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Total synthesis of (−)-hennoxazole A

Fumiaki Yokokawa,* Toshinobu Asano and Takayuki Shioiri

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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Abstract—The antiviral marine natural product (−)-hennoxazole A was efficiently synthesized by a convergent approach. The stereoselective synthesis of the functionalized tetrahydropyran fragment was accomplished by the Mukaiyama aldol reaction, chelation-controlled 1,3-*syn* reduction, Wacker oxidation, and acid catalyzed intramolecular ketalization. The nonconjugated triene fragment was synthesized by S_N2 displacement of an allylic bromide with vinyllithium and the $CrCl_2$-mediated iodoolefination followed by palladium-catalyzed cross coupling with MeMgBr. The final steps include the fragment coupling using DEPC and oxazole synthesis via an oxidation/cyclodehydration process.

1. Introduction

Hennoxazoles A–D (**1**–**4**) are marine natural products, isolated by Scheuer, Higa, and co-workers from the marine sponge *Polyfibrospongia* sp. near Miyako island, Okinawa, Japan.[1] Hennoxazole A (**1**) is active against herpes simplex virus type 1 (IC_{50}=0.6 μg mL^{-1}) and displays peripheral analgesic activity comparable with that of indomethacin. The most unique feature of its structure is a directly linked bisoxazole core, (Fig. 1) which is only found in the complex polycyclic marine alkaloid diazonamide A–B (**5**–**6**),[2] cyanobacterium-derived muscoride A (**7**),[3] and the hennoxazole family.[4] Other unique structural features of hennoxazole A are a highly functionalized tetrahydropyranyl ring moiety, and a nonconjugated triene unit. The unique structural features and interesting biological activity of hennoxazole A have attracted the attention of several synthetic research groups. Wipf and Lim have accomplished the total synthesis of the antipode of **1**, and their synthesis has elucidated the absolute configuration of **1** and relative

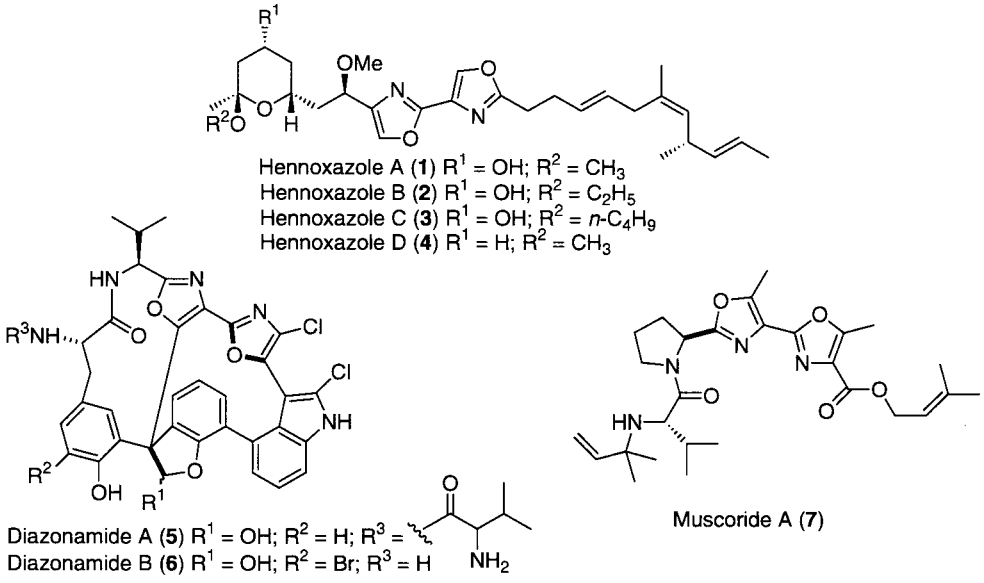

Figure 1. Bisoxazole based natural products.

Keywords: hennoxazole A; total synthesis; aldol reaction; Wacker oxidation.
* Corresponding author. Tel.: +81-52-836-3440; fax: +81-52-834-9309; e-mail: yokokawa@phar.nagoya-cu.ac.jp

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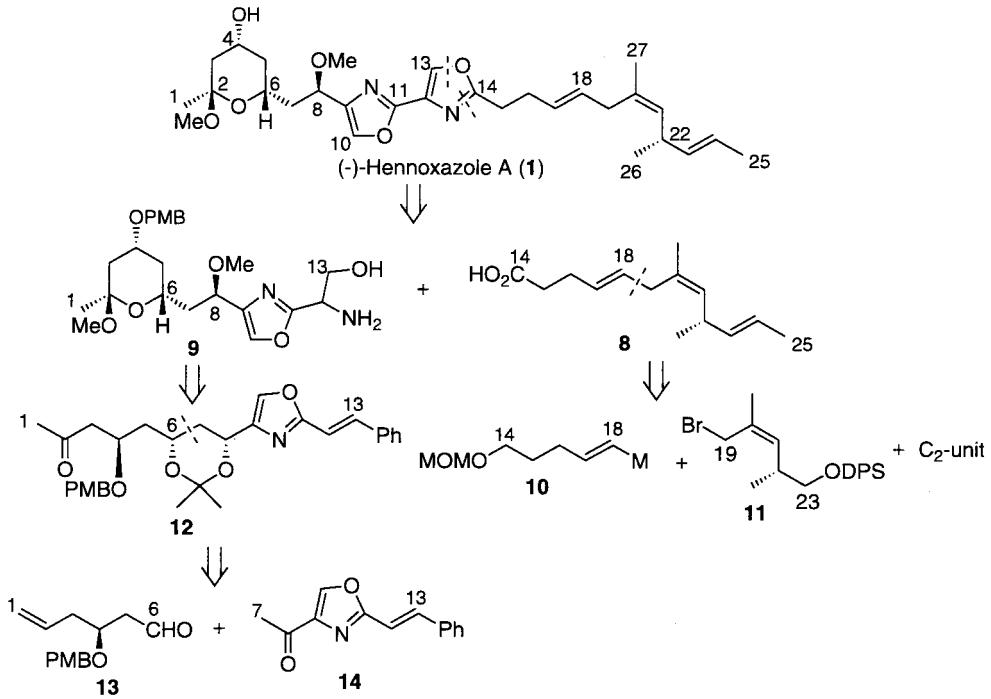


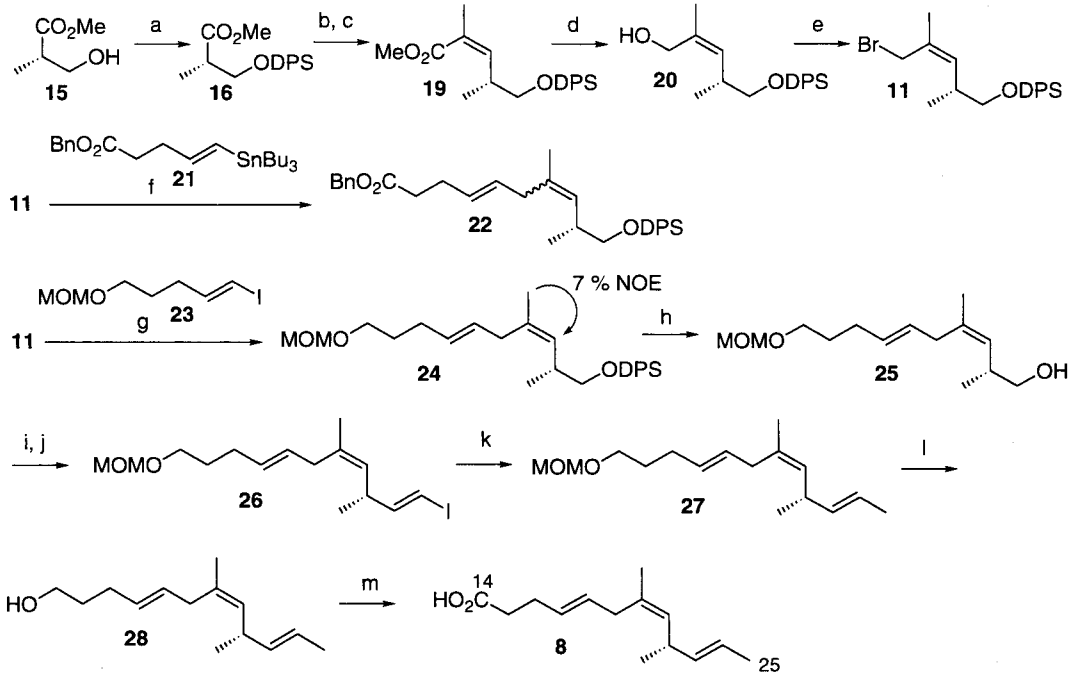
Scheme 1. Retrosynthetic analysis of (−)-hennoxazole A.

stereochemistries at C_8 and C_{22}.[5] Recently, the total synthesis of hennoxazole A (**1**) having the natural configuration has been reported by Williams and co-workers.[6] Our interest in the total synthesis of oxazole/oxazoline/thiazole/thiazoline based marine natural products[7] led us to hennoxazole A (**1**) as a challenging synthetic target.[8,9] Here, we report the details of our synthetic work on (−)-hennoxazole A (**1**).[10]

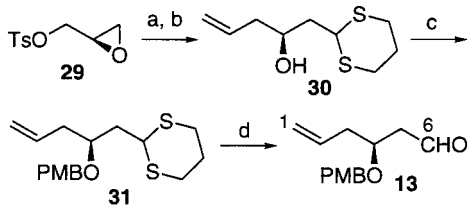
2. Results and discussions

2.1. Synthetic plan

Our initial synthetic plan called for disconnection at C_{14} to provide the C_{14}–C_{25} triene fragment **8** and the C_1–C_{13} tetrahydropyran fragment **9**. The triene fragment **8** was further divided into the C_{19}–C_{23} allylic bromide **11**, the C_2 unit, and



Scheme 2. Synthesis of C_{14}–C_{25} fragment (a) DPSCl, imidazole, DMF, 95%; (b) DIBAL, Et_2O, −78°C; (c) (method A) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2CH_3$ (**17**), KHMDS, 18-crown-6, THF, −78°C, 48%; (method B) $(PhO)_2P(O)CH(CH_3)CO_2CH_3$ (**18**), NaI, DBU, THF, −78°C–0°C, 82%; (d) DIBAL, Et_2O, −78°C, 94%; (e) CBr_4, Ph_3P, CH_3CN, 99%; (f) **21**, $Pd(CH_3CN)_2Cl_2$, NMP, 76% (*E*/*Z*=1:1); (g) **23**, *t*-BuLi, HMPA, THF, −78°C, 53%; (h) TBAF, THF, 90%; (i) Py·SO_3, DMSO, Et_3N, CH_2Cl_2; (j) $CrCl_2$, CHI_3, THF, 68%; (k) MeMgBr, $Pd(Ph_3P)_4$, THF, quant., (l) aq. HCl, MeOH, THF, 83%; (m) PDC, DMF, 72%.



