Total Synthesis of the Antiviral Marine Natural Product (–)-Hennoxazole A

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Supporting Information

Experimental procedures and spectral data for all compounds of the synthetic pathway to (–)-hennoxazole A are provided.

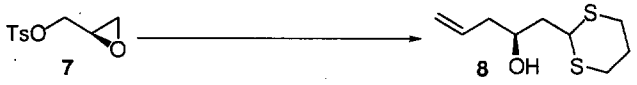
General information: Melting points were measured with YANACO melting point apparatus and are uncorrected. Infrared spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a DIP-1000 digital polarimeters with a sodium lump (l=589 nm, D line) and are reported as follows: $[\alpha]^{T}_{D}$(c g/100 ml, solvent).

^{1}H NMR spectra were recorded on a JEOL EX-270 (270MHz) or ALPHA 500 (500 MHz) or LAMBDA (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and assignment. Hennoxazole A numbering is used for assignments on all intermediates. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm).

Analytical thin layer chromatography were performed on Merck Art. 5715, Kieselgel 60F_{254}/0.25mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, or ninhydrin solution followed by heating. Preparative thin layer chromatography were performed on Merck Art. 5744, Kiselgel 60F_{254}/0.5mm thickness plates. Elementary analysis (Anal) and high resolution mass spectra (HRMS) were done at the Analytical Facility at Nagoya City University.

Solvents for extraction and chromatography were reagent grade. Liquid chromatography was performed with forced flow (flash chromatography of the indicated solvent mixture on silica gel BW-820MH or BW-200 (Fuji Davison Co.)). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Diethyl ether was distilled from lithium aluminum hydride. Dichloromethane (CH_2Cl_2), methanol and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Toluene, acetonitrile (CH_3CN), dimethylsulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were dried over 4-Å molecular sieves. Triethylamine and *N*,*N*-diisopropylethylamine were dried over potassium hydroxide. All other commercially obtained reagents were used as received.

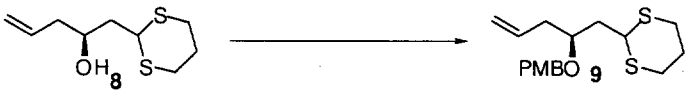
2-[(2*S*)-2-Hydroxy-4-pentenyl]-1,3-dithiane (8).



1,3-Dithiane (2.765 g, 23.0 mmol) was dissolved in THF (31 ml) and cooled to -10 ℃. *n*-Butyllithium (1.5 *M* in hexane, 16 ml, 24.0 mmol) was added and the solution was stirred at -10 ℃ for 2 h, and then cooled to -78 ℃. A solution of (*R*)-glycidyl tosylate (**7**) (5 g, 21.9 mmol) in THF (8 ml, plus 3 ml x 2 of rinse) was added by cannula, and the solution was maintained at -78 ℃ for 3.5 h and allowed to warm to room temperature over 2 h. At this time saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with ether (x 1). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 10 : 1 - 4 : 1) to afford the epoxide as a colorless oil (2.625 g, 14.9 mmol), which was directly employed for the next step.

To a stirred suspension of CuI (425 mg, 2.23 mmol) in THF (70 ml) was added vinylmagnesium bromide (0.95 M in THF, 23.5 ml, 22.3 mmol) at -50 ℃. After the mixture was stirred for 30 min, a solution of the epoxide (2.625 g, 14.9 mmol) in THF (10 ml, plus 2 ml of rinse) was added by cannula. The resulting mixture was stirred at -40 ℃ for 40 min, and then allowed to warm to -10 ℃ over 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the bulk of THF was removed. The residue was extracted with ether (x 1), and the organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 6 : 1 - 4 : 1) to afford the desired product **8** as a colorless oil (2.803 g, 13.7 mmol, 63 %): $[\alpha]^{26}_D$ +24.2 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432, 1640, 1422, 1275, 1244; ^1H NMR (270 MHz, $CDCl_3$) δ 1.89 (2H, t, J = 6.8 Hz, -$SCH_2\mathbf{CH_2}CH_2S$-), 2.03 (1H, br, **OH**), 2.10-2.18 (2H, m, C_5-$\mathbf{CH_2}$), 2.20-2.33 (2H, m, $\mathbf{CH_2}CH{=}CH_2$), 2.81-2.97 (4H, m, -$S\mathbf{CH_2}CH_2\mathbf{CH_2}S$-), 3.99 (1H, br, C_4-**CH**), 4.27 (1H, t, J = 7.3 Hz, C_6-**CH**), 5.14 (2H, d, J = 12.9 Hz, $CH_2CH{=}\mathbf{CH_2}$), 5.74-5.89 (1H, m, $CH_2\mathbf{CH}{=}CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.9, 30.0, 30.3, 41.9, 42.1, 44.4, 67.4, 118.2, 133.9. HRMS (EI) m/z Calcd for $C_9H_{16}OS_2$: 204.0643. Found: 204.0651.

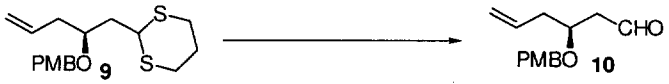
2-[(2*S*)-2-*p*-Methoxybenzyloxy-4-pentenyl]-1,3-dithiane (9).



KH (35 % oil dispersion, 1.2 g, 10.5 mmol) was suspended in THF (15 ml) and cooled to -15 ℃. A solution of the alcohol **8** (1.482 g, 7.25 mmol) in THF (5 ml, plus 3+2 ml of rinse) was added by cannula, and the solution was stirred for 5 min. To

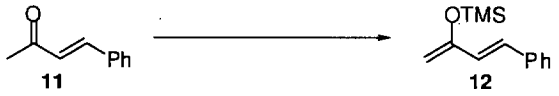
the resulting solution was added PMBCl (1.2 ml, 8.85 mmol) and Bu_4NI (1.3 g, 3.52 mmol). The reaction mixture was stirred at -10 ℃ for 30 min, and then allowed to warm to room temperature over 1 h. The excess KH was quenched by the addition of methanol, followed by 1*M* aqueous $KHSO_4$. The resulting mixture was extracted with ether (x 1), and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 10 : 1) to afford the desired product **9** as a pale yellow oil (2.022 g, 6.23 mmol, 86 %): $[\alpha]^{25}_D$ +35.9 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1640, 1613, 1586, 1514, 1464, 1422, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.87-2.02 (3H, m, -$SCH_2\mathbf{CH_2}CH_2S$-, C_5-$\mathbf{CH_2}$), 2.08-2.13 (1H, m, C_5-$\mathbf{CH_2}$), 2.31-2.34 (2H, m, $\mathbf{CH_2}CH{=}CH_2$), 2.74-2.92 (4H, m, -$S\mathbf{CH_2}CH_2\mathbf{CH_2}S$-), 3.74 (1H, m, C_4-**CH**), 3.81 (3H, s, $O\mathbf{CH_3}$), 4.16 (1H, dd, J = 9.4, 5.1 Hz, C_6-**CH**), 4.44 (1H, d, J = 11.0 Hz, $\mathbf{CH_2}$Ar), 4.57 (1H, d, J = 11.0 Hz, $\mathbf{CH_2}$Ar), 5.07-5.14 (2H, m, $CH_2CH{=}\mathbf{CH_2}$), 5.74-5.90 (1H, m, $CH_2\mathbf{CH}{=}CH_2$), 6.88 (2H, d, J = 8.4 Hz, Ar**H**), 7.28 (2H, J = 8.6 Hz, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.9, 29.8, 30.2, 38.4, 40.0, 43.8, 55.1, 71.0, 74.5, 113.5, 117.4, 129.2, 130.5, 133.9, 158.8. HRMS (EI) m/z Calcd for $C_{17}H_{24}O_2S_2$: 324.1218. Found: 324.1216.

(3*S*)-3-*p*-Methoxybenzyloxy-5-hexenal (10).



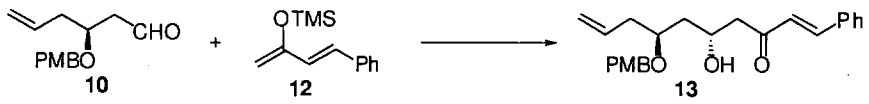
To a stirred solution of **9** in CH_3CN/H_2O (9 : 1, 20 ml) was added $CaCO_3$ (6 g, 59.9 mmol) and MeI (3.4 ml, 54.6 mmol). The resulting mixture was stirred at 40 ℃ for 11 h, and then filtered through a pad of celite, and the filtrate was concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 8 : 1) to afford the desired product **10** as a colorless oil (939 mg, 4.01 mmol, 74 %): $[\alpha]^{26}_D$ +39.6 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1725, 1642, 1613, 1586, 1514, 1466, 1443, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 2.31-2.52 (2H, m, $\mathbf{CH_2}CH{=}CH_2$), 2.57-2.72 (2H, m, C_5-$\mathbf{CH_2}$), 3.80 (3H, s, $O\mathbf{CH_3}$), 3.97-4.06 (1H, m, C_4-**CH**), 4.45 (1H, d, J = 11.0 Hz, $\mathbf{CH_2}$Ar), 4.56 (1H, d, J = 11.0 Hz, $\mathbf{CH_2}$Ar), 5.10-5.15 (2H, m, $CH_2CH{=}\mathbf{CH_2}$), 5.73-5.88 (1H, m, $CH_2\mathbf{CH}{=}CH_2$), 6.87 (2H, d, J = 8.6 Hz, Ar**H**), 7.24 (2H, J = 8.9 Hz, Ar**H**), 9.76 (1H, s, **CHO**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 38.3, 48.0, 55.2, 70.8, 73.2, 113.7, 118.0, 129.2, 130.0, 133.4, 159.1, 201.1. HRMS (EI) m/z Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1257.

2-Trimethylsiloxy-4-phenyl-1,3-butadiene (12).



