole was stirred at rt for 5 min. The mixture was poured into H_2O, then the whole was extracted with EtOAc. The EtOAc extract was successively washed with aq satd Rochelle salt and aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 5 g, *n*-hexane/EtOAc=8:1) to afford **13** (40.5 mg, 82%, 94% ee) as colorless oil: $[\alpha]_D^{24}$ +58.9 (*c* 0.98, MeOH); IR ν_{max} (KBr) 3456, 2172, 1732, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (1H, t, *J*=7.5 Hz), 5.30–5.40 (2H, m), 5.24 (1H, d, *J*=7.5 Hz), 4.85 (1H, d, *J*=12.5 Hz), 4.61 (1H, d, *J*=12.5 Hz), 2.70 (1H, d, *J*=7.5 Hz, 3-OH), 2.16 (2H, dt, *J*=7.5, 7.5 Hz), 2.00 (4H, m), 1.26–1.43 (22H, m), 1.22 (9H, s), 0.89 (3H, t, *J*=6.8 Hz), 0.15 (9H, s); MS (FAB) *m*/*z* 527 $[M+Na]^+$; HRMS (FAB) *m*/*z* calcd for $C_{31}H_{56}O_3SiNa$: 527.3896, found: 527.3897. Optical purity of **13** was determined by chiral HPLC analysis under the following condition; column: Chiralcel OD 4.6×250 mm (DAICEL Chemical Industries), mobile phase: *n*-hexane/EtOAc=10:1, flow rate: 1.0 mL, detection: UV=220 nm, retention time: (*S*)-**13**; 5.5 min, (*R*)-**13**; 10.6 min.

*4.3.2. (S)-(4Z,17Z)-4-Hydroxymethyl-1-trimethylsilyl-3-O-triethylsilyl-4,17-docosadien-1-yn-3-ol (**14**).* A solution of **13** (36.2 mg, 0.072 mmol) in CH_2Cl_2 (2.4 mL) was treated with imidazole (24.6 mg, 0.36 mmol) and TESCl (0.050 mL, 0.29 mmol) at rt for 1 h. After the reaction mixture was poured into H_2O, the whole was

extracted with EtOAc. The EtOAc extract was successively washed with aq 5% HCl, aq satd $NaHCO_3$, and aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave crude TES ether. A solution of the crude TES ether in THF (2.4 mL) was heated under reflux in the presence of $LiBH_4$ (15.9 mg, 0.73 mmol) for 1 h. After gradual addition of EtOAc, the mixture was poured into H_2O. The whole was extracted with EtOAc, then the EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 5 g, *n*-hexane/EtOAc=15:1) to afford **14** (38.5 mg, quant. for two steps) as colorless oil: $[\alpha]_D^{24}$ +41.2 (*c* 0.65, MeOH); IR ν_{max} (KBr) 3343, 2170, 1668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (1H, t, *J*=7.3 Hz), 5.38 (1H, t, *J*=3.7 Hz), 5.33–5.36 (2H, m), 4.45 (1H, dd, *J*=11.6, 3.7 Hz), 4.05 (1H, dt, *J*=11.6, 3.7 Hz), 2.67 (1H, d, *J*=3.7 Hz, OH), 1.97–2.09 (6H, m), 1.26–1.39 (22H, m), 0.98 (9H, t, *J*=7.9 Hz), 0.89 (3H, t, *J*=6.8 Hz), 0.68 (6H, m), 0.15 (9H, s); MS (FAB) *m*/*z* 557 $[M+Na]^+$; HRMS (FAB) *m*/*z* calcd for $C_{32}H_{62}O_2Si_2Na$: 557.4186, found: 557.4181.