Scheme 3. Synthesis of C_1–C_6 fragment (a) *n*-BuLi, 1,3-dithiane, THF; (b) vinylmagnesium bromide, CuI, THF, 63%; (c) KH, PMBCl, *n*-Bu_4NI, THF, 86%; (d) MeI, $CaCO_3$, aq. CH_3CN, 74%.

the C_{14}–C_{18} vinyl metal **10**. The linear precursor **12** of the tetrahydropyran fragment was disconnected at the C_6–C_7 bond to lead to the C_1–C_6 aldehyde **13** and the C_7–C_{13} oxazole methyl ketone **14** (Scheme 1).

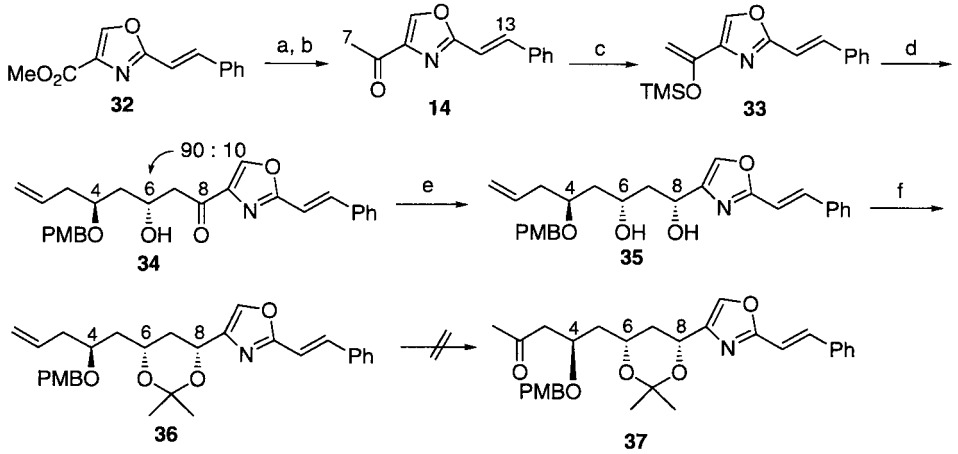
2.2. Synthesis of the C_{14}–C_{25} triene fragment

The synthesis of the C_{14}–C_{25} triene unit was initiated by protection of methyl (*S*)-3-hydroxy-2-methylpropionate (**15**) as its DPS (*tert*-butyldiphenylsilyl)ether to give **16** in 95% yield. Diisobutylaluminum hydride (DIBAL) reduction of **16** afforded the corresponding aldehyde, which was directly treated with the phosphonate **17** under (*Z*)-selective Still–Horner olefination conditions[11] to provide the (*Z*)-ester **19** in 48% yield as a single isomer. We also found that (*Z*)-selective olefination using the Ando's phosphonate **18**[12] in the presence of NaI-1,8-diazabicyclo[5.4.0]-7-undecene (DBU) gave the (*Z*)-ester **19** in much better yield (82%) as a single isomer. Reduction of the methyl ester **19** with DIBAL followed by bromination of the resulting allylic alcohol **20** using CBr_4 and Ph_3P gave the allylic bromide **11** in 93% yield.[13] Although we initially attempted the Stille coupling[14] of the allylic bromide **11** with the vinyl stannane **21**,[15] this coupling reaction caused the loss of the C_{20}–C_{21} double bond stereochemistry to give the inseparable *E*/*Z* mixture **22** in 76% yield due to the π–σ–π isomerization of the π-allyl intermediate derived from **11**. In spite of an extensive variation of reaction parameters, we were unable to suppress the isomerization of the C_{20}–C_{21} double bond. However, we were able to solve this problem by S_N2 displacement of the allylic bromide **11** with the vinyl lithium derived from the vinyl iodide **23**[16] to afford the skipped diene **24** in 53% yield. The (*Z*)-configuration of the C_{20}–C_{21} double bond in **24** was confirmed by the existence of 7% NOE enhancement between the olefinic proton and the olefinic methyl protons. After deprotection of the DPS group, the resulting primary alcohol **25** was oxidized by the Parikh–Doering oxidation[17] to furnish the corresponding aldehyde, which was immediately subjected to the Takai's $CrCl_2$-mediated iodoolefination process[18] to give the (*E*)-vinyl iodide **26** in 61% yield. Cross coupling of the vinyl iodide **26** with MeMgBr in the presence of palladium catalyst[19] constructed the nonconjugated triene unit **27** in quantitative yield. Finally, deprotection of the methoxymethyl group (MOM) followed by oxidation using pyridinium dichromate (PDC) gave the C_{14}–C_{25} triene fragment **8** in 60% yield (Scheme 2).

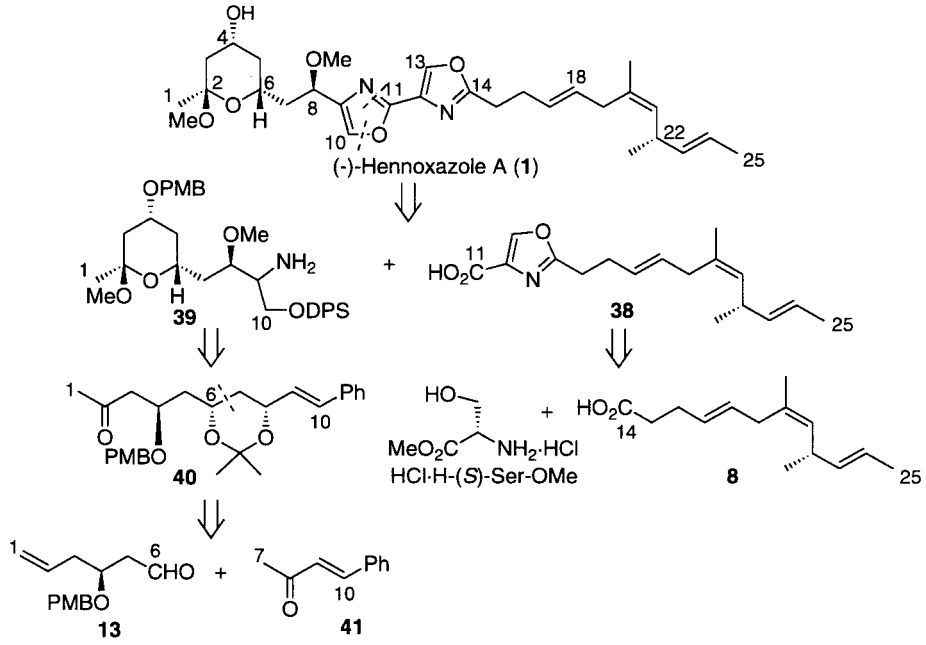
2.3. Synthesis of the C_1–C_{14} tetrahydropyran fragment

The synthesis of the C_1–C_6 aldehyde **13** was started by treatment of commercially available (*R*)-glycidyl tosylate (**29**) with lithiated 1,3-dithiane followed by copper-catalyzed Grignard addition to afford the alcohol **30** in 63% yield. Protection of the alcohol **30** as its *p*-methoxybenzyl (PMB) ether **31** and removal of the 1,3-dithiane provided the aldehyde **13** in 64% yield (Scheme 3).

The C_7–C_{14} oxazole methyl ketone **14** was synthesized from the ester **32**[20] via the Weinreb amide formation[21] followed by the Grignard addition. The $BF_3{\cdot}OEt_2$ mediated Mukaiyama aldol reaction between the trimethylsilyl enol ether **33** derived from the oxazole methyl ketone **14** and the aldehyde **13** to provide the aldol adduct **34** in 75% yield with good diastereoselectivity (90:10 *anti*/*syn*).[22] This transformation established the C_6 stereocenter with a good level of 1,3-*anti* induction.[24] Subsequent chelation-controlled reduction[25] of the C_8 ketone from the aldol adduct **34** afforded the *syn* diol **35** in 91% yield, which was protected as an acetonide to give **36** in 90% yield.[26] In spite of the stereoselective formation of the linear precursor of the tetrahydropyran unit, we were unable to convert the terminal olefin of **36** to the methyl ketone **37** using Wacker oxidation[27] or oxymercuration protocols.[28] We speculated that the chelation of two valent metal between the oxazole nitrogen and C_8 oxygen would prevent the oxidation of the



Scheme 4. Synthesis of C_1–C_{13} fragment (a) HCl·HNMe(OMe), Me_3Al, CH_2Cl_2; (b) MeMgBr, THF, 59%; (c) TMSOTf, Et_3N, CH_2Cl_2; (d) **13**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C, 75% (90:10); (e) Et_2BOMe, $NaBH_4$, THF, 91%; (f) 2,2-dimethoxy propane, *p*-TsOH, 90%.