To a solution of benzalacetone (**11**) (1.08 g, 7.39 mmol) and triethylamine (1.54 ml, 11.1 mmol) in CH_2Cl_2 (25 ml) at -10 ℃ was added dropwise TMSOTf (1.8 ml, 9.95 mmol). After 15 min, the solution was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (x 3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 5 : 1) to afford the labile silyl enol ether **12** as a colorless oil (1.554 g, 7.12 mmol, 96 %), which was directly used for the next step: IR ν_{max}^{neat} cm^{-1} 1634, 1599, 1589, 1495, 1449, 1329, 1312, 1287, 1254; ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, Si(C**H**$_3$)$_3$), 4.43 (1H, s, C7-C**H**$_2$), 4.47 (1H, s, C7-C**H**$_2$), 6.58 (1H, d, J = 15.7 Hz, C**H**=CHPh), 6.80 (1H, d, J = 15.7 Hz, CH=C**H**Ph), 7.20-7.25 (1H, m, Ar**H**), 7.29-7.34 (2H, m, Ar**H**), 7.40-7.43 (2H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 0.20, 96.9, 126.3, 126.7, 127.5, 128.4, 129.1, 136.7, 154.9.

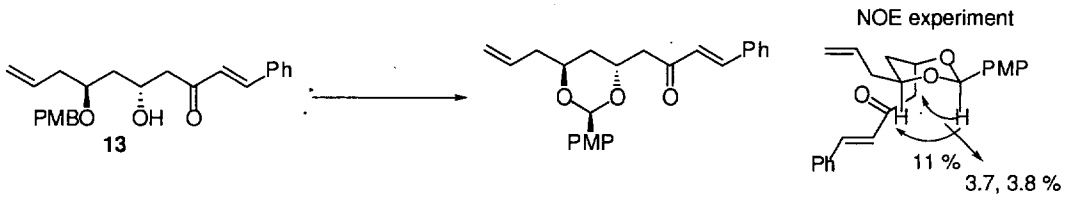
(1*E*, 5*R*, 7*S*)-1-Phenyl-5-hydroxy-7-*p*-methoxybenzyloxy-1,9-decadiene-3-one (13).



To a solution of the aldehyde **10** (818 mg, 3.49 mmol) and the silyl enol ether **12** (948 mg, 4.34 mmol) in CH_2Cl_2 (20 ml) at -78 ℃ was added dropwise $BF_3 \cdot OEt_2$ (0.55 ml, 4.34 mmol). The resulting solution was stirred at -78 ℃ for 2 h and then quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ (x 3), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 6 : 1 - 4 : 1 - 3 : 1) to afford the desired product **13** as a colorless oil (1.178 g, 3.10 mmol, 89 %) in an inseparable 88 : 12 mixture of diastereomers, which were directly used for the next step: $[\alpha]^{26}_D$ +25.9 (c 1.4, MeOH); IR ν_{max}^{neat} cm^{-1} 1684, 1651, 1611, 1514, 1451, 1339, 1248; ^1H NMR (500 MHz, $CDCl_3$) δ 1.61-1.66 (1H, m, C5-C**H**$_2$), 1.70-1.75 (1H, m, C5-C**H**$_2$), 2.33-2.45 (2H, m, C**H**$_2$CH=CH$_2$), 2.78 (1H, dd, J = 17.1, 8.2 Hz, C7-C**H**$_2$) (2.69, dd, J = 16.4, 4.6 Hz), 2.86 (1H, dd, J

= 17.1, 3.7 Hz, C7-C**H**2), 3.43 (1H, d, J = 3.0 Hz, O**H**), 3.77 (3H, s, OC**H**3) (3.75, s), 3.79-3.85 (1H, m, C4-C**H**), 4.32-4.43 (1H, m, C6-C**H**), 4.45 (1H, d, J = 11.0 Hz, C**H**2Ar), 4.60 (1H, d, J = 11.0 Hz, C**H**2Ar) (4.61, d, J = 11.0 Hz), 5.08-5.14 (2H, m, CH2CH=C**H**2), 5.80-5.89 (1H, m, CH2C**H**=CH2), 6.67 (1H, d, J = 16.4 Hz, CH=C**H**Ph) (6.72, d, J = 16.4 Hz), 6.86 (2H, d, J = 8.8 Hz, Ar**H**), 7.27 (2H, d, J = 8.6 Hz, Ar**H**), 7.39-7.42 (3H, m, C**H**=CHPh & Ar**H**), 7.50-7.55 (3H, m, Ar**H**); ^{13}C NMR (67.8 MHz, CDCl3) δ 37.5 (37.9), 40.8 (40.4), 47.3, 55.2 (55.15), 65.1 (67.1), 71.2 (70.3), 76.5, 113.7 (113.8), 117.3 (117.6), 126.2 (126.4), 128.2 (128.4), 128.8 (128.6), 129.4 (129.9), 130.4, 130.5, 134.1 (133.8), 134.3 (134.2), 143.2 (143.0), 159.0 (159.2), 200.2 (199.5). Figures in parentheses show signals of the minor diastereomer. Anal. Calcd for C24H28O4: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.43.

4-[(2*S*, 4*S*, 6*R*)-2-*p*-Methoxybenzyloxy-4-(2-propenyl)-1,3-dioxan-6-yl]-1-phenyl-2-buten-3-one.

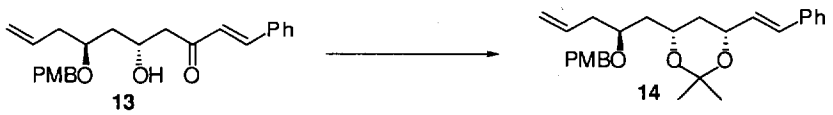


A suspension of the aldol adduct **13** (48 mg, 0.126 mmol) and powdered 4A molecular sieves in CH2Cl2 (1.3 ml) was stirred for 15 min prior to the addition of DDQ (40 mg, 0.176 mmol). After 20 min, the mixture was diluted with ether and filtered through a pad of celite. The filtrate was washed with saturated aqueous NaHCO3, water, and brine, dried (MgSO4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 7 : 1) to afford the desired product as a colorless oil (31 mg, 0.082 mmol, 65 %): $[\alpha]^{26}_{D}$ -32.2 (c 1.0, CHCl3); IR ν_{max}^{neat} cm^{-1} 1688, 1659, 1613, 1576, 1518, 1248; ^{1}H NMR (270 MHz, C6D6) δ 1.31-1.36 (1H, m, C5-C**H**2), 1.90 (1H, td, J = 12.7, 6.1 Hz, C5-C**H**2), 2.09-2.17 (1H, m, C**H**2CH=CH2), 2.29-2.40 (1H, m, C**H**2CH=CH2), 2.66 (1H, dd, J = 15.2, 7.9 Hz, C7-C**H**2), 3.00 (1H, dd, J = 15.2, 6.6 Hz, C7-C**H**2), 3.24 (3H, s, OC**H**3), 3.81 (1H, m, C4-C**H**), 4.80-4.85 (1H, m, C6-C**H**), 5.02-5.09 (2H, m, CH2CH=C**H**2), 5.80 (1H, s, C**H**MP), 5.80-5.93 (1H, m, CH2C**H**=CH2), 6.59 (1H, d, J = 16.2 Hz, CH=C**H**Ph), 6.81 (2H, d, J = 8.7 Hz, Ar**H**), 7.01 (3H, m, Ar**H**), 7.19 (2H, m, Ar**H**), 7.52 (1H, d, J = 16.2 Hz, C**H**=CHPh), 7.65 (2H, d, J = 8.6 Hz, Ar**H**); ^{13}C NMR (67.8 MHz,

$CDCl_3$) δ 33.1, 40.5, 42.6, 55.3, 69.2, 71.9, 94.8, 113.5, 117.4, 125.9, 127.3, 128.3, 128.9, 130.6, 131.1, 133.6, 134.1, 143.2, 159.7, 197.2. HRMS (EI) m/z Calcd for $C_{24}H_{26}O_4$: 378.1831. Found: 378.1837.

Stereochemical Proof of 13. DDQ oxidation of the aldol adduct **13** produced the cyclic *p*-methoxybenzylidene acetal. NOE analysis established the 1,3-*anti* dioxygen relationship of the acetal, thereby securing the stereochemical assignment of the aldol adduct **13**.

(4*S*)-5-[(4*R*, 6*R*)-4-(2-Phenylethenyl)-2,2-dimethyl-1,3-dioxan-6-yl]-4-*p*-methoxybenzyloxy-2-pentene (14).



To a stirred solution of the aldol adduct **13** (660 mg, 1.73 mmol) in THF (7 ml) at -78 ℃ was added Et_2BOMe (1.0 *M* in THF, 1.9 ml, 1.9 mmol). After 30 min, $NaBH_4$ (66 mg, 1.74 mmol) was added, and the mixture was stirred at -78 ℃ for 1 h. The reaction mixture was quenched by the addition of pH 7 phosphate buffer (1.1 ml) and methanol (3.1 ml), then allowed to warm to 0 ℃. To this was added 2 : 1 methanol/30 % aqueous H_2O_2 (3 ml) carefully. The mixture was stirred at 0 ℃ for 1.5 h, and then allowed to warm to room temperature over 1.5 h. The mixture was extracted with $CHCl_3$ (x 3), and the combined organic extracts were washed with 1*M* aqueous $KHSO_4$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 3 : 1 - 2 : 1) to afford the *syn*-diol as a colorless oil (690 mg, 1.80 mmol), which was directly used for the next step.

Syn-diol (690 mg, 1.80 mmol) was dissolved in 2,2-dimethoxypropane (6 ml), and then PPTs (270 mg) was added. After 26 h, an additional PPTs (270 mg) was added and the mixture was stirred for 10 h. An additional PPTs (270 mg) was added and the mixture was stirred for additional 11 h. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-200, hexane : ether = 10 : 1 - hexane : EtOAc = 5 : 1 - 2 : 1) to afford the desired product **14** as a colorless oil (430 mg, 1.02 mmol, 59 %), the minor diastereomer **15** as white crystals

(64 mg, 0.15 mmol, 9 %), and the starting material (208 mg, 0.54 mmol, 31 %). Data for the desired product **14**: $[\alpha]^{26}_{D}$ +31.1 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1640, 1613, 1586, 1514, 1379, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.27-1.41 (1H, m, C_5-**CH2**), 1.46 (3H, s, **CH3**), 1.50 (3H, s, **CH3**), 1.56-1.63 (3H, m, C_5 & C_7-**CH2**), 2.33-2.37 (2H, m, **CH2**CH=CH_2), 3.73-3.78 (1H, m, C_4-**CH**), 3.81 (3H, s, O**CH3**), 4.16-4.20 (1H, m, C_6-**CH**), 4.40 (1H, d, J = 10.9 Hz, **CH2**Ar), 4.50-4.53 (1H, m, C_8-**CH**), 4.58 (1H, d, J = 10.9 Hz, **CH2**Ar), 5.07-5.15 (2H, m, CH_2CH=**CH2**), 5.79-5.95 (1H, m, CH_2**CH**=CH_2), 6.16 (1H, dd, J = 16.0, 6.3 Hz, **CH**=CHPh), 6.58 (1H, d, J = 16.0 Hz, CH=**CH**Ph), 6.89 (2H, d, J = 8.7 Hz, Ar**H**), 7.19-7.39 (7H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.1, 30.4, 37.7, 38.9, 41.9, 55.3, 65.3, 70.2, 71.4, 74.0, 98.7, 113.8, 117.2, 126.4, 127.5, 128.4, 129.3, 129.9, 130.5, 130.8, 134.5, 136.6, 159.1. Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.59; H, 8.22.