*4.3.3. (S)-(4Z,17Z)-4-Carboxy-1-trimethylsilyl-4,17-docosadien-1-yn-3-ol (**2**).* A solution of **14** (35.0 mg, 0.066 mmol) in $(CH_2Cl)_2$ (4.20 mL) was heated under reflux in the presence of MnO_2 (46.9 mg, 0.66 mmol) for 6 h. After the reaction mixture was filtered with Celite, the filtrate was concentrated under reduced pressure to give crude aldehyde. To a solution of the crude aldehyde in *t*-BuOH/H_2O (2:1, 5.66 mL) were successively added 2-methyl-2-butene (0.70 mL, 6.6 mmol), $NaH_2PO_4 \cdot H_2O$ (91.1 mg, 0.66 mmol), and $NaClO_2$ (29.7 mg, 0.33 mmol), then the reaction mixture was stirred at 40 °C for 5 h. After the mixture was treated with aq satd $Na_2S_2O_3$ at rt for 5 min, the whole was poured into aq satd NH_4Cl. The mixture was extracted with EtOAc, then the EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography [SiO_2 3 g, $CHCl_3$/MeOH/H_2O=50:3:1 (lower layer)] to afford **2** (20.2 mg, 71% for two steps) as colorless oil: $[\alpha]_D^{24}$ +27.6 (*c* 0.34, $CHCl_3$); IR ν_{max} (KBr) 3324, 3000, 2174, 1693, 1662 (sh) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (1H, t, *J*=7.3 Hz), 5.30–5.38 (3H, m), 2.32–2.37 (2H, m), 1.97–2.02 (4H, m), 1.26–1.64 (22H, m), 0.90 (3H, t, *J*=6.8 Hz), 0.15 (9H, s); MS (FAB) *m*/*z* 457 $[M+Na]^+$; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{46}O_3SiNa$: 457.3114, found: 457.3108.

*4.3.4. (S)-Peumusolide A (**1**).* A solution of **2** (16.4 mg, 0.038 mmol) in MeOH/THF (1:1, 1.82 mL) was treated with K_2CO_3 (52.4 mg, 0.38 mmol) at rt for 1 h. After the reaction mixture was neutralized with Amberlyst-15, the whole was filtered. The filtrate was concentrated under reduced pressure to give free alkyne. A solution of the free alkyne in benzene (0.83 mL) was treated with Ag_2CO_3 (2.1 mg, 7.6 μmol) at 80 °C for 1 h. After the reaction mixture was poured into H_2O, the whole was extracted with EtOAc. The EtOAc extract was washed with aq satd NaCl and dried over $MgSO_4$. Removal of the solvent from the EtOAc extract under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 2 g, *n*-hexane/EtOAc=12:1) to afford the lactone (10.7 mg, 78% for two steps) as colorless oil. The resulting lactone was purified by HPLC [column: Chiralcel OD 10.0×250 mm, mobile phase: *n*-hexane/EtOAc=9:1, flow rate: 4.0 mL/min, detection: UV 220 nm, retention time: (*S*)-**1**; 5.8 min, (*R*)-**1**; 11.1 min] to furnish (*S*)-peumusolide A (**1**, 9.6 mg, 90%) as colorless oil: $[\alpha]_D^{25}$ −23.4 (*c* 0.4, MeOH); IR ν_{max} (KBr) 3418, 1770, 1672 cm^{-1}; MS (FAB) *m*/*z* 363 $[M+H]^+$; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{39}O_3$: 363.2899, found: 363.2904; CD λ^{MeOH} ($\Delta\epsilon$): 226 nm (−3.2). ^1H and ^{13}C NMR data entirely coincided with those for the enantiomeric mixture reported in our literature.[4]

(*S*)-peumusolide A (**1**) from the natural resource: colorless oil; $[\alpha]_D^{25}$ −23.7 (*c* 0.4, MeOH); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{39}O_3$: 363.2899, found: 363.2878; CD λ^{MeOH} ($\Delta\epsilon$): 226 nm (−3.3). ^1H and ^{13}C NMR, IR, and FABMS spectra were superimposable on those of the synthesized (*S*)-peumusolide A (**1**). The synthesized and isolated (*S*)-peumusolide A (**1**), respectively, inhibited nuclear-export of MEK with IC_{50} of 3.9 μM and 3.7 μM according to our procedure described previously.[4]

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