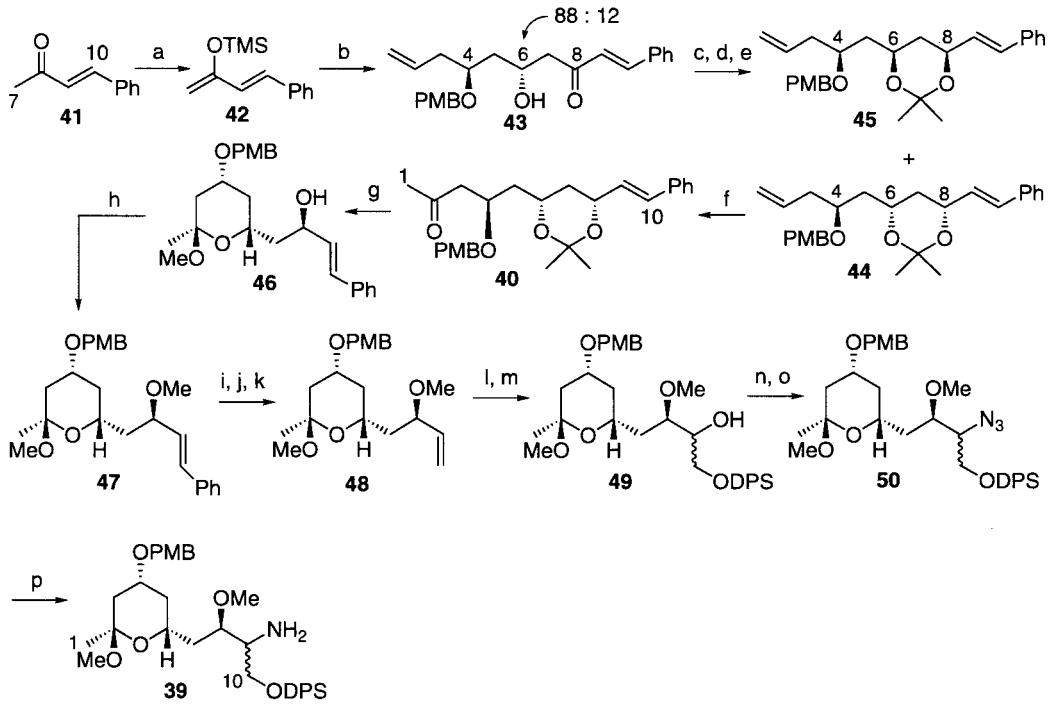


Scheme 5. Revised retrosynthetic analysis of (−)-hennoxazole A.

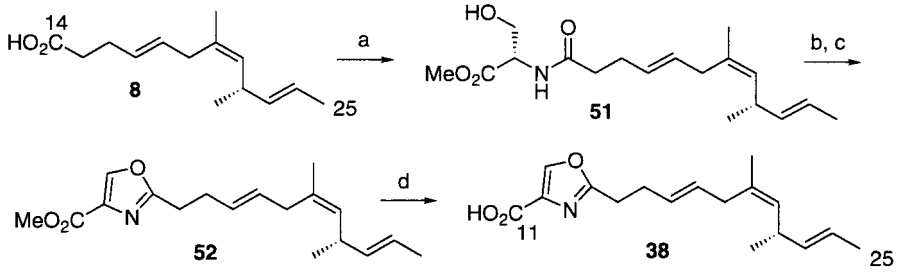
terminal olefin.[29] Therefore, we had to revise the initial synthetic plan for the tetrahydropyran fragment (Scheme 4).

2.4. Revised synthetic plan

The sluggish oxidation of the terminal olefin of the C_1–C_{14} segment **36** led us to shift the position of disconnection from C_{14} to C_{11}. Accordingly, hennoxazole A (**1**) was divided into the C_1–C_{10} tetrahydropyran fragment **39** and the C_{11}–C_{25} triene–oxazole fragment **38** in our revised synthetic strategy. The linear precursor **40** of the C_1–C_{10} tetrahydropyran fragment **39** would be obtained by aldol reaction of the C_1–C_6 aldehyde **13** with benzalacetone (**41**). The C_{11}–C_{25} triene–oxazole fragment **38** would be synthesized from the C_{14}–C_{25} triene unit **8** and serine methyl ester (Scheme 5).



Scheme 6. Synthesis of C_1–C_{10} fragment (a) TMSOTf, Et_3N, CH_2Cl_2, 96%; (b) **13**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C, 89% (88:12); (c) Et_2BOMe, $NaBH_4$, THF; (d) 2,2-dimethoxy propane, PPTs; (e) silica gel column chromatography, **44**; 59%, **45**; 9%; (f) $PdCl_2$, $Cu(OAc)_2{\cdot}H_2O$, $AcNMe_2/H_2O$ (7:1), 77%; (g) PPTs, MeOH, 85%; (h) NaH, MeI, THF, 98%; (i) OsO_4, NMO, aq. acetone; (j) $NaIO_4$, pH 7 phosphate buffer, THF; (k) $Cp_2TiCH_2AlClMe_2$, THF, 72%; (l) OsO_4, NMO, aq. acetone; (m) DPSCl, Et_3N, DMAP, CH_2Cl_2, 94%; (n) MsCl, Et_3N, DMAP, CH_2Cl_2; (o) *n*-Bu_4NN_3, DMF, 100°C, 68%; (p) Ph_3P, aq. THF, 55°C, 68%.



Scheme 7. Synthesis of C_{11}–C_{25} fragment (a) DEPC, HCl·H-(*S*)-Ser-OMe, Et_3N, DMF, 91%; (b) Deoxo-fluor, CH_2Cl_2, −20 to −30°C; (c) $BrCCl_3$, DBU, CH_2Cl_2, 80%: (d) aq. LiOH, THF, quant.

2.5. Synthesis of the C_1–C_{10} tetrahydropyran fragment and C_{11}–C_{25} triene–oxazole fragment

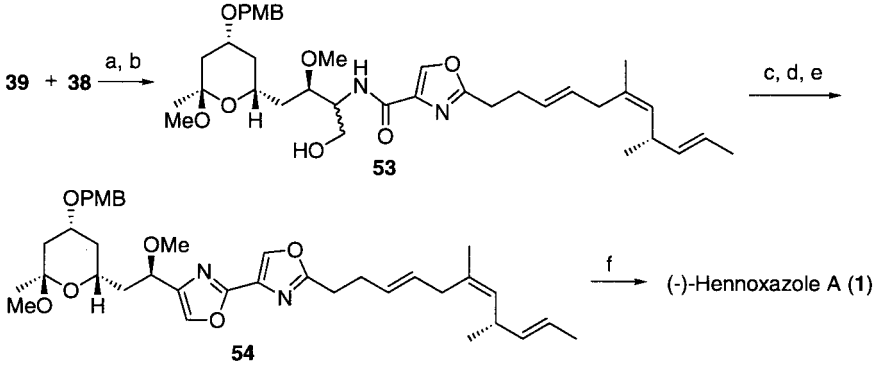
The synthesis of the C_1–C_{10} tetrahydropyran fragment **39** was started by the $BF_3{\cdot}OEt_2$ mediated aldol reaction between the trimethylsilyl enol ether **42** derived from benzalacetone (**41**) and the C_1–C_6 aldehyde **13** afforded the aldol adduct **43** in 89% yield with similar diastereoselectivity (88:12 *anti*/*syn*).[22] Subsequent chelation-controlled reduction of the C_8 ketone, protection of the corresponding *syn*-diols as acetonides followed by separation on silica gel gave the desired isomer **44** (59%),[26] the minor isomer **45** (9%),[26] and recovered starting diol (31%). In contrast to the failure of the Wacker oxidation of **36**, the modified Wacker oxidation[30] of the terminal olefin of **44** proceeded smoothly to give the methyl ketone **40** in 77% yield. Mild acidic treatment of **40** simultaneously caused the cleavage of the acetonide and the intramolecular ketalization to produce the tetrahydropyran **46** in 85% yield. *O*-Methylation of **46**, oxidative cleavage of the styryl group in **47** and Tebbe olefination[31] afforded **48** in 72% yield. Dihydroxylation of the terminal olefin **48** with osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO), and selective protection of the primary alcohol led to the mono-*tert*-butyldiphenylsilyl (DPS) ether **49** in 94% yield as mixture of diastereoisomers (3.2:1). Treatment of the resulting alcohol with methanesulfonyl chloride (MsCl) and then displacement with *n*-Bu_4NN_3 provided the azide **50** in 68% yield. Mild reduction of the azide **50** with Ph_3P/H_2O completed the formation of the C_1–C_{10} tetrahydropyran segment **39** in 68% yield (Scheme 6).

For the preparation of the C_{11}–C_{25} triene–oxazole fragment **38**, coupling of the C_{14}–C_{25} triene unit **8** with (*S*)-serine methyl ester hydrochloride using diethyl phosphorocyanidate (DEPC)[32] afforded the amide **51** in 91% yield. According to the Wipf and Williams' methodology,[33] dehydrative cyclization of the β-hydroxy amide **51** with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) to the oxazoline followed by oxidation with $BrCCl_3$ and DBU provided the oxazole **52** in 80% yield. Saponification of the methyl ester **52** in quantitative yield completed the construction of the C_{11}–C_{25} triene–oxazole fragment **38** (Scheme 7).

2.6. Synthesis of hennoxazole A

The final steps of the synthesis began with the condensation of **39** and **38** using DEPC[32] and removal of the DPS group provided the amido alcohol **53** in 86% yield. Oxazole synthesis via an oxidation/cyclodehydration process[5,34] was performed through intermediary bromo-oxazoline under Wipf's conditions to afford the bisoxazole **54** in 60% yield. The final oxidative removal of the C_4-PMB group with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[35] provided (−)-hennoxazole A (**1**) in 36% yield. The spectral data recorded on synthetic hennoxazole A were identical in all respects with spectra provided for the natural product (Scheme 8).

In summary, we have developed an efficient, convergent strategy for the preparation of the structurally and biologically attractive marine natural product hennoxazole A.



Scheme 8. Synthesis of (−)-hennoxazole A (a) DEPC, Et_3N, DMF; (b) TBAF, THF, 86%; (c) Dess–Martin periodinane, CH_2Cl_2; (d) $BrCCl_2CCl_2Br$, Ph_3P, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0°C; (e) DBU, CH_3CN, 60%; (f) DDQ, pH 7 phosphate buffer, CH_2Cl_2, 36%.