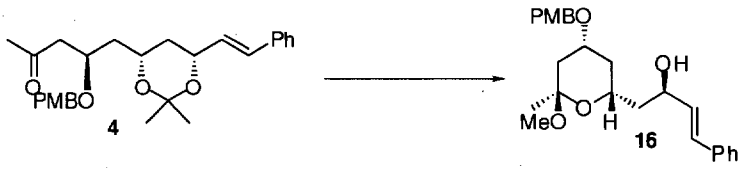
Data for the minor diastereomer **15**: mp 87-89 °C (ether - *n*-pentane); $[\alpha]^{25}_{D}$ +29.3 (c 0.7, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 1640, 1611, 1584, 1512, 1464, 1375, 1250; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20-1.27 (2H, m, C_5-**CH2**), 1.43 (3H, s, **CH3**), 1.49 (3H, s, **CH3**), 1.53-1.58 (1H, m, C_7-**CH2**), 1.80-1.91 (1H, m, C_7-**CH2**), 2.33-2.38 (2H, m, **CH2**CH=CH_2), 3.52-3.56 (1H, m, C_4-**CH**), 3.75 (3H, s, O**CH3**), 4.00 (1H, m, C_6-**CH**), 4.36 (1H, d, J = 11.5 Hz, **CH2**Ar), 4.34-4.38 (1H, m, C_8-**CH**), 4.55 (1H, d, J = 11.5 Hz, **CH2**Ar), 5.06-5.13 (2H, m, CH_2CH=**CH2**), 5.76-5.92 (1H, m, CH_2**CH**=CH_2), 6.08 (1H, dd, J = 16.0, 6.3 Hz, **CH**=CHPh), 6.53 (1H, d, J = 16.0 Hz, CH=**CH**Ph), 6.88 (2H, d, J = 8.4 Hz, Ar**H**), 7.19-7.38 (7H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.0, 30.3, 36.8, 38.3, 40.5, 55.3, 65.9, 70.1, 70.2, 73.5, 98.6, 113.7, 117.3, 126.4, 127.5, 128.3, 129.7, 129.8, 130.4, 130.6, 134.4, 136.6, 159.1. Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.48; H, 7.94.

(4*R*)-5-[(4*R*, 6*R*)-4-(2-Phenylethenyl)-2,2-dimethyl-1,3-dioxan-6-yl]-4-*p*-methoxybenzyloxy-2-pentanone (4).

A suspension of **14** (286 mg, 0.677 mmol), $PdCl_2$ (12 mg, 0.068 mmol), and $Cu(OAc)_2 \cdot H_2O$ (27 mg, 0.135 mmol) in $AcNMe_2/H_2O$ (7 : 1, 6 ml) was placed under O_2 (balloon) and stirred at room temperature for 19.5 h. The reaction mixture was

diluted with ether, and washed with water (x 2) and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 2 : 1 - 1 : 1) to afford the desired product **4** as a colorless oil (230 mg, 0.525 mmol, 77 %): $[\alpha]^{26}_D$ +7.6 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1713, 1613, 1586, 1514, 1379, 1360, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.37-1.70 (4H, m, C_5 & C_7-CH_2), 1.46 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.17 (3H, s, C_1-CH_3), 2.59 (1H, dd, J = 15.8, 4.9 Hz, C_3-CH_2), 2.75 (1H, dd, J = 15.8, 6.9 Hz, C_3-CH_2), 3.80 (3H, s, OCH_3), 4.11-4.18 (2H, m, C_4 & C_6-CH), 4.45 (1H, d, J = 10.7 Hz, CH_2Ar), 4.53 (1H, d, J = 10.9 Hz, CH_2Ar), 4.44-4.55 (1H, m, C_8-CH), 6.15 (1H, dd, J = 16.0, 6.3 Hz, CH=CHPh), 6.59 (1H, d, J = 16.0 Hz, CH=CHPh), 6.88 (2H, d, J = 8.2 Hz, ArH), 7.23-7.39 (7H, m, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.0, 30.3, 31.3, 37.6, 42.5, 49.5, 55.3, 65.3, 70.1, 71.8, 72.1, 98.7, 113.8, 126.4, 127.5, 128.4, 129.3, 129.7, 130.4, 130.6, 136.5, 159.1, 207.2. Anal. Calcd for $C_{27}H_{34}O_5$: C, 73.94; H, 7.81. Found: C, 74.30; H, 8.12.

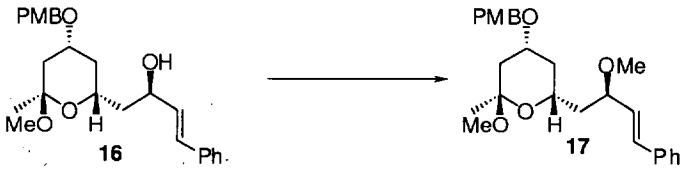
(3*R*)-4-[(2*R*, 4*R*, 6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-1-phenyl-3-hydroxy-1-butene (16).



Methyl ketone **4** (230 mg, 0.525 mmol) was dissolved in anhydrous methanol (5 ml) and PPTs (10 mg, 0.040 mmol) was added in one portion. After 6.5 h, $NaHCO_3$ was added, and the mixture was filtered. The filtrate was concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 2 : 1) to afford the desired product **16** as a colorless oil (183 mg, 0.444 mmol, 85 %): $[\alpha]^{26}_D$ -50.3 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3475, 1613, 1586, 1514, 1495, 1383, 1362, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.19-1.45 (2H, m, C_3 & C_5-CH_2), 1.39 (3H, s, C_1-CH_3), 1.73-1.93 (2H, m, C_7-CH_2), 2.02 (1H, d, J = 12.4 Hz, C_5-CH_2), 2.26 (1H, dd, J = 12.7, 3.5 Hz, C_3-CH_2), 3.23 (3H, s, C_{29}-OCH_3), 3.72 (1H, s, OH), 3.80 (3H, s, OCH_3), 3.83-3.92 (2H, m, C_4 & C_6-CH), 4.47 (2H, s, CH_2Ar), 4.54 (1H, br, C_8-CH), 6.20 (1H, dd, J = 15.8, 6.1 Hz, CH=CHPh), 6.64 (1H, d, J = 15.8 Hz, CH=CHPh), 6.86 (2H, d, J = 8.4 Hz, ArH), 7.23-7.39 (7H, m, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.8, 38.0, 41.9, 43.1, 48.0, 55.3, 69.7, 70.0, 70.9, 72.4,

100.1, 113.8, 126.3, 127.4, 128.4, 129.0, 129.6, 130.6, 131.6, 136.8, 159.0. Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.58; H, 8.01.

(3*R*)-4-[(2*R*, 4*R*, 6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-1-phenyl-3-methoxy-1-butene (17).



To a solution of the alcohol **16** (108 mg, 0.262 mmol) in THF (2.5 ml) at 0 ℃ was added NaH (60 % oil dispersion, 26 mg, 0.650 mmol) in one portion. After 30 min, to this mixture was added dropwise MeI (0.033 ml, 0.530 mmol). The reaction mixture was stirred at 0 ℃ for 40 min and then at room temperature for 14 h. The excess hydride was quenched by dropwise addition of saturated aqueous $NaHCO_3$. Ether was added, the layers were separated, and the organic layer was washed with 1*M* aqueous $KHSO_4$, water, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 7 : 1 - 5 : 1) to afford the desired product **17** as a colorless oil (109 mg, 0.256 mmol, 98 %): $[\alpha]^{26}_D$ -37.8 (c 1.3, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1613, 1588, 1514, 1495, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (1H, q, J = 11.4 Hz, C_5-C**H**$_2$), 1.34 (3H, s, C_1-C**H**$_3$), 1.35 (1H, dd, J = 12.4, 11.4 Hz, C_3-C**H**$_2$), 1.64-1.72 (1H, m, C_5-C**H**$_2$), 1.99-2.04 (2H, m, C_3 & C_7-C**H**$_2$), 2.21 (1H, d, J = 12.4 Hz, C_7-C**H**$_2$), 3.14 (3H, s, C_{29}-OC**H**$_3$), 3.30 (3H, s, C_{28}-OC**H**$_3$), 3.65 (1H, br, C_6-C**H**), 3.78 (3H, s, OC**H**$_3$), 3.83 (1H, m, C_4-C**H**), 3.88-3.95 (1H, m, C_8-C**H**), 4.45 (2H, s, C**H**$_2$Ar), 6.04 (1H, dd, J = 16.0, 8.2 Hz, C**H**=CHPh), 6.55 (1H, d, J = 15.9 Hz, CH=C**H**Ph), 6.85 (2H, d, J = 8.4 Hz, Ar**H**), 7.22-7.39 (7H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.9, 37.9, 42.1, 42.2, 47.9, 55.3, 56.0, 65.8, 69.6, 71.4, 79.3, 99.6, 113.7, 126.3, 127.7, 128.5, 129.0, 129.6, 130.8, 133.3, 136.3, 158.9. Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 72.96; H, 8.14.

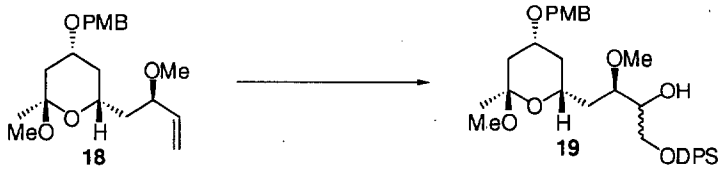
(3*R*)-4-[(2*R*, 4*R*, 6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-3-hydroxy-1-butene (18).