3. Experimental

3.1. General information

Melting points were measured on a 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 lamp (λ=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 (270 MHz) 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 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (chloroform: δ 77.0 ppm).

Analytical thin layer chromatography were performed on Merck Art. 5715, Kieselgel 60F_{254}/0.25 mm 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}/0.5 mm thickness plates. Elementary analysis (Anal) and high resolution mass spectra (HRMS) were performed 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-820 MH or BW-200 (Fuji Silysia 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 available reagents were used as received.

3.1.1. (*S*)-Methyl 3-*tert*-butyldiphenylsiloxy-2-methylpropionate (16). To a stirred solution of **15** (3 g, 25.4 mmol) in DMF (50 mL) at 0°C was added imidazole (3.63 g, 53.3 mmol) and DPSCl (7 mL, 26.9 mmol). The reaction mixture was stirred at 0°C 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-820 MH, hexane/ether=10:1) to afford the desired product **16** 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; ^{1}H 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}–C*H*), 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, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{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.

3.1.2. Methyl (2*Z*,4*R*)-5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-2-pentenoate (19). *(Method A)*: To a stirred solution of **16** (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°C. After being stirred at −78°C for 20 min, the reaction mixture was quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with $CHCl_3$ (×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 $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2CH_3$ (**17**) (2.3 g, 6.92 mmol) and 18-crown-6 (6.6 g, 25.0 mmol) in THF (50 mL) was cooled to −78°C 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°C for 2.5 h and then at −10°C 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 (×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 **19** as a colorless oil (1.13 g, 2.85 mmol, 48%).

(Method B): To a stirred solution of **16** (271 mg, 0.76 mmol) in ether (3 mL) was added DIBAL (1.5 M in toluene, 0.54 mL, 0.81 mmol) at −78°C. After being stirred at −78°C for 20 min, the reaction mixture was quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with $CHCl_3$ (×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 $(PhO)_2P(O)CH(CH_3)CO_2CH_3$ (**18**) (305 mg, 0.952 mmol) in THF (2.4 mL) was treated with NaI (171 mg, 1.14 mmol) and DBU (0.14 mL, 0.94 mmol) at 0°C for 10 min. After the mixture was cooled to −78°C, a solution of the aldehyde in THF (1 mL, plus 0.7 mL of rinse) was added by cannula. The resulting mixture was stirred at −78°C for 30 min and then at 0°C for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with ether (×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 **19** as a colorless oil (247 mg, 0.62 mmol, 82%): $[\alpha]^{25}_{D}$=−41.9 (*c* 1.2, $CHCl_3$); IR ν_{max}-(neat) cm^{-1} 1721, 1429, 1225, 1113; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (3H, d, *J*=5.9 Hz, C_{26}–CH_3), 1.04 (9H, s,

(CH_3)$_3$C), 1.89 (3H, d, J=1.3 Hz, C_{27}–CH_3), 3.33–3.44 (1H, m, C_{22}–C*H*), 3.54 (2H, d, J=5.9 Hz, CH_2), 3.68 (3H, s, CH_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.

3.1.3. (2*Z*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethyl-2-pentenol (20). To a stirred solution of **19** (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°C. After being stirred at −78°C for 30 min, the reaction mixture was quenched by the addition of 10% aqueous potassium sodium tartrate. The mixture was extracted with $CHCl_3$ (×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-820 MH, hexane/EtOAc=5:1) to afford the desired product **20** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, d, J=6.6 Hz, C_{26}–CH_3), 1.04 (9H, s, (CH_3)$_3$C), 1.81 (3H, d, J=1.3 Hz, C_{27}–CH_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, CH_2), 3.49 (1H, dd, J=9.6, 5.6 Hz, CH_2), 3.94 (1H, dd, J=11.9, 6.9 Hz, C_{19}–CH_2), 4.16 (1H, dd, J=11.9, 4.0 Hz, C_{19}–CH_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.

3.1.4. (2*Z*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethyl-2-pentenyl bromide (11). To a stirred solution of **20** (611 mg, 1.66 mmol) and Ph_3P (522 mg, 1.99 mmol) in CH_3CN (5.6 mL) at 0°C was added CBr_4 (660 mg, 1.99 mmol). The reaction mixture was stirred at 0°C 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-820 MH, hexane/ether=100:1–50:1) to afford the desired product **11** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J=6.6 Hz, C_{26}–CH_3), 1.04 (9H, s, (CH_3)$_3$C), 1.81 (3H, d, J=1.3 Hz, C_{27}–CH_3), 2.60–2.70 (1H, m, C_{22}–C*H*), 3.45–3.50 (2H, m, CH_2), 3.79 (1H, A of AB, J=9.6 Hz, C_{19}–CH_2), 4.01 (1H, B of AB, J=9.6 Hz, C_{19}–CH_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 $C_{19}H_{22}{}^{79}BrOSi$: 373.0623 (M^+−*t*-Bu). Found: 373.0622.

3.1.5. (1*E*)-5-(Methoxymethyloxy)-1-pentenyl iodide (23). To a stirred solution of (4*E*)-5-iodo-4-penten-1-ol[16] (844 mg, 3.98 mmol) in CH_2Cl_2 (13 mL) at 0°C 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°C 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-820 MH, hexane/EtOAc=20:1), followed by vacuum distillation (Kugelrohr, bp 110°C/9 mmHg) to afford the desired product **23** as a colorless oil (819 mg, 3.20 mmol, 80%): IR ν_{max}(neat) cm^{-1} 1607, 1441, 1385, 1210, 1146, 1111, 1042; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.64–1.74 (2H, m, C_{15}–CH_2), 2.16 (2H, apparent q, J=7.3 Hz, C_{16}–CH_2), 3.35 (3H, d, J=1.0 Hz, OCH_2OCH_3), 3.52 (2H, t, J=6.3 Hz, C_{14}–CH_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.

3.1.6. (2*R*,3*Z*,6*E*)-1-(*tert*-Butyldiphenylsiloxy)-10-(methoxymethyloxy)-2,4-dimethyl-3,6-decadiene (24). To a stirred solution of **23** (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°C. After 5 min, HMPA (0.2 mL) was added and then a solution of **11** (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°C for 30 min, then quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with ether (×1), and the organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/ether=50:1–20:1) to afford the desired product **24** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, J=6.6 Hz, C_{26}–CH_3), 1.05 (9H, s, (CH_3)$_3$C), 1.59–1.67 (2H, m, C_{15}–CH_2), 1.62 (3H, d, J=1.7 Hz, C_{27}–CH_3), 2.00–2.07 (2H, m, C_{16}–CH_2), 2.53–2.73 (3H, m, C_{19}–CH_2 and C_{22}–C*H*), 3.35 (3H, s, OCH_2OCH_3), 3.40–3.53 (4H, m, C_{23}–CH_2 and C_{14}–CH_2), 4.61 (2H, s, OCH_2OCH_3), 4.92 (1H, d, J=8.6 Hz, C_{21}–C*H*), 5.25–5.40 (2H, m, C_{17} and C_{18}–C*H*), 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.

3.1.7. (2*R*,3*Z*,6*E*)-10-(Methoxymethyloxy)-2,4-dimethyl-3,6-decadien-1-ol (25). To a stirred solution of **24** (86 mg, 0.18 mmol) in THF (1 mL) was added TBAF (140 mg, 0.54 mmol) at 0°C. The reaction mixture was stirred at 0°C 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-820 MH, hexane/EtOAc=5:1) to afford the desired product **25** 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, C_{26}–CH_3), 1.45 (1H, br, O*H*), 1.63–1.69 (2H, m, C_{15}–CH_2), 1.71 (3H, d, J=1.0 Hz,

C_{27}–CH_3), 2.05–2.13 (2H, m, C_{16}–CH_2), 2.55–2.70 (1H, m, C_{22}–CH), 2.75 (2H, m, C_{19}–CH_2), 3.28–3.35 (1H, m, C_{23}–CH_2), 3.36 (3H, s, OCH_2OCH_3), 3.43–3.45 (1H, m, C_{23}–CH_2), 3.52 (2H, t, J=6.6 Hz, C_{14}–CH_2), 4.61 (2H, s, OCH_2OCH_3), 4.93 (1H, d, J=9.9 Hz, C_{21}–CH), 5.33–5.52 (2H, m, C_{17} and C_{18}–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.

3.1.8. (1*E*,3*R*,4*Z*,7*E*)-11-(Methoxymethyloxy)-3,5-dimethyl-1,4,7-undecatrienyl iodide (26). To a stirred solution of **25** (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°C. 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 (×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°C. 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 (×2). The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane only, hexane/ether=40:1–30:1) to afford the desired product **26** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.04 (3H, d, J=6.9 Hz, C_{26}–CH_3), 1.61–1.71 (2H, m, C_{15}–CH_2), 1.66 (3H, d, J=1.3 Hz, C_{27}–CH_3), 2.05–2.13 (2H, m, C_{16}–CH_2), 2.68 (2H, d, J=5.9 Hz, C_{19}–CH_2), 3.07–3.15 (1H, m, C_{22}–CH), 3.36 (3H, s, OCH_2OCH_3), 3.52 (2H, t, J=6.6 Hz, C_{14}–CH_2), 4.62 (2H, s, OCH_2OCH_3), 4.96 (1H, d, J=8.9 Hz, C_{21}–CH), 5.28–5.48 (2H, m, C_{17} and C_{18}–CH), 5.96 (1H, dd, J=14.5, 1.7 Hz, C_{24}–CH), 6.45 (1H, dd, J=14.5, 6.6 Hz, C_{23}–CH); ^{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.

3.1.9. (4*E*,7*Z*,9*R*,10*E*)-1-(Methoxymethyloxy)-7,9-dimethyl-4,7,10-dodecatriene (27). To a solution of **26** (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 (×1). The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/ether=100:1–50:1) to afford the desired product **27** 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; ^{1}H 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} and C_{27}–CH_3 and 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} and C_{18} and C_{23} and 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.

3.1.10. (4*E*,7*Z*,9*S*,10*E*)-7,9-Dimethyl-4,7,10-dodecatrienol (28). To a stirred solution of **27** (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 (×1). The organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/ether=5:1) to afford the desired product **28** 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; ^{1}H 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} and C_{27}–CH_3 and 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} and C_{18} and C_{23} and 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.

3.1.11. (4*E*,7*Z*,9*S*,10*E*)-7,9-Dimethyl-4,7,10-dodecatrienoic acid (8). To a stirred solution of **28** (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 (×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-820 MH, hexane/EtOAc=4:1) to afford the desired product **8** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J=6.9 Hz, C_{26}–CH_3), 1.63 (6H, m, C_{25} and C_{27}–CH_3), 2.29–2.45 (4H, m, C_{16} and C_{19}–CH_2), 2.69–2.71 (2H, m, C_{15}–CH_2), 2.99 (1H, m, C_{22}–CH), 5.00 (1H, d, J=9.6 Hz, C_{21}–CH), 5.35–5.45 (4H, m, C_{17} and C_{18} and C_{23} and C_{24}–CH), 11.22 (1H, br, OH); ^{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.

3.1.12. 2-[(2*S*)-2-Hydroxy-4-pentenyl]-1,3-dithiane (30). 1,3-Dithiane (2.765 g, 23.0 mmol) was dissolved in THF (31 mL) and cooled to −10°C. *n*-Butyllithium (1.5 M in hexane, 16 mL, 24.0 mmol) was added and the solution was stirred at −10°C for 2 h, and then cooled to −78°C. A solution of (*R*)-glycidyl tosylate (**29**) (5 g, 21.9 mmol) in THF (8 mL, plus 3 mL ×2 of rinse) was added by cannula, and the solution was maintained at −78°C for 3.5 h and

allowed to warm to room temperature over 2 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with ether (×1). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, 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°C. 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°C for 40 min, and then allowed to warm to −10°C 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 (×1), and the organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=6:1–4:1) to afford the desired product **30** 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, $-SCH_2CH_2CH_2S-$), 2.03 (1H, br, O*H*), 2.10–2.18 (2H, m, C_5-CH_2), 2.20–2.33 (2H, m, $CH_2CH=CH_2$), 2.81–2.97 (4H, m, $-SCH_2CH_2CH_2S-$), 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, $CH_2CH=CH_2$), 5.74–5.89 (1H, m, $CH_2CH=CH_2$); ^{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.

3.1.13. 2-[(2*S*)-2-*p*-Methoxybenzyloxy-4-pentenyl]-1,3-dithiane (31). KH (35% oil dispersion, 1.2 g, 10.5 mmol) was suspended in THF (15 mL) and cooled to −15°C. A solution of the alcohol **30** (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°C 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 (×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-820 MH, hexane/ether=10:1) to afford the desired product **31** 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, $-SCH_2CH_2CH_2S-$, C_5-CH_2), 2.08–2.13 (1H, m, C_5-CH_2), 2.31–2.34 (2H, m, $CH_2CH=CH_2$), 2.74–2.92 (4H, m, $-SCH_2CH_2CH_2S-$), 3.74 (1H, m, C_4-CH), 3.81 (3H, s, OCH_3), 4.16 (1H, dd, *J*=9.4, 5.1 Hz, C_6-CH), 4.44 (1H, d, *J*=11.0 Hz, CH_2Ar), 4.57 (1H, d, *J*=11.0 Hz, CH_2Ar), 5.07–5.14 (2H, m, $CH_2CH=CH_2$), 5.74–5.90 (1H, m, $CH_2CH=CH_2$), 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.

3.1.14. (3*S*)-3-*p*-Methoxybenzyloxy-5-hexenal (13). To a stirred solution of **31** 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°C for 11 h, then filtered through a pad of celite, and the filtrate was concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=8:1) to afford the desired product **13** 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, $CH_2CH=CH_2$), 2.57–2.72 (2H, m, C_5-CH_2), 3.80 (3H, s, OCH_3), 3.97–4.06 (1H, m, C_4-CH), 4.45 (1H, d, *J*=11.0 Hz, CH_2Ar), 4.56 (1H, d, *J*=11.0 Hz, CH_2Ar), 5.10–5.15 (2H, m, $CH_2CH=CH_2$), 5.73–5.88 (1H, m, $CH_2CH=CH_2$), 6.87 (2H, d, *J*=8.6 Hz, Ar*H*), 7.24 (2H, *J*=8.9 Hz, Ar*H*), 9.76 (1H, s, C*H*O); ^{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.

3.1.15. 4-Acetyl-2-((*E*)-2-phenylethenyl)oxazole (14). To a slurry of the *N*,*O*-dimethyl hydroxylamine hydrochloride (130 mg, 1.33 mmol) in CH_2Cl_2 (3 mL) was added dropwise trimethylaluminum (1.02 M in hexane, 1.3 mL, 1.33 mmol) at 0°C. After 30 min, a solution of the ester **32**[20] in CH_2Cl_2 (2 mL plus 1 mL ×2 of rinse) was added by cannula. The reaction mixture was stirred at 0°C for 1 h, then warmed to room temperature, and stirred for 40 h. Aqueous $KHSO_4$ (1 M) was added and then the mixture was diluted with water. The aqueous layer was extracted with $CHCl_3$ (×3) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude Weinreb amide. This intermediate was used in the next reaction without further purification.

To a solution of the above amide in THF (5 mL) was added MeMgBr (0.93 M in THF, 1.3 mL, 1.15 mmol) at −78°C. After 15 min, the mixture was warmed to −20°C and stirred at this temperature for 30 min. After addition of 1 M aqueous $KHSO_4$, the mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=4:1–2:1) to afford the desired product **14** as a pale yellow solid (111 mg, 0.520 mmol, 59%): mp 153–154°C (hexane/EtOAc); IR ν_{max}($CHCl_3$) cm^{-1} 3021, 1690, 1559, 1474, 1217, 1113; ^1H NMR (270 MHz, $CDCl_3$) δ 2.57 (3H, s, CH_3CO), 6.95 (1H, d, *J*=16.4 Hz, Ph–C*H*=), 7.34–7.44 (3H, m, Ar*H*), 7.53–7.57 (2H, m, Ar*H*), 7.61 (1H, d, *J*=16.4 Hz, Ph–CH=C*H*), 8.18 (1H, s, oxazole-5-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.5, 112.8, 127.3, 128.9, 129.6, 134.8, 138.2, 141.6, 141.8, 161.6, 192.5. HRMS (EI) *m/z* Calcd for $C_{13}H_{11}NO_2$: 213.0790. Found: 213.0780.

3.1.16. 4-[(3*R*,5*R*)-3-Hydroxy-5-(*p*-methoxybenzyloxy)-7-octenoyl]-2-((*E*)-2-phenylethenyl)oxazole (34). To a solution of the methyl ketone **14** (32.2 mg, 0.151 mmol) in CH_2Cl_2 (1 mL) was added triethylamine (52 μL,

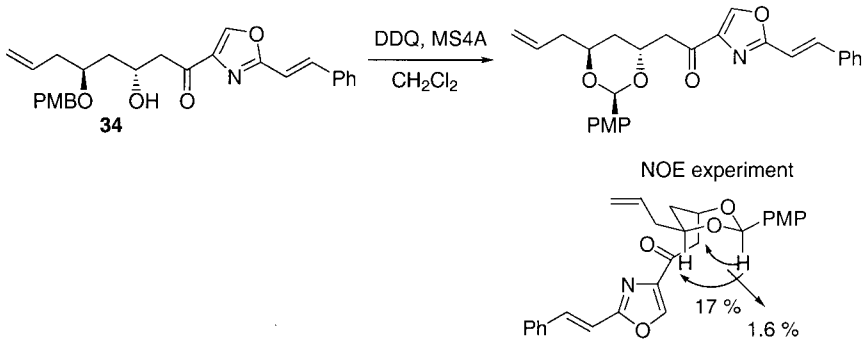


Figure 2.

0.378 mmol) and trimethylsilyl triflate (41 μL, 0.227 mmol) at 0°C. After 30 min, saturated aqueous $NaHCO_3$ was added to the mixture, which was diluted with water. The aqueous layer was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. This intermediate was used in the next reaction without further purification.

To a solution of the above silyl ether **33** in CH_2Cl_2 (0.3 mL) was added a solution of the aldehyde **13** (37.1 mg, 0.158 mmol) in CH_2Cl_2 (0.3 mL plus 0.2 mL ×2 of rinse) via cannula at −78°C. Successively $BF_3{\cdot}Et_2O$ (21 μL, 0.166 mmol) was added dropwise. After 30 min, pH 7 phosphate buffer was added and the mixture was warmed to room temperature. The mixture was diluted with EtOAc, and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=2:1) to afford the desired product **34** as a white powder (50.6 mg, 0.113 mmol, 75%): mp 104–106°C (hexane/EtOAc); $[\alpha]_D^{25}=+10.7$ (*c* 0.70, $CHCl_3$); IR $\nu_{max}(CHCl_3)$ cm^{-1} 3544 (br), 3013, 1684, 1646, 1612, 1559, 1514, 1302, 1248, 1217, 1075; ^1H NMR (270 MHz, $CDCl_3$) δ 1.68–1.79 (2H, m, C_5–C*H*$_2$), 2.33–2.43 (2H, m, C_3–C*H*$_2$), 3.05–3.08 (2H, m, C_7–C*H*$_2$), 3.39 (1H, d, *J*=3.3 Hz, C_6–O*H*), 3.78 (3H, s, Ar–OC*H*$_3$), 3.76–3.82 (1H, m, C_4–C*H*), 4.38–4.54 (1H, m, C_6–C*H*), 4.45 (1H, d, *J*=11.0 Hz, Ar–C*H*$_2$), 4.60 (1H, d, *J*=11.0 Hz, Ar–C*H*$_2$), 5.07–5.14 (2H, m, CH=C*H*$_2$), 5.76–5.91 (1H, m, C*H*=CH$_2$), 6.83–6.96 (3H, m, Ar*H*, Ph–CH=C*H*), 7.24–7.33 (2H, m, Ar*H*), 7.34–7.43 (3H, m, Ar*H*), 7.45–7.62 (3H, m, Ar*H*, Ph–C*H*=CH), 8.15 (1H, s, C_{10}–*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 38.5 (38.0), 40.7 (40.5), 47.2, 55.3, 64.8 (67.0), 71.2 (70.4), 75.2, 112.7, 113.8, 117.4, 127.3, 128.9, 129.4, 129.6, 130.4, 134.3, 134.8, 138.3, 141.5, 141.8, 159.1, 161.6, 194.7. Figures in parentheses show signals of the minor diastereomer. Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.59; H, 6.52; N, 3.10.