To a solution of **17** (228 mg, 0.534 mmol) and NMO (125 mg, 1.07 mmol) in acetone/water (8 : 1, 3.94 ml) at room temperature was added OsO_4 (0.1 *M* in *tert*-butanol, 0.54 ml, 0.054 mmol). The mixture was stirred for 5 h, and then quenched by the addition of saturated aqueous Na_2SO_3. The resulting mixture was extracted with EtOAc (x 1), and the organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated to afford the diol (250 mg), which was used for the next step without further purification.

To a solution of the diol in THF/pH 7 phosphate buffer (1 : 1, 4.6 ml) at 0 ℃ was added $NaIO_4$ (171 mg, 0.80 mmol) in one portion. The reaction mixture was stirred at 0 ℃ for 5 min, and then at room temperature for 20 min. Ether and water were added, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the aldehyde (194 mg), which was used for the next step without further purification.

To a solution of the aldehyde in THF (1.9 ml) at -78 ℃ was added dropwise Tebbe reagent ($Cp_2TiCH_2AlClMe_2$) (0.5 *M* in toluene, 1.85 ml, 0.93 mmol). The reaction mixture was stirred at -78 ℃ for 4 min, and then allowed to warm to 0 ℃ over 8 min, and quenched by the addition of 0.1 *N* aqueous NaOH. The mixture was stirred at room temperature, and then filtered through a pad of celite by washing with ether. The filtrate was separated and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 5 : 1) to afford the desired product **18** as a colorless oil (134 mg, 0.382 mmol, 72 %): $[\alpha]^{26}_{D}$ -51.4 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1615, 1588, 1514, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (1H, q, J = 11.7 Hz, C_5-C**H**$_2$), 1.34 (3H, s, C_1-C**H**$_3$), 1.38 (1H, d, J = 11.9 Hz, C_3-C**H**$_2$), 1.53-1.62 (1H, m, C_5-C**H**$_2$), 1.89-1.92 (1H, m, C_3-C**H**$_2$), 1.94-2.04 (1H, m, C_7-C**H**$_2$), 2.22 (1H, dd, J = 12.5, 3.1 Hz, C_7-C**H**$_2$), 3.15 (3H, s, C_{29}-OC**H**$_3$), 3.26 (3H, s, C_{28}-OC**H**$_3$), 3.61-3.66 (1H, br, C_6-C**H**), 3.68-3.76 (1H, m, C_4-C**H**), 3.80 (3H, s, OC**H**$_3$), 3.83-3.90 (1H, m, C_8-C**H**), 4.47 (2H, s, C**H**$_2$Ar), 5.19-5.27 (2H, m, CH=C**H**$_2$), 5.60-5.73 (1H, m, C**H**=CH_2), 6.86 (2H, d, J = 8.6 Hz, Ar**H**), 7.25 (2H, d, J = 7.9 Hz, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.8, 37.7, 41.8, 42.0, 47.8, 55.2, 55.8, 65.7, 69.4, 71.4, 79.6, 99.5, 113.6, 117.9, 128.9, 130.7, 138.2, 158.8. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.32; H, 8.72.

Mono silylether (19).



To a solution of **18** (77 mg, 0.220 mmol) and NMO (52 mg, 0.444 mmol) in acetone/water (8 : 1, 1.8 ml) at room temperature was added OsO_4 (0.1 *M* in *tert*-butanol, 0.22 ml, 0.022 mmol). The mixture was stirred for 4.5 h, and then quenched by the addition of saturated aqueous Na_2SO_3. The resulting mixture was extracted with EtOAc (x 1), and the organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 1 : 2 - EtOAc : EtOH = 10 : 1) to afford the diol (83 mg), which was directly used for the next step.

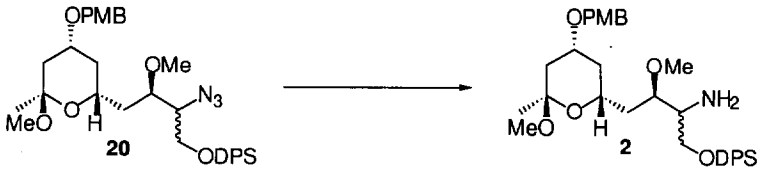
To a stirred solution of the diol (83 mg) in CH_2Cl_2 (1.2 ml) at 0 ℃ was added triethylamine (0.063 ml, 0.432 mmol), DMAP (4 mg, 0.033 mmol), and DPSCl (0.084 ml, 0.323 mmol). The reaction mixture was stirred at 0 ℃ for 50 min and then at room temperature for 13 h. After dilution with ether, the mixture was washed with 1 *M* aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 3 : 1) to afford the desired product **19** as a colorless oil (129 mg, 0.207 mmol, 94 %): $[\alpha]^{26}_{D}$ -33.6 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3475, 1615, 1588, 1514, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (9H, s, $(CH_3)_3C$), 1.17-1.41 (2H, m, C_3 & C_5-CH_2), 1.33 (3H, s, C_1-CH_3) (1.30, s), 1.69-1.84 (2H, m, C_3 & C_5-CH_2), 1.89-2.02 (1H, m, C_7-CH_2), 2.20-2.24 (1H, m, C_7-CH_2), 2.96 (1H, br, OH) (2.59, d, J = 5.4 Hz), 3.15 (3H, s, C_{29}-OCH_3) (3.10, s), 3.31 (3H, s, C_{28}-OCH_3) (3.37, s), 3.46-3.50 (1H, m, C_6-CH), 3.63-3.90 (5H, m, C_4, C_8, C_9-CH & C_{10}-CH_2), 3.80 (3H, s, OCH_3) (3.77, s), 4.47 (2H, s, CH_2Ar), 6.87 (2H, d, J = 8.4 Hz, ArH), 7.25 (2H, d, J = 6.8 Hz, ArH), 7.38-7.43 (6H, m, ArH), 7.66-7.69 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.3, 23.7, 26.9, 35.5 (35.7), 37.7 (37.9), 42.0, 48.0 (47.9), 55.2, 57.2 (57.6), 64.7 (64.4), 65.7 (65.5), 69.5, 71.3, 72.9 (72.6), 78.1, 99.7 (99.6), 113.7, 127.6, 129.0, 129.6, 130.7, 133.1, 135.4 (135.3), 158.9. Figures in parentheses show signals of the minor diastereomer. Anal. Calcd for $C_{36}H_{50}O_7Si$: C, 69.42; H, 8.09. Found: C, 69.21; H, 8.07.

Azide (20).

To a stirred solution of the alcohol **19** (105 mg, 0.169 mmol) in CH_2Cl_2 (1 ml) at 0 ℃ was added triethylamine (0.24 ml, 1.73 mmol), DMAP (2 mg, 0.016 mmol), and MsCl (0.078 ml, 1.01 mmol). The reaction mixture was stirred at 0 ℃ for 15 min and then at room temperature for 2 h. After dilution with ether, the mixture was washed with 1 *M* aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the mesylate (117 mg), which was used for the next step without further purification.

To a solution of the mesylate (117 mg) in DMF (0.2 ml) was added a solution of Bu_4NN_3 (480 mg, 1.69 mmol) in THF (0.8 ml). The reaction mixture was stirred at 100 ℃ for 4 h. After dilution with ether, the mixture was washed with water (x 2) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 6 : 1) to afford the desired product **20** as a colorless oil (75 mg, 0.116 mmol, 68 %): $[\alpha]^{25}_D$ -35.9 (c 0.6, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2101, 1613, 1588, 1514, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08 (9H, s, $(CH_3)_3C$), 1.16-1.44 (2H, m, C_3 & C_5-CH_2), 1.29 (3H, s, C_1-CH_3) (1.27, s), 1.76 (2H, t, J = 6.2 Hz, C_7-CH_2), 1.99-2.03 (1H, m, C_5-CH_2), 2.20-2.24 (1H, m, C_3-CH_2), 3.10 (3H, s, C_{29}-OCH_3) (3.14, s), 3.32 (3H, s, C_{28}-OCH_3) (3.29, s), 3.56-3.66 (3H, m, C_4, C_6, & C_8-CH), 3.80 (3H, s, OCH_3), 3.84 (1H, m, C_9-CH), 3.88 (2H, d, J = 5.8 Hz, C_{10}-CH_2), 4.48 (2H, s, CH_2Ar), 6.88 (2H, d, J = 8.6 Hz, ArH), 7.25 (2H, d, J = 6.3 Hz, ArH), 7.40-7.45 (6H, m, ArH), 7.66-7.69 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.2, 23.7, 26.8, 35.9 (36.2), 37.6 (37.7), 42.0, 47.9 (47.9), 55.3, 57.6 (57.3), 63.7 (63.9), 65.2 (65.7), 65.6 (65.8), 69.6, 71.3 (71.4), 76.9 (77.3), 99.6, 113.7, 127.6 (127.7), 129.0, 129.7, 130.7 (132.8), 132.9 (132.9), 135.4 (135.4), 158.9. Figures in parentheses show signals of the minor diastereomer. Anal. Calcd for $C_{36}H_{49}N_3O_6Si$: C, 66.74; H, 7.62; N, 6.49. Found: C, 66.65; H, 7.67; N, 6.38.

Amine (2).

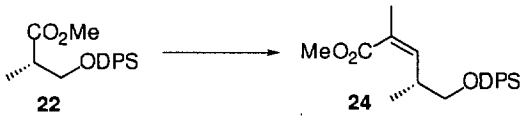


To a solution of the azide **20** (40 mg, 0.062 mmol) in THF (0.6 ml) was added Ph_3P (49 mg, 0.187 mmol) and water (0.011 ml, 0.611 mmol). The resulting solution was heated to 55 ℃ for 70 min before it was cooled to room temperature. The solvent was removed and the residue was purified by flash chromatography (BW-200, $CHCl_3$: methanol = 200 : 1) to afford the desired product **2** as a colorless oil (26 mg, 0.042 mmol, 68 %), which was directly used for the next step.

(*S*)-Methyl 3-*tert*-butyldiphenylsiloxy-2-methylpropionate (22).