3.1.17. 2-((*E*)-2-Phenylethenyl)-4-{[(2*S*,4*R*,6*R*)-2-(*p*-methoxyphenyl)-6-(2-methyl-1,3-dioxolan-2-yl)methyl]-1,3-dioxan-4-yl}acetyloxazole. To a solution of the aldol adduct **34** (28.4 mg, 63.4 μmol) in CH_2Cl_2 (1 mL) was added molecular sieves 4 Å powder (60 mg) and DDQ (16 mg, 69.8 μmol). After 30 min, the reaction mixture was diluted with Et_2O, and then washed with saturated aqueous $NaHCO_3$ (×3) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=4:1) to afford the desired cyclic *p*-methoxybenzylidene acetal (Fig. 2) as a pale yellow solid (21.7 mg, 48.7 μmol, 77%): mp 108–110°C (hexane/EtOAc); $[\alpha]_D^{21}=-16.5$ (*c* 0.49, $CHCl_3$); IR $\nu_{max}(CHCl_3)$ cm^{-1} 2942, 1688, 1646, 1617, 1559, 1516, 1248, 1171, 1117, 1038; ^1H NMR (270 MHz, $CDCl_3$) δ 1.63 (1H, br–s, C_5–C*H*$_2$), 2.02–2.14 (1H, m, C_5–C*H*$_2$), 2.23–2.34 (1H, m, C_3–C*H*$_2$), 2.37–2.52 (1H, m, C_3–C*H*$_2$), 3.35 (1H, dd, *J*=7.1, 15.0 Hz, C_7–C*H*$_2$), 3.68–3.76 (1H, m, C_7–C*H*$_2$), 3.76 (3H, s, Ar–OC*H*$_3$), 4.08–4.19 (1H, m, C_4–C*H*), 4.92–5.01 (1H, m, C_6–C*H*), 5.07–5.16 (2H, m, CH=C*H*$_2$), 5.80–5.95 (1H, m, C*H*=CH$_2$), 5.92 (1H, s, PMP–C*H*), 6.82–6.96 (3H, m, Ar*H*, Ph–CH=C*H*), 7.35–7.43 (5H, m, Ar*H*), 7.51–7.63 (3H, m, Ar**H,** Ph–C*H*=CH), 8.19 (1H, s, C_{10}–*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 33.3, 40.5, 41.5, 55.3, 69.3, 71.8, 94.7, 112.7, 113.5, 117.4, 127.3 (CH ×2), 128.9 (CH ×2), 129.6, 131.1, 133.6, 134.8, 138.2, 141.5, 159.6, 161.5, 192.8. Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.46; H, 6.18; N, 3.26.

3.2. Stereochemical proof of 34

The NOE analysis of the above cyclic *p*-methoxybenzylidene acetal established the 1,3-*anti* dioxygen relationship of the acetal, thereby securing the stereochemical assignment of the aldol adduct **34**.

3.2.1. 2-((*E*)-Phenylethenyl)-4-{(4*R*,6*R*)-2,2-dimethyl-4-[(2*S*)-2-(*p*-methoxybenzoloxy)-4-pentenyl]-1,3-dioxan-6-yl}oxazole (36). To a solution of the aldol adduct **34** (21.8 mg, 48.7 μmol) in THF (0.5 mL) was added diethylmethoxyborane (1.0 M in THF, 97 μL, 97.4 μmol) at −78°C. After 40 min, $NaBH_4$ (5 mg, 0.122 mmol) was added and the reaction mixture was stirred at this temperature for 4 h. After addition of pH 7 phosphate buffer (0.5 mL), MeOH (0.3 mL) and 30% aqueous H_2O_2 (0.4 mL) were added at 0°C. The mixture was stirred at 0°C for 15 min and then warmed to room temperature over 30 min. After dilution with water, the aqueous layer was extracted with EtOAc (×3) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=2:1–1:1) to afford the desired *syn*-diol **35** as a white powder (19.9 mg, 44.3 μmol, 91%), which was directly used for the next step.

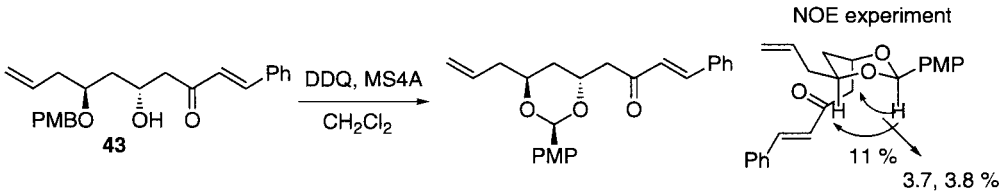


Figure 3.

The above *syn*-diol (13.7 mg, 30.5 μmol) was dissolved in 2,2-dimethoxypropane (0.8 mL), and then *p*-toluenesulfonic acid (1 mg) was added. After 1 h, saturated aqueous $NaHCO_3$ was added and then the mixture was diluted with water. The aqueous layer was extracted with EtOAc and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=4:1) to afford the desired product as a colorless oil (13.4 mg, 27.4 μmol, 90%): $[\alpha]_D^{25}$=+22.8 (*c* 0.79, $CHCl_3$); IR ν_{max}($CHCl_3$) cm^{-1} 2914, 1644, 1613, 1514, 1381, 1250, 1165, 1094; ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.58–1.70 (3H, m, C_5–CH_2, C_7–CH_2), 1.79–1.85 (1H, m, C_7–CH_2), 2.32–2.40 (2H, m, C_3–CH_2), 3.72–3.79 (1H, m, C_4–C*H*), 3.80 (3H, s, Ar–OCH_3), 4.18–4.29 (1H, m, C_6–C*H*), 4.40 (1H, d, *J*=10.9 Hz, Ar–CH_2), 4.57 (1H, d, *J*=10.9 Hz, Ar–CH_2), 4.93–4.99 (1H, m, C_8–C*H*), 5.06–5.13 (2H, m, CH=CH_2), 5.78–5.93 (1H, m, C*H*=CH_2), 6.86–6.95 (3H, m, Ar*H*, Ph–CH=C*H*), 7.29–7.53 (9H, m, Ar**H,** Ph–C*H*=CH, C_{10}–*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.9 (19.8), 30.3, 36.6, 38.9 (38.3), 41.8, 55.3, 65.3 (65.4), 65.5 (66.0), 71.3 (70.3), 73.9, 99.1, 113.7, 113.8, 117.2, 127.0, 128.7, 129.1, 129.3, 129.5, 134.39, 134.42, 135.3, 136.1, 143.2, 159.0, 161.4. Figures in parentheses show signals of the minor diastereomer. HRMS (EI) *m/z* Calcd for $C_{30}H_{35}NO_5$: 489.2515. Found: 489.2503.

3.2.2. 2-Trimethylsiloxy-4-phenyl-1,3-butadiene (42). To a solution of benzalacetone (**41**) (1.08 g, 7.39 mmol) and triethylamine (1.54 mL, 11.1 mmol) in CH_2Cl_2 (25 mL) at −10°C 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 $CHCl_3$ (×3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=5:1) to afford the labile silyl enol ether **42** 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(CH_3)$_3$), 4.43 (1H, s, C_7–CH_2), 4.47 (1H, s, C_7–CH_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.

3.2.3. (1*E*,5*R*,7*S*)-1-Phenyl-5-hydroxy-7-*p*-methoxybenzyloxy-1,9-decadiene-3-one (43). To a solution of the aldehyde **13** (818 mg, 3.49 mmol) and the silyl enol ether **42** (948 mg, 4.34 mmol) in CH_2Cl_2 (20 mL) at −78°C was added dropwise $BF_3{\cdot}OEt_2$ (0.55 mL, 4.34 mmol). The resulting solution was stirred at −78°C for 2 h and then quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ (×3), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=6:1–4:1–3:1) to afford the desired product **43** 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, C_5–CH_2), 1.70–1.75 (1H, m, C_5–CH_2), 2.33–2.45 (2H, m, CH_2CH=CH_2), 2.78 (1H, dd, *J*=17.1, 8.2 Hz, C_7–CH_2) (2.69, dd, *J*=16.4, 4.6 Hz), 2.86 (1H, dd, *J*=17.1, 3.7 Hz, C_7–CH_2), 3.43 (1H, d, *J*=3.0 Hz, O*H*), 3.77 (3H, s, OCH_3) (3.75, s), 3.79–3.85 (1H, m, C_4–C*H*), 4.32–4.43 (1H, m, C_6–C*H*), 4.45 (1H, d, *J*=11.0 Hz, CH_2Ar), 4.60 (1H, d, *J*=11.0 Hz, CH_2Ar) (4.61, d, *J*=11.0 Hz), 5.08–5.14 (2H, m, CH_2CH=CH_2), 5.80–5.89 (1H, m, CH_2C*H*=CH_2), 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 and Ar*H*), 7.50–7.55 (3H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.43.