To a stirred solution of **21** (3 g, 25.4 mmol) in DMF (50 ml) at 0 ℃ was added imidazole (3.63 g, 53.3 mmol) and DPSCl (7 ml, 26.9 mmol). The reaction mixture was stirred at 0 ℃ for 30 min and then at room temperature for 7.5 h. After dilution with ether, the mixture was washed with 1 *M* aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 10 : 1) to afford the desired product **22** as a colorless oil (8.62 g, 24.2 mmol, 95 %): $[\alpha]^{26}_D$ -16.5 (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1742, 1429, 1200, 1113; ^1H NMR (270 MHz, $CDCl_3$) δ 1.03 (9H, s, $(CH_3)_3C$), 1.15 (3H, d, J = 6.9 Hz, C_{26}-CH_3), 2.68-2.76 (1H, m, C_{22}-CH), 3.68 (3H, s, CH_3 ester), 3.72 (1H, dd, J = 9.6, 5.6 Hz, CH_2), 3.83 (1H, dd, J = 9.6, 6.9 Hz, CH_2), 7.34-7.42 (6H, m, ArH), 7.64-7.67 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.4, 19.2, 26.7, 42.3, 51.5, 65.9, 127.6, 129.6, 133.5, 135.5, 175.3. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.68; H, 8.00.

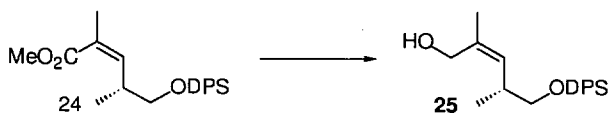
(2*Z*, 4*R*)-Methyl-5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-2-pentenoate (24).



To a stirred solution of **22** (2.1 g, 5.89 mmol) in ether (20 ml) was added DIBAL (0.95 *M* in hexane, 6.2 ml, 5.89 mmol) at -78 ℃. After being stirred at -78 ℃ for 20 min, the reaction mixture was quenched by the addition of 1*M* aqueous $KHSO_4$. The mixture was extracted with $CHCl_3$ (x 3). The organic extracts were washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford the aldehyde.

A solution of $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2CH_3$ (**23**) (2.3 g, 6.92 mmol) and 18-crown-6 (6.6 g, 25.0 mmol) in THF (50 ml) was cooled to -78 ℃ and treated with KHMDS (0.5 *M* in toluene, 13.8 ml, 6.9 mmol). After the mixture was stirred for 15 min, a solution of the aldehyde in THF (10 ml, plus 5 ml of rinse) was added by cannula. The resulting mixture was stirred at -78 ℃ for 2.5 h and then at -10 ℃ for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the bulk of THF was removed. The residue was extracted with ether (x 1), and the organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-200, hexane : ether = 30 : 1) to afford the desired product **24** as a colorless oil (1.13 g, 2.85 mmol, 48 %): $[\alpha]^{25}_D$ -41.9 (c 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1721, 1429, 1225, 1113; ^1H NMR (270 MHz, $CDCl_3$) δ 1.02 (3H, d, J = 5.9 Hz, C_{26}-C**H**$_3$), 1.04 (9H, s, (C**H**$_3$)$_3$C), 1.89 (3H, d, J = 1.3 Hz, C_{27}-C**H**$_3$), 3.33-3.44 (1H, m, C_{22}-C**H**), 3.54 (2H, d, J = 5.9 Hz, C**H**$_2$), 3.68 (3H, s, C**H**$_3$ ester), 5.78 (1H, dd, J = 9.6, 1.3 Hz, C_{21}-C**H**), 7.34-7.44 (6H, m, Ar**H**), 7.62-7.67 (4H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.8, 19.3, 20.8, 26.8, 36.2, 51.2, 68.3, 126.9, 127.5, 129.5, 133.9, 135.6, 145.7, 168.3. HRMS (EI) m/z Calcd for $C_{24}H_{32}O_3Si$: 396.2121. Found: 396.2111.

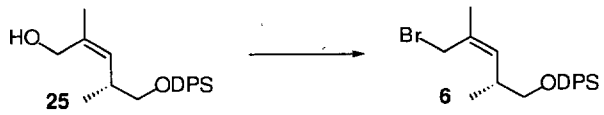
(2*Z*, 4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethyl-2-pentenol(25).



To a stirred solution of **24** (2.15 g, 5.40 mmol) in ether (19 ml) was added DIBAL (0.95 *M* in hexane, 15 ml, 14.3 mmol) at -78 ℃. After being stirred at -78 ℃ for 30 min, the reaction mixture was quenched by the addition of 10 % aqueous potassium sodium tartrate. The mixture was extracted with $CHCl_3$ (x 3). The organic

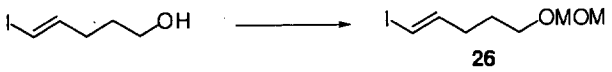
extracts were washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 5 : 1) to afford the desired product **25** as a colorless oil (1.87 g, 5.06 mmol, 94 %): $[\alpha]^{24}_D$ -14.8 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368, 1428, 1113, 1084, 1007; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 6.6 Hz, C_{26}-C**H**$_3$), 1.04 (9H, s, (C**H**$_3$)$_3$C), 1.81 (3H, d, J = 1.3 Hz, C_{27}-C**H**$_3$), 1.92 (1H, br, O**H**), 2.74-2.81 (1H, m, C_{22}-C**H**), 3.30 (1H, dd, J = 9.6, 8.2 Hz, C**H**$_2$), 3.49 (1H, dd, J = 9.6, 5.6 Hz, C**H**$_2$), 3.94 (1H, dd, J = 11.9, 6.9 Hz, C_{19}-C**H**$_2$), 4.16 (1H, dd, J = 11.9, 4.0 Hz, C_{19}-C**H**$_2$), 5.03 (1H, d, J = 9.9 Hz, C_{21}-C**H**), 7.35-7.46 (6H, m, Ar**H**), 7.63-7.68 (4H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.4, 19.1, 21.9, 26.8, 35.0, 62.1, 68.8, 127.6, 129.7, 131.7, 133.4, 135.5, 135.6. HRMS (EI) m/z Calcd for $C_{19}H_{23}O_2Si$: 311.1467 (M^+-*t*-Bu). Found: 311.1461.

(2*Z*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethyl-2-pentenyl bromide (6).



To a stirred solution of **25** (611 mg, 1.66 mmol) and Ph_3P (522 mg, 1.99 mmol) in CH_3CN (5.6 ml) at 0 ℃ was added CBr_4 (660 mg, 1.99 mmol). The reaction mixture was stirred at 0 ℃ for 5 min and then at room temperature for 15 min. The reaction mixture was filtered through silica gel (hexane : ether = 10 : 1 wash) and the combined filtrate was concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 100 : 1 - 50 : 1) to afford the desired product **6** as a colorless oil (706 mg, 1.64 mmol, 99 %): $[\alpha]^{24}_D$ -97.3 (c 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1428, 1206, 1113, 1084; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.6 Hz, C_{26}-C**H**$_3$), 1.04 (9H, s, (C**H**$_3$)$_3$C), 1.81 (3H, d, J = 1.3 Hz, C_{27}-C**H**$_3$), 2.60-2.70 (1H, m, C_{22}-C**H**), 3.45-3.50 (2H, m, C**H**$_2$), 3.79 (1H, A of AB, J = 9.6 Hz, C_{19}-C**H**$_2$), 4.01 (1H, B of AB, J = 9.6 Hz, C_{19}-C**H**$_2$), 5.15 (1H, dd, J = 9.9, 1.3 Hz, C_{21}-C**H**), 7.34-7.45 (6H, m, Ar**H**), 7.63-7.67 (4H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.0, 19.2, 22.0, 26.8, 32.6, 35.7, 68.1, 127.6, 129.6, 131.9, 133.8, 134.4, 135.6. HRMS (EI) m/z Calcd for $C_{19}H_{22}Br^{79}OSi$: 373.0623 (M^+-*t*-Bu). Found: 373.0622.

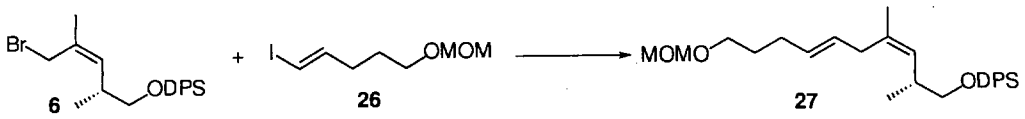
(1*E*)-5-(Methoxymethyloxy)-1-pentenyl iodide (26).



26

To a stirred solution of the alcohol (ref. 21) (844 mg, 3.98 mmol) in CH_2Cl_2 (13 ml) at 0 ℃ was added *i*-Pr_2NEt (1.4 ml, 8.04 mmol) and MOMCl (0.47 ml, 5.86 mmol). The reaction mixture was stirred at 0 ℃ for 30 min and then at room temperature for 15 h. After the bulk of CH_2Cl_2 was removed, the residue was diluted with ether, and washed with 1 *M* aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 20 : 1), followed by reduced distillation (Kugelrohr, b.p. 110 ℃/9 mmHg) to afford the desired product **26** as a colorless oil (819 mg, 3.20 mmol, 80 %): IR ν_{max}^{neat} cm^{-1} 1607, 1441, 1385, 1210, 1146, 1111, 1042; ^1H NMR (270 MHz, $CDCl_3$) δ 1.64-1.74 (2H, m, C_{15}-C**H**$_2$), 2.16 (2H, q, J = 7.3 Hz, C_{16}-C**H**$_2$), 3.35 (3H, d, J = 1.0 Hz, OCH_2OCH_3), 3.52 (2H, t, J = 6.3 Hz, C_{14}-C**H**$_2$), 4.61 (2H, d, J = 0.7 Hz, OCH_2OCH_3), 6.03 (1H, dd, J = 14.2, 1.3 Hz, C_{18}-C**H**), 6.52 (1H, dt, J = 14.2, 7.3 Hz, C_{17}-C**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 32.7, 55.1, 66.6, 75.0, 96.4, 145.7. Anal. Calcd for $C_7H_{13}IO_2$: C, 32.83; H, 5.12. Found: C, 32.56; H, 5.04.

(1*R*, 3*Z*, 6*E*)-1-(*tert*-Butyldiphenylsiloxy)-10-(methoxymethyloxy)-2,4-dimethyl-3,6-decadiene (27).



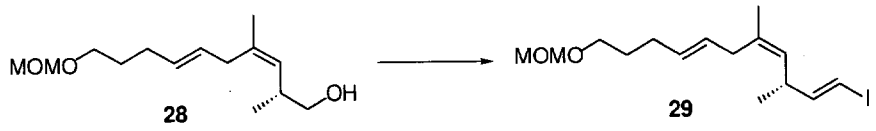
To a stirred solution of **26** (161 mg, 0.63 mmol) in THF (2 ml) was added *t*-BuLi (1.47 *M* in pentane, 0.86 ml, 1.3 mmol) at -78 ℃. After 5 min, HMPA (0.2 ml) was added and then a solution of **6** (163 mg, 0.38 mmol) in THF (0.5 ml, plus 0.5 ml of rinse) was added via cannula. The reaction mixture was stirred at -78 ℃ for 30 min, then quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with ether (x 1), and the organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 50 : 1 - 20 : 1) to afford the desired product **27** as a colorless oil (96 mg, 0.20 mmol, 53 %): $[\alpha]^{25}_D$ -34.7 (c 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1428, 1150, 1113, 1082, 1044; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.6 Hz, C_{26}-

CH3), 1.05 (9H, s, (**CH3**)3C), 1.59-1.67 (2H, m, C15-**CH2**), 1.62 (3H, d, J = 1.7 Hz, C27-**CH3**), 2.00-2.07 (2H, m, C16-**CH2**), 2.53-2.73 (3H, m, C19-**CH2** & C22-**CH**), 3.35 (3H, s, OCH2O**CH3**), 3.40-3.53 (4H, m, **CH2** & C14-**CH2**), 4.61 (2H, s, O**CH2**OCH3), 4.92 (1H, d, J = 8.6 Hz, C21-**CH**), 5.25-5.40 (2H, m, C17 & C18-**CH**), 7.33-7.42 (6H, m, Ar**H**), 7.65-7.68 (4H, m, Ar**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.7, 19.2, 23.3, 26.8, 29.0, 29.5, 35.2, 35.5, 55.0, 67.1, 68.8, 96.3, 127.5, 128.4, 128.5, 129.4, 130.3, 134.0, 134.1, 135.6. HRMS (EI) m/z Calcd for $C_{30}H_{44}O_3Si$: 480.3060. Found: 480.3042.

(2*R*, 3*Z*, 6*E*)-10-(Methoxymethyloxy)-2,4-dimethyl-3,6-decadien-1-ol (28).

To a stirred solution of **27** (86 mg, 0.18 mmol) in THF (1 ml) was added TBAF (140 mg, 0.54 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 30 min and then at room temperature for 1.5 h. After dilution with ether, the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 5 : 1) to afford the desired product **28** as a colorless oil (39 mg, 0.16 mmol, 90 %): $[\alpha]^{26}_D$ 15.3 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432, 1443, 1150, 1113, 1040; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 6.6 Hz, C26-**CH3**), 1.45 (1H, br, O**H**), 1.63-1.69 (2H, m, C15-**CH2**), 1.71 (3H, d, J = 1.0 Hz, C27-**CH3**), 2.05-2.13 (2H, m, C16-**CH2**), 2.55-2.70 (1H, m, C22-**CH**), 2.75 (2H, m, C19-**CH2**), 3.28-3.35 (1H, m, **CH2**), 3.36 (3H, s, OCH2O**CH3**), 3.43-3.45 (1H, m, **CH2**), 3.52 (2H, t, J = 6.6 Hz, C14-**CH2**), 4.61 (2H, s, O**CH2**OCH3), 4.93 (1H, d, J = 9.9 Hz, C21-**CH**), 5.33-5.52 (2H, m, C17 & C18-**CH**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.3, 23.5, 29.0, 29.5, 35.3, 35.5, 55.0, 67.1, 67.8, 96.3, 128.0, 128.1, 130.6, 136.4. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.14; H, 10.83.

(1*E*, 3*R*, 4*Z*, 7*E*)-11-(Methoxymethyloxy)-3,5-dimethyl-1,4,7-undecatrienyl iodide (29).



To a stirred solution of **28** (138 mg, 0.57 mmol) and triethylamine (0.24 ml, 1.73 mmol) in CH_2Cl_2 (1.3 ml)-DMSO (1.3 ml) was added Py·SO_3 (272 mg, 1.71 mmol) at 0 ℃. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether (x 1). The organic extracts were washed with 1*M* aqueous $KHSO_4$, water and brine, dried ($MgSO_4$), filtered, and concentrated to afford the aldehyde.

To a suspension of $CrCl_2$ (420 mg, 3.42 mmol) in THF (3 ml) was added a solution of the aldehyde and iodoform (449 mg, 1.14 mmol) in THF (1 ml, plus 0.5 ml of rinse) via cannula at 0 ℃. The reaction mixture was allowed to warm to room temperature and stirred for 50 min. The mixture was poured into water, and extracted with ether (x 2). The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane only - hexane : ether = 40 : 1 - 30 :1) to afford the desired product **29** as a pale yellow oil (142 mg, 0.39 mmol, 68 %): $[\alpha]^{25}_D$ -118.5 (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1453, 1150, 1113, 1044; ^1H NMR (270 MHz, $CDCl_3$) δ 1.04 (3H, d, J = 6.9 Hz, C_{26}-C**H**$_3$), 1.61-1.71 (2H, m, C_{15}-C**H**$_2$), 1.66 (3H, d, J = 1.3 Hz, C_{27}-C**H**$_3$), 2.05-2.13 (2H, m, C_{16}-C**H**$_2$), 2.68 (2H, d, J = 5.9 Hz, C_{19}-C**H**$_2$), 3.07-3.15 (1H, m, C_{22}-C**H**), 3.36 (3H, s, OCH_2OCH_3), 3.52 (2H, t, J = 6.6 Hz, C_{14}-C**H**$_2$), 4.62 (2H, s, OCH_2OCH_3), 4.96 (1H, d, J = 8.9 Hz, C_{21}-C**H**), 5.28-5.48 (2H, m, C_{17} & C_{18}-C**H**), 5.96 (1H, dd, J = 14.5, 1.7 Hz, C_{24}-C**H**), 6.45 (1H, dd, J = 14.5, 6.6 Hz, C_{23}-C**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 23.4, 29.0, 29.5, 35.4, 39.0, 55.1, 67.1, 73.8, 96.4, 127.4, 127.6, 130.8, 134.5, 150.5. Anal. Calcd for $C_{15}H_{25}IO_2$: C, 49.46; H, 6.92. Found: C, 49.56; H, 6.91.

(4*E*, 7*Z*, 9*R*, 10*E*)-1-(Methoxymethyloxy)-7,9-dimethyl-4,7,10-dodecatriene (30).

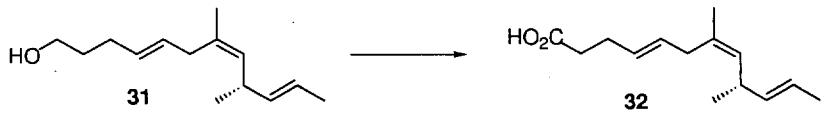
To a solution of **29** (62 mg, 0.17 mmol) in THF (1 ml) was added $Pd(Ph_3P)_4$ (20 mg, 0.017 mmol) and MeMgBr (0.93 *M* in THF, 1.1 ml, 1 mmol). The reaction

mixture was stirred at room temperature for 1.5 h, and then quenched by the addition of saturated aqueous NH_4Cl, and extracted with ether (x 1). The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 100 : 1 - 50 :1) to afford the desired product **30** as a colorless oil (46 mg, 0.17 mmol, 100 %): $[\alpha]^{25}_D$ -60.1 (c 0.9, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1453, 1385, 1377, 1150, 1113, 1044; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 6.6 Hz, C_{26}-**CH$_3$**), 1.61-1.71 (8H, m, C_{25} & C_{27}-**CH$_3$** & C_{15}-**CH$_2$**), 2.05-2.12 (2H, m, C_{16}-**CH$_2$**), 2.68-2.72 (2H, m, C_{19}-**CH$_2$**), 2.99-3.09 (1H, m, C_{22}-**CH**), 3.36 (3H, s, OCH_2OCH_3), 3.52 (2H, t, J = 6.6 Hz, C_{14}-**CH$_2$**), 4.61 (2H, s, OCH_2OCH_3), 5.00 (1H, d, J = 8.9 Hz, C_{21}-**CH**), 5.30-5.49 (4H, m, C_{17} & C_{18} & C_{23} & C_{24}-**CH**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.9, 21.4, 23.3, 29.1, 29.5, 35.2, 35.3, 55.1, 67.1, 96.4, 122.5, 128.2, 130.2, 130.4, 132.4, 136.2. HRMS (EI) m/z Calcd for $C_{16}H_{28}O_2$: 252.2089. Found: 252.2087.

(4*E*, 7*Z*, 9*S*, 10*E*)-7,9-Dimethyl-4,7,10-dodecatrienol (31).

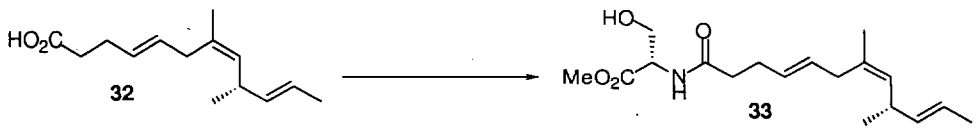
To a stirred solution of **30** (66 mg, 0.26 mmol) in THF (0.8 ml) was added 20 % aqueous HCl (0.8 ml). The reaction mixture was stirred at room temperature for 6 h, and then MeOH (0.1 ml) was added. After 3.5 h, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with ether (x 1). The organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 5 :1) to afford the desired product **31** as a colorless oil (45 mg, 0.22 mmol, 83 %): $[\alpha]^{25}_D$ -57.2 (c 0.8, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3346, 1449, 1375, 1057; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.9 Hz, C_{26}-**CH$_3$**), 1.43 (1H, br, **OH**), 1.61-1.69 (8H, m, C_{25} & C_{27}-**CH$_3$** & C_{15}-**CH$_2$**), 2.05-2.13 (2H, m, C_{16}-**CH$_2$**), 2.69-2.75 (2H, m, C_{19}-**CH$_2$**), 3.01 (1H, m, C_{22}-**CH**), 3.65 (2H, t, J = 6.6 Hz, C_{14}-**CH$_2$**), 5.00 (1H, d, J = 9.2 Hz, C_{21}-**CH**), 5.36-5.48 (4H, m, C_{17} & C_{18} & C_{23} & C_{24}-**CH**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.9, 21.4, 23.3, 28.8, 32.4, 35.2, 35.3, 62.4, 122.5, 128.3, 130.2, 130.4, 132.3, 136.2. HRMS (EI) m/z Calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1827.