3.2.4. 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 **43** (48 mg, 0.126 mmol) and powdered 4 Å molecular sieves in CH_2Cl_2 (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 $NaHCO_3$, water, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=7:1) to afford the cyclic *p*-methoxybenzylidene acetal (Fig. 3) product as a colorless oil (31 mg, 0.082 mmol, 65%): $[\alpha]^{26}_D$=−32.2 (*c* 1.0, $CHCl_3$); IR ν_{max}(neat) cm^{-1} 1688, 1659, 1613, 1576, 1518, 1248; ^1H NMR (270 MHz, C_6D_6) δ 1.31–1.36 (1H, m, C_5–CH_2), 1.90 (1H, td, *J*=12.7, 6.1 Hz, C_5–CH_2), 2.09–2.17 (1H, m, CH_2CH=CH_2), 2.29–2.40 (1H, m, CH_2CH=CH_2), 2.66 (1H, dd, *J*=15.2, 7.9 Hz, C_7–CH_2), 3.00 (1H, dd, *J*=15.2, 6.6 Hz, C_7–CH_2), 3.24 (3H, s, OCH_3), 3.81 (1H, m, C_4–C*H*), 4.80–4.85 (1H, m, C_6–C*H*), 5.02–5.09 (2H, m, CH_2CH=CH_2), 5.80 (1H, s, C*H*MP), 5.80–5.93 (1H, m, CH_2C*H*=CH_2), 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.

3.3. Stereochemical proof of 43

The NOE analysis of the above cyclic *p*-methoxybenzylidene acetal established the 1,3-*anti* dioxygen relationship of the acetal, thereby securing the stereochemical assignment of the aldol adduct **43**.

3.3.1. (4*S*)-5-[(4*R*,6*R*)-4-((*E*)-2-Phenylethenyl)-2,2-dimethyl-1,3-dioxan-6-yl]-4-*p*-methoxybenzyloxy-2-pentene (44). To a stirred solution of the aldol adduct **43** (660 mg, 1.73 mmol) in THF (7 mL) at −78°C 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°C 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°C. To this was added 2:1 methanol/30% aqueous H_2O_2 (3 mL) carefully. The mixture was stirred at 0°C for 1.5 h, and then allowed to warm to room temperature over 1.5 h. The mixture was extracted with $CHCl_3$ (×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-820 MH, 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 **44** as a colorless oil (430 mg, 1.02 mmol, 59%), the minor diastereomer **45** as white crystals (64 mg, 0.15 mmol, 9%), and the starting material (208 mg, 0.54 mmol, 31%). *Data for the desired product* **44**: $[\alpha]^{26}_D$=+31.1 (c 1.0, $CHCl_3$); IR ν_{max}(neat) cm^{-1} 1640, 1613, 1586, 1514, 1379, 1248; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27–1.41 (1H, m, C_5–CH_2), 1.46 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.56–1.63 (3H, m, C_5 and C_7–CH_2), 2.33–2.37 (2H, m, CH_2CH=CH_2), 3.73–3.78 (1H, m, C_4–C*H*), 3.81 (3H, s, OCH_3), 4.16–4.20 (1H, m, C_6–C*H*), 4.40 (1H, d, J=10.9 Hz, CH_2Ar), 4.50–4.53 (1H, m, C_8–C*H*), 4.58 (1H, d, J=10.9 Hz, CH_2Ar), 5.07–5.15 (2H, m, CH_2CH=CH_2), 5.79–5.95 (1H, m, CH_2C*H*=CH_2), 6.16 (1H, dd, J=16.0, 6.3 Hz, C*H*=CHPh), 6.58 (1H, d, J=16.0 Hz, CH=C*H*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 **45**: 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20–1.27 (2H, m, C_5–CH_2), 1.43 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.53–1.58 (1H, m, C_7–CH_2), 1.80–1.91 (1H, m, C_7–CH_2), 2.33–2.38 (2H, m, CH_2CH=CH_2), 3.52–3.56 (1H, m, C_4–C*H*), 3.75 (3H, s, OCH_3), 4.00 (1H, m, C_6–C*H*), 4.36 (1H, d, J=11.5 Hz, CH_2Ar), 4.34–4.38 (1H, m, C_8–C*H*), 4.55 (1H, d, J=11.5 Hz, CH_2Ar), 5.06–5.13 (2H, m, CH_2CH=CH_2), 5.76–5.92 (1H, m, CH_2C*H*=CH_2), 6.08 (1H, dd, J=16.0, 6.3 Hz, C*H*=CHPh), 6.53 (1H, d, J=16.0 Hz, CH=C*H*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.

3.3.2. (4*R*)-5-[(4*R*,6*R*)-4-((*E*)-2-Phenylethenyl)-2,2-dimethyl-1,3-dioxan-6-yl]-4-*p*-methoxybenzyloxy-2-pentanone (40). A suspension of **44** (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 (×2) and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/ether=2:1–1:1) to afford the desired product **40** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37–1.70 (4H, m, C_5 and 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 and C_6–C*H*), 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–C*H*), 6.15 (1H, dd, J=16.0, 6.3 Hz, C*H*=CHPh), 6.59 (1H, d, J=16.0 Hz, CH=C*H*Ph), 6.88 (2H, d, J=8.2 Hz, Ar*H*), 7.23–7.39 (7H, m, Ar*H*); ^{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.

3.3.3. (1*E*,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 (46). Methyl ketone **40** (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-820 MH, hexane/EtOAc=2:1) to afford the desired product **46** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19–1.45 (2H, m, C_3 and 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 and 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.

3.3.4. (1*E*,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 (47). To a solution of the alcohol **46** (108 mg, 0.262 mmol) in THF (2.5 mL) at 0°C 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°C 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-820 MH, hexane/EtOAc=7:1–5:1) to afford the desired product **47** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22 (1H, q, J=11.4 Hz, C_5–CH_2), 1.34 (3H, s, C_1–CH_3), 1.35 (1H, dd, J=12.4, 11.4 Hz, C_3–CH_2), 1.64–1.72 (1H, m, C_5–CH_2), 1.99–2.04 (2H, m, C_3 and C_7–CH_2), 2.21 (1H, d, J=12.4 Hz, C_7–CH_2), 3.14 (3H, s, C_{29}–OCH_3), 3.30 (3H, s, C_{28}–OCH_3), 3.65 (1H, br, C_6–CH), 3.78 (3H, s, OCH_3), 3.83 (1H, m, C_4–CH), 3.88–3.95 (1H, m, C_8–CH), 4.45 (2H, s, CH_2Ar), 6.04 (1H, dd, J=16.0, 8.2 Hz, CH=CHPh), 6.55 (1H, d, J=15.9 Hz, CH=CHPh), 6.85 (2H, d, J=8.4 Hz, ArH), 7.22–7.39 (7H, m, ArH); ^{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.

3.3.5. (3*R*)-4-[(2*R*,4*R*,6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-3-methoxy-1-butene (48). To a solution of **47** (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 (×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°C was added $NaIO_4$ (171 mg, 0.80 mmol) in one portion. The reaction mixture was stirred at 0°C 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°C 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°C for 4 min, and then allowed to warm to 0°C over 8 min, and quenched by the addition of 0.1N 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-820 MH, hexane/ether=5:1) to afford the desired product **48** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (1H, q, J=11.7 Hz, C_5–CH_2), 1.34 (3H, s, C_1–CH_3), 1.38 (1H, d, J=11.9 Hz, C_3–CH_2), 1.53–1.62 (1H, m, C_5–CH_2), 1.89–1.92 (1H, m, C_3–CH_2), 1.94–2.04 (1H, m, C_7–CH_2), 2.22 (1H, dd, J=12.5, 3.1 Hz, C_7–CH_2), 3.15 (3H, s, C_{29}–OCH_3), 3.26 (3H, s, C_{28}–OCH_3), 3.61–3.66 (1H, br, C_6–CH), 3.68–3.76 (1H, m, C_4–CH), 3.80 (3H, s, OCH_3), 3.83–3.90 (1H, m, C_8–CH), 4.47 (2H, s, CH_2Ar), 5.19–5.27 (2H, m, CH=CH_2), 5.60–5.73 (1H, m, CH=CH_2), 6.86 (2H, d, J=8.6 Hz, ArH), 7.25 (2H, d, J=7.9 Hz, ArH); ^{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.

3.3.6. (3*R*)-4-[(2*R*,4*R*,6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-3-methoxy-1-*tert*-butyldiphenylsiloxy-2-butanol (49). To a solution of **48** (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 (×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-820 MH, 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°C 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°C 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-820 MH, hexane/EtOAc=3:1) to afford the desired product **49** as a colorless oil (129 mg, 0.207 mmol, 94%, 3.2:1 mixture of diastereoisomers): $[\alpha]^{26}_D$=−33.6 (c 1.0, $CHCl_3$); IR ν_{max}(neat) cm^{-1} 3475, 1615, 1588, 1514, 1248; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.07 (9H, s, $(CH_3)_3C$), 1.17–1.41 (2H, m, C_3 and C_5–CH_2), 1.33 (3H, s, C_1–CH_3) (1.30, s), 1.69–1.84 (2H, m, C_3 and 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, O*H*) (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–C*H*), 3.63–3.90 (5H, m, C_4, C_8, C_9–C*H* and 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, Ar*H*), 7.25 (2H, d, *J*=6.8 Hz, Ar*H*), 7.38–7.43 (6H, m, Ar*H*), 7.66–7.69 (4H, m, Ar*H*); ^{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.

3.3.7. (3*R*)-4-[(2*R*,4*R*,6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-3-methoxy-1-*tert*-butyldiphenylsiloxy-2-butylazide (50). To a stirred solution of the alcohol **49** (105 mg, 0.169 mmol) in CH_2Cl_2 (1 mL) at 0°C 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°C 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°C for 4 h. After dilution with ether, the mixture was washed with water (×2) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=6:1) to afford the desired product **50** as a colorless oil (75 mg, 0.116 mmol, 68%, 3.8:1 mixture of diastereoisomers): $[\alpha]^{25}_D$=−35.9 (*c* 0.6, $CHCl_3$); IR ν_{max}(neat) cm^{-1} 2101, 1613, 1588, 1514, 1248; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08 (9H, s, $(CH_3)_3C$), 1.16–1.44 (2H, m, C_3 and 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, and C_8–C*H*), 3.80 (3H, s, OCH_3), 3.84 (1H, m, C_9–C*H*), 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, Ar*H*), 7.25 (2H, d, *J*=6.3 Hz, Ar*H*), 7.40–7.45 (6H, m, Ar*H*), 7.66–7.69 (4H, m, Ar*H*); ^{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.