(4*E*, 7*Z*, 9*S*, 10*E*)-7,9-Dimethyl-4,7,10-dodecatrienoic acid (32).



To a stirred solution of **31** (62 mg, 0.30 mmol) in DMF (2.7 ml) was added PDC (784 mg, 2.08 mmol). The reaction mixture was stirred at room temperature for 3.5 h, and then poured into water. The mixture was extracted with ether (x 2), and the organic extracts were washed with 1*M* aqueous $KHSO_4$ and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 4 :1) to afford the desired product **32** as a colorless oil (48 mg, 0.22 mmol, 72 %): $[\alpha]^{25}_D$ -78.1 (c 0.6, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3500-2500, 1713, 1441, 1412, 1283; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.9 Hz, C_{26}-C**H**$_3$), 1.63 (6H, m, C_{25} & C_{27}-C**H**$_3$), 2.29-2.45 (4H, m, C_{16} & C_{19}-C**H**$_2$), 2.69-2.71 (2H, m, C_{15}-C**H**$_2$), 2.99 (1H, m, C_{22}-C**H**), 5.00 (1H, d, J = 9.6 Hz, C_{21}-C**H**), 5.35-5.45 (4H, m, C_{17} & C_{18} & C_{23} & C_{24}-C**H**), 11.22 (1H, br, O**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.9, 21.4, 23.3, 27.5, 34.1, 35.3, 35.4, 122.5, 128.6, 129.3, 130.4, 132.1, 136.2, 179.7. HRMS (EI) m/z Calcd for $C_{14}H_{22}O_2$: 222.1620. Found: 222.1618.

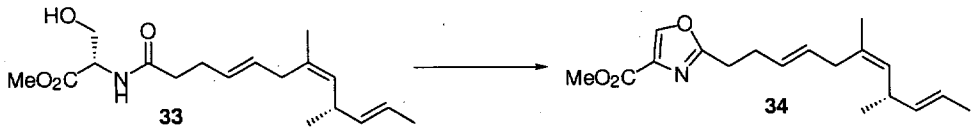
Methyl [2S,2(4*E*,7*Z*,9*S*,10*E*)]-2-[7,9-dimethyl-4,7,10-dodecatrienyl-1-carbonyl(amino)]-3-hydroxypropanoate (33).



To a stirred solution of the carboxylic acid **32** (44 mg, 0.198 mmol) and (*S*)-serine methyl ester hydrochloride (34 mg, 0.219 mmol) in DMF (0.8 ml) at 0 ℃ was successively added dropwise DEPC (0.036 ml, 0.221 mmol) and triethylamine (0.060 ml, 0.432 mmol). After being stirred at 0 ℃ for 1 h and then at room temperature for 2.5 h, the reaction mixture was diluted with ether and washed with 1 *M* aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 1 : 1-1 : 2) to afford the desired product **33** as a colorless oil (58 mg, 0.179 mmol, 91 %): $[\alpha]^{26}_D$ -27.3 (c 0.8, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368,

1748, 1651, 1538, 1439, 1211; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.8 Hz, C_{26}-C**H$_3$**), 1.64 (6H, m, C_{25} & C_{27}-C**H$_3$**), 2.04 (1H, br, O**H**), 2.34 (4H, m, C_{16} & C_{19}-C**H$_2$**), 2.64-2.70 (2H, m, C_{15}-C**H$_2$**), 3.01 (1H, br, C_{22}-C**H**), 3.78 (3H, s, OC**H$_3$**), 3.92 (2H, qd, J = 11.0, 3.1 Hz, C_{13}-C**H$_2$**), 4.65-4.67 (1H, m, C_{12}-C**H**), 4.99 (1H, d, J = 9.4 Hz, C_{21}-C**H**), 5.35-5.43 (4H, m, C_{17} & C_{18} & C_{23} & C_{24}-C**H**), 6.55 (1H, d, J = 6.8 Hz, N**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.4, 28.4, 35.27, 35.32, 36.3, 52.7, 54.7, 63.4, 122.4, 128.9, 129.2, 130.3, 131.9, 136.0, 170.8, 172.9. HRMS (EI) m/z Calcd for $C_{18}H_{29}NO_4$: 323.2097. Found: 323.2086.

Methyl (3*E*,6*Z*,8*S*,9*E*)-2-(6,8-dimethyl-3,6,9-undecatrienyl)-oxazole-4-carboxylate (34).



To a stirred solution of the amido alcohol **33** (28 mg, 0.087 mmol) in CH_2Cl_2 (0.9 ml) at -20 ℃ was added dropwise Deoxo-fluor (0.032 ml, 0.174 mmol). The reaction mixture was stirred at -20 ℃ for 25 min, and then quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ (x 3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford the oxazoline (48 mg), which was used for the next step without further purification.

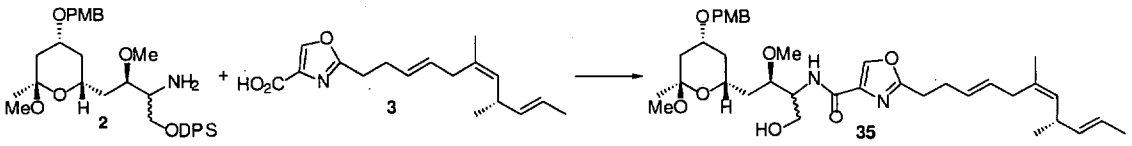
To a solution of the oxazoline (48 mg) in CH_2Cl_2 (0.9 ml) at 0 ℃ was successively added $BrCCl_3$ (0.026 ml, 0.256 mmol) and DBU (0.040 ml, 0.268 mmol). The reaction mixture was stirred at 0 ℃ for 2 h, and then allowed to warm to room temperature over 12 h. The mixture was diluted with ether, washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : ether = 5 : 1) to afford the desired product **34** as a colorless oil (21 mg, 0.069 mmol, 80 %): $[\alpha]^{26}_D$ -47.2 (c 0.9, $CHCl_3$) (ref. 28 $[\alpha]_D$ +42.3 (c 0.8, $CHCl_3$)); IR ν_{max}^{neat} cm^{-1} 1752, 1588, 1439, 1377, 1323; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.8 Hz, C_{26}-C**H$_3$**), 1.61 (3H, s, C_{27}-C**H$_3$**), 1.62 (3H, d, J = 4.0 Hz, C_{25}-C**H$_3$**), 2.48 (2H, m, C_{16}-C**H$_2$**), 2.68 (2H, m, C_{19}-C**H$_2$**), 2.87 (2H, t, J = 7.3 Hz, C_{15}-C**H$_2$**), 3.00 (1H, m, C_{22}-C**H**), 3.90 (3H, s, OC**H$_3$**), 4.98 (1H, d, J = 9.4 Hz, C_{21}-C**H**), 5.34-5.36 (2H, m, C_{23} & C_{24}-C**H**), 5.41-5.42 (2H, m, C_{17} & C_{18}-C**H**), 8.13 (1H, s, C_{13}-C**H**); ^{13}C NMR

(67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.3, 28.3, 29.9, 35.3, 52.1, 122.4, 128.2, 129.6, 130.3, 131.8, 133.0, 136.0, 143.5, 161.6, 165.2. HRMS (EI) m/z Calcd for $C_{18}H_{25}NO_3$: 303.1834. Found: 303.1827.

(3*E*, 6*Z*, 8*S*, 9*E*)-2-(6,8-dimethyl-3,6,9-undecatrienyl)-oxazole-4-carboxylic acid (3).

To a solution of the ester **34** (45 mg, 0.148 mmol) in THF (0.6 ml) at 0 ℃ was added 0.5 *N* aqueous LiOH (0.5 ml, 0.25 mmol). After 10 min, the reaction mixture was stirred at room temperature for 70 min. After the reaction mixture was acidified by the addition of 1*M* aqueous $KHSO_4$, the mixture was extracted with ether (x 3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford the desired product **3** as a white wax (42 mg, 100 %): $[\alpha]^{27}_D$ -42.8 (c 0.5, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3500-2500, 1682, 1592, 1439, 1113; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.8 Hz, C_{26}-C**H**$_3$), 1.61 (3H, s, C_{27}-C**H**$_3$), 1.63 (3H, d, J = 4.0 Hz, C_{25}-C**H**$_3$), 2.49-2.54 (2H, m, C_{16}-C**H**$_2$), 2.67 (2H, m, C_{19}-C**H**$_2$), 2.92 (2H, t, J = 7.4 Hz, C_{15}-C**H**$_2$), 2.95 (1H, m, C_{22}-C**H**), 4.99 (1H, d, J = 9.2 Hz, C_{21}-C**H**), 5.35-5.40 (2H, m, C_{23} & C_{24}-C**H**), 5.41-5.51 (2H, m, C_{17} & C_{18}-C**H**), 8.23 (1H, s, C_{13}-C**H**), 8.62 (1H, br, O**H**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.3, 28.2, 29.8, 35.3, 122.4, 128.1, 129.8, 130.3, 131.8, 132.5, 136.0, 144.6, 165.0, 165.7. HRMS (EI) m/z Calcd for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1700.

Amido alcohol (35).

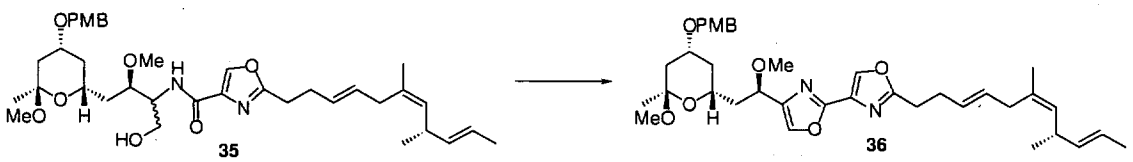


To a stirred solution of the carboxylic acid **3**(14 mg, 0.048 mmol) and the amine **2** (32 mg, 0.052 mmol) in DMF (0.3 ml) at 0 ℃ was successively added dropwise DEPC (0.010 ml, 0.061 mmol) and triethylamine (0.014 ml, 0.101 mmol). After being stirred at 0 ℃ for 2 h and then at room temperature for 7.5 h, the reaction mixture was diluted

with ether and washed with 1 *M* aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 5 : 1- 4 : 1 - 2 : 1) to afford the coupling product as a colorless oil (39 mg), which was directly used for the next step.