3.3.8. (3*R*)-4-[(2*R*,4*R*,6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-3-methoxy-1-*tert*-butyldiphenylsiloxy-2-butylamine (39). To a solution of the azide **50** (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°C 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 **39** as a colorless oil (26 mg, 0.042 mmol, 68%), which was directly used for the next step.

3.3.9. Methyl [2*S*,2(4*E*,7*Z*,9*S*,10*E*)]-2-[7,9-dimethyl-4,7,10-dodecatrienyl-1-carbonyl(amino)]-3-hydroxypropanoate (51). To a stirred solution of the carboxylic acid **8** (44 mg, 0.198 mmol) and (*S*)-serine methyl ester hydrochloride (34 mg, 0.219 mmol) in DMF (0.8 mL) at 0°C was successively added dropwise DEPC (0.036 mL, 0.221 mmol) and triethylamine (0.060 mL, 0.432 mmol). After being stirred at 0°C 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-820 MH, hexane/EtOAc=1:1–1:2) to afford the desired product **51** 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}–CH_3), 1.64 (6H, m, C_{25} and C_{27}–CH_3), 2.04 (1H, br, O*H*), 2.34 (4H, m, C_{16} and C_{19}–CH_2), 2.64–2.70 (2H, m, C_{15}–CH_2), 3.01 (1H, br, C_{22}–C*H*), 3.78 (3H, s, OCH_3), 3.92 (2H, qd, *J*=11.0, 3.1 Hz, C_{13}–CH_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} and C_{18} and C_{23} and 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.

3.3.10. Methyl (3*E*,6*Z*,8*S*,9*E*)-2-(6,8-dimethyl-3,6,9-undecatrienyl)-oxazole-4-carboxylate (52). To a stirred solution of the amido alcohol **51** (28 mg, 0.087 mmol) in CH_2Cl_2 (0.9 mL) at −20°C was added dropwise Deoxofluor (0.032 mL, 0.174 mmol). The reaction mixture was stirred at −20°C for 25 min, and then quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ (×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°C 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°C 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-820 MH, hexane/ether=5:1) to afford the desired product **52** as a colorless oil (21 mg, 0.069 mmol, 80%): $[\alpha]^{26}_D$=−47.2 (*c* 0.9, $CHCl_3$); 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}–CH_3), 1.61 (3H, s, C_{27}–CH_3), 1.62 (3H, d, *J*=4.0 Hz, C_{25}–CH_3), 2.48 (2H, m, C_{16}–CH_2), 2.68 (2H, m, C_{19}–CH_2),

2.87 (2H, t, J=7.3 Hz, C_{15}–CH_2), 3.00 (1H, m, C_{22}–CH), 3.90 (3H, s, OCH_3), 4.98 (1H, d, J=9.4 Hz, C_{21}–CH), 5.34–5.36 (2H, m, C_{23} and C_{24}–CH), 5.41–5.42 (2H, m, C_{17} and C_{18}–CH), 8.13 (1H, s, C_{13}–CH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.3, 28.3, 29.9, 35.3×2, 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.

3.3.11. (3*E*,6*Z*,8*S*,9*E*)-2-(6,8-dimethyl-3,6,9-undecatrienyl)-oxazole-4-carboxylic acid (38). To a solution of the ester **52** (45 mg, 0.148 mmol) in THF (0.6 mL) at 0°C was added 0.5N 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 (×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford the desired product **38** 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; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, J=6.8 Hz, C_{26}–CH_3), 1.61 (3H, s, C_{27}–CH_3), 1.63 (3H, d, J=4.0 Hz, C_{25}–CH_3), 2.49–2.54 (2H, m, C_{16}–CH_2), 2.67 (2H, m, C_{19}–CH_2), 2.92 (2H, t, J=7.4 Hz, C_{15}–CH_2), 2.95 (1H, m, C_{22}–CH), 4.99 (1H, d, J=9.2 Hz, C_{21}–CH), 5.35–5.40 (2H, m, C_{23} and C_{24}–CH), 5.41–5.51 (2H, m, C_{17} and C_{18}–CH), 8.23 (1H, s, C_{13}–CH), 8.62 (1H, br, OH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 21.5, 23.3, 28.2, 29.8, 35.3×2, 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.

3.3.12. (3*R*)-4-[(2*R*,4*R*,6*R*)-4-*p*-Methoxybenzyloxy-2-methoxy-2-methyl tetrahydropyran-6-yl]-2-[(3*E*,6*Z*,8*S*,9*E*)-2-(6,8-dimethyl-3,6,9-undecatrienyl)-oxazole-4-carbonyl]-amino-3-methoxy-1-butanol (53). To a stirred solution of the carboxylic acid **38**(14 mg, 0.048 mmol) and the amine **39** (32 mg, 0.052 mmol) in DMF (0.3 mL) at 0°C was successively added dropwise DEPC (0.010 mL, 0.061 mmol) and triethylamine (0.014 mL, 0.101 mmol). After being stirred at 0°C 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-820 MH, 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°C. The reaction mixture was stirred at 0°C for 30 min and then at room temperature for 40 min. After dilution with EtOAc, the organic layer was washed with water (×2) and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (BW-820 MH, hexane/EtOAc=1:1–1:2–1:5) to afford the desired product **53** as a colorless oil (27 mg, 0.041 mmol, 86%, 3.7:1 mixture of diastereoisomers): $[\alpha]^{26}_D$=−79.8 (c 0.7, $CHCl_3$); IR ν_{max}(neat) cm^{-1} 3407, 1661, 1599, 1514, 1451, 1375, 1248; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, d, J=6.8 Hz, C_{26}–CH_3), 1.11–1.43 (2H, m, C_3 and C_5–CH_2), 1.34 (3H, s, C_1–CH_3) (1.26, s), 1.62 (3H, s, C_{27}–CH_3), 1.65 (4H, m, C_5–CH_2 and C_{25}–CH_3), 1.71 (1H, br, OH), 1.81–1.90 (1H, m, C_3–CH_2), 1.95–2.05 (1H, m, C_7–CH_2), 2.20–2.25 (1H, m, C_7–CH_2), 2.49 (2H, m, C_{19}–CH_2), 2.69 (2H, m, C_{16}–CH_2), 2.83 (2H, t, J=7.7 Hz, C_{15}–CH_2), 3.00 (1H, m, C_{22}–CH), 3.19 (3H, s, C_{29}–OCH_3), 3.43 (3H, s, C_{28}–OCH_3), 3.64–3.91 (5H, m, C_4, C_6, C_8–CH and C_{10}–CH_2), 3.79 (3H, s, OCH_3), 4.28 (1H, m, C_9–CH), 4.45 (2H, s, CH_2Ar) (4.47, s), 4.99 (1H, d, J=9.2 Hz, C_{21}–CH), 5.36 (2H, m, C_{23} and C_{24}–CH), 5.44 (2H, m, C_{17} and C_{18}–CH), 6.86 (2H, d, J=8.6 Hz, ArH), 7.23 (2H, d, J=8.4 Hz, ArH), 7.32 (1H, d, J=8.9 Hz, NH) (7.61, d, J=7.9 Hz), 8.08 (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, 23.4, 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 $C_{37}H_{54}N_2O_8$·1/2n-hexane: C, 68.84; H, 8.81; N, 4.01. Found: C, 68.84; H, 8.49; N, 4.01.

3.3.13. Protected hennoxazole A (54). To a stirred solution of the alcohol **53** (27 mg, 0.041 mmol) in CH_2Cl_2 (0.3 mL) at 0°C 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°C, 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-820 MH, hexane/EtOAc=3:1–2:1) to afford the desired product **54** 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^{-11} 1615, 1584, 1514, 1449, 1375, 1248; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, J=6.8 Hz, C_{26}–CH_3), 1.22–1.43 (2H, m, C_3 and C_5–CH_2), 1.32 (3H, s, C_1–CH_3), 1.62 (3H, s, C_{27}–CH_3), 1.64 (3H, m, C_{25}–CH_3), 2.05–2.21 (4H, m, C_3, C_5 and C_7–CH_2), 2.50–2.55 (2H, m, C_{16}–CH_2), 2.68 (2H, m, C_{19}–CH_2), 2.90 (2H, t, J=7.4 Hz, C_{15}–CH_2), 2.98 (1H, m, C_{22}–CH), 3.07 (3H, s, C_{29}–OCH_3), 3.31 (3H, s, C_{28}–OCH_3), 3.54 (1H, m, C_6–CH), 3.79 (3H, s, OCH_3), 3.79 (1H, m, C_4–CH), 4.42 (1H, m, C_8–CH), 4.45 (2H, s, CH_2Ar), 4.99 (1H, d, J=9.2 Hz, C_{21}–CH), 5.35 (2H, m, C_{23} and C_{24}–CH), 5.41–5.45 (2H, m, C_{17} and C_{18}–CH), 6.86 (2H, d, J=8.6 Hz, ArH), 7.23 (2H, d, J=8.6 Hz, ArH), 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, 77.2, 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 $C_{37}H_{50}N_2O_7$·1/2n-hexane: C, 70.87; H, 8.47; N, 4.13. Found: C, 71.09; H, 8.19; N, 4.19.

3.3.14. (−)-Hennoxazole A (1). To a solution of **54** (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°C. 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°C, 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 $CHCl_3$ (×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×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}–C*H*$_3$), 1.10 (1H, q, *J*=11.6 Hz, C_5–C*H*$_2$), 1.21 (1H, dd, *J*=12.2, 11.0 Hz, C_3–C*H*$_2$), 1.24 (3H, s, C_1–C*H*$_3$), 1.58 (3H, dd, *J*=3.7, 1.2 Hz, C_{25}–C*H*$_3$), 1.59 (3H, d, *J*=1.5 Hz, C_{27}–C*H*$_3$), 1.88 (1H, ddt, *J*=12.2, 4.6, 2.4 Hz, C_5–C*H*$_2$), 1.97 (1H, ddd, *J*=12.5, 4.6, 1.8 Hz, C_7–C*H*$_2$), 2.05 (2H, m, C_3 and C_7–C*H*$_2$), 2