To a stirred solution of the coupling product (39 mg) in THF (0.4 ml) was added TBAF (29 mg, 0.111 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 30 min and then at room temperature for 40 min. After dilution with EtOAc, the organic layer was washed with water (x 2) and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 1 : 1 - 1 : 2 - 1 : 5) to afford the desired product **35** as a colorless oil (27 mg, 0.041 mmol, 86 %): $[\alpha]^{26}_{D}$ -79.8 (c 0.7, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3407, 1661, 1599, 1514, 1451, 1375, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.8 Hz, C_{26}-C**H**$_3$), 1.11-1.43 (2H, m, C_3 & C_5-C**H**$_2$), 1.34 (3H, s, C_1-C**H**$_3$) (1.26, s), 1.62 (3H, s, C_{27}-C**H**$_3$), 1.65 (4H, m, C_5-C**H**$_2$ & C_{25}-C**H**$_3$), 1.71 (1H, br, O**H**), 1.81-1.90 (1H, m, C_3-C**H**$_2$), 1.95-2.05 (1H, m, C_7-C**H**$_2$), 2.20-2.25 (1H, m, C_7-C**H**$_2$), 2.49 (2H, m, C_{19}-C**H**$_2$), 2.69 (2H, m, C_{16}-C**H**$_2$), 2.83 (2H, t, J = 7.7 Hz, C_{15}-C**H**$_2$), 3.00 (1H, m, C_{22}-C**H**), 3.19 (3H, s, C_{29}-OC**H**$_3$), 3.43 (3H, s, C_{28}-OC**H**$_3$), 3.64-3.91 (5H, m, C_4, C_6, C_8-C**H** & C_{10}-C**H**$_2$), 3.79 (3H, s, OC**H**$_3$), 4.28 (1H, m, C_9-C**H**), 4.45 (2H, s, C**H**$_2$Ar) (4.47, s), 4.99 (1H, d, J = 9.2 Hz, C_{21}-C**H**), 5.36 (2H, m, C_{23} & C_{24}-C**H**), 5.44 (2H, m, C_{17} & C_{18}-C**H**), 6.86 (2H, d, J = 8.6 Hz, Ar**H**), 7.23 (2H, d, J = 8.4 Hz, Ar**H**), 7.32 (1H, d, J = 8.9 Hz, N**H**) (7.61, d, J = 7.9 Hz), 8.08 (1H, s, C_{13}-C**H**) (The peaks of *n*-hexane were observed.); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.4, 23.8, 28.3, 29.8 (30.4), 35.3 (35.3), 36.3 (36.7), 38.0 (37.7), 42.1, 47.9 (48.2), 52.3 (52.6), 55.3, 57.4 (58.0), 64.3, 65.5 (65.8), 69.7, 71.4 (71.3), 77.2, 77.6, 99.6 (99.7), 113.7, 122.4, 128.3, 129.0, 129.6, 130.4, 130.7, 131.8, 135.6, 136.0, 140.7, 158.9, 161.5, 164.2. Anal. Calcd for $C_{37}H_{54}N_2O_8 \cdot 1/2n$-hexane: C, 68.84; H, 8.81; N, 4.01. Found: C, 68.84; H, 8.49; N, 4.01.

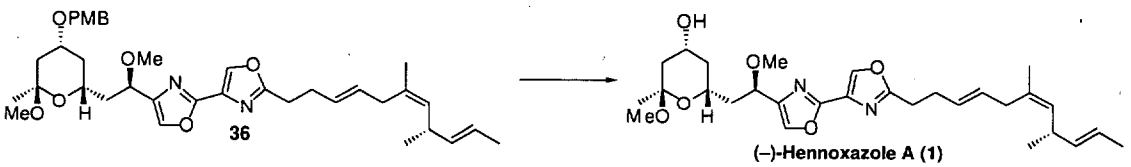
Protected Hennoxazole A (36).



To a stirred solution of the alcohol **35** (27 mg, 0.041 mmol) in CH_2Cl_2 (0.3 ml)

at 0 ℃ was added Dess-Martin periodinane (52 mg, 0.123 mmol). The reaction mixture was stirred at room temperature for 15 min, and then diluted with ether. The mixture was washed with aqueous $NaHCO_3/Na_2S_2O_3$ (1 : 1), and brine, dried ($MgSO_4$), filtered, and concentrated to afford the aldehyde. The aldehyde was then immediately dissolved in CH_2Cl_2 (1.9 ml) cooled to 0℃, and treated with Ph_3P (53 mg, 0.202 mmol) and 2,6-di-*tert*-butyl pyridine (0.23 ml, 1.02 mmol). Then, $BrCCl_2CCl_2Br$ (66 mg, 0.203 mmol) was added. After 30 min, DBU (0.16 ml, 1.07 mmol) in CH_3CN (1.9 ml) was added by cannula. The reaction mixture was then warmed to room temperature for 1 h and concentrated. The residue was purified by flash chromatography (BW-820MH, hexane : EtOAc = 3 : 1 - 2 : 1) to afford the desired product **36** as a colorless oil (16 mg, 0.024 mmol, 60 %): $[\alpha]^{26}_D$ -31.5 (c 0.7, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1615, 1584, 1514, 1449, 1375, 1248; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.8 Hz, C_{26}-**CH3**), 1.22-1.43 (3H, m, C_3 & C_5-**CH2**), 1.32 (3H, s, C_1-**CH3**), 1.62 (3H, s, C_{27}-**CH3**), 1.64 (3H, m, C_{25}-**CH3**), 2.05-2.21 (4H, m, C_5 & C_7-**CH2**), 2.50-2.55 (2H, m, C_{16}-**CH2**), 2.68 (2H, m, C_{19}-**CH2**), 2.90 (2H, t, J = 7.4 Hz, C_{15}-**CH2**), 2.98 (1H, m, C_{22}-**CH**), 3.07 (3H, s, C_{29}-O**CH3**), 3.31 (3H, s, C_{28}-O**CH3**), 3.54 (1H, m, C_6-**CH**), 3.79 (3H, s, O**CH3**), 3.79 (1H, m, C_4-**CH**), 4.42 (1H, m, C_8-**CH**), 4.45 (2H, s, **CH2**Ar), 4.99 (1H, d, J = 9.2 Hz, C_{21}-**CH**), 5.35 (2H, m, C_{23} & C_{24}-**CH**), 5.41-5.45 (2H, m, C_{17} & C_{18}-**CH**), 6.86 (2H, d, J = 8.6 Hz, Ar**H**), 7.23 (2H, d, J = 8.6 Hz, Ar**H**), 7.62 (1H, s, C_{10}-**CH**), 8.13 (1H, s, C_{13}-**CH**) (The peaks of *n*-hexane were observed.); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.3, 23.8, 28.3, 29.9, 35.3, 37.5, 40.7, 42.1, 47.7, 55.3, 56.5, 65.8, 69.5, 71.4, 72.8, 99.6, 113.7, 122.4, 128.3, 129.0, 129.6, 130.2, 130.3, 130.8, 131.9, 135.7, 136.0, 138.0, 141.6, 155.4, 158.9, 165.4. Anal. Calcd for $C_{37}H_{50}N_2O_7 \cdot 1/2$*n*-hexane: C, 70.87; H, 8.47; N, 4.13. Found: C, 71.09; H, 8.19; N, 4.19.

(–)-Hennoxazole A (1).



To a solution of **36** (10 mg, 0.016 mmol) in CH_2Cl_2 (0.2 ml) was added pH 7 phosphate buffer (0.011 ml). DDQ (4 mg, 0.018 mmol) was added to the mixture at 0 ℃. After 5 min, the mixture was allowed to warm to room temperature for 15 min. An additional DDQ (1 mg, 0.004 mmol) was added at 0 ℃, and then the mixture was

stirred at room temperature for 10 min. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ (x 3). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative thin layer chromatography plate (10 cm x 20 cm, 0.5 mm, hexane : EtOAc = 1 : 4) to afford the synthetic (–)-hennoxazole A (**1**) as a colorless oil (3.0 mg, 0.006 mmol, 36 %): $[\alpha]^{26}_{D}$ -42.7 (c 0.12, $CHCl_3$) (ref. 1 $[\alpha]_D$ -47 (c 3.1, $CHCl_3$)); IR ν_{max}^{neat} cm^{-1} 3432, 1634, 1580, 1451, 1375, 1231; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, d, J = 7.0 Hz, C_{26}-**CH3**), 1.10 (1H, q, J = 11.6 Hz, C_5-**CH2**), 1.21 (1H, dd, J = 12.2, 11.0 Hz, C_3-**CH2**), 1.24 (3H, s, C_1-**CH3**), 1.58 (3H, dd, J = 3.7, 1.2 Hz, C_{25}-**CH3**), 1.59 (3H, d, J = 1.5 Hz, C_{27}-**CH3**), 1.88 (1H, ddt, J = 12.2, 4.6, 2.4 Hz, C_5-**CH2**), 1.97 (1H, ddd, J = 12.5, 4.6, 1.8 Hz, C_7-**CH2**), 2.05 (2H, m, C_3 & C_7-**CH2**), 2.50 (2H, q, J = 6.7 Hz, C_{16}-**CH2**), 2.69 (2H, m, C_{19}-**CH2**), 2.89 (2H, t, J = 7.3 Hz, C_{15}-**CH2**), 3.01 (1H, m, C_{22}-**CH**), 3.03 (3H, s, C_{29}-O**CH3**), 3.22 (3H, s, C_{28}-O**CH3**), 3.52 (1H, m, C_6-**CH**), 3.61 (1H, d, J = 5.2 Hz, **OH**), 3.89 (1H, m, C_4-**CH**), 4.46 (1H, dd, J = 7.9, 6.1 Hz, C_8-**CH**), 4.95 (1H, dd, J = 9.8, 0.9 Hz, C_{21}-**CH**), 5.34 (2H, m, C_{23} & C_{24}-**CH**), 5.41-5.56 (2H, m, C_{17} & C_{18}-**CH**), 7.98 (1H, s, C_{10}-**CH**), 8.40 (1H, s, C_{13}-**CH**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.8, 23.5, 24.0, 28.6, 30.4, 35.8, 35.9, 41.5, 41.7, 46.0, 47.8, 56.1, 64.2, 66.5, 73.2, 100.0, 122.8, 129.5, 130.0, 130.9, 131.3, 132.5, 136.8, 137.5, 139.4, 142.1, 156.2, 165.9. HRMS (EI) m/z Calcd for $C_{29}H_{42}N_2O_6$: 514.3043. Found: 514.3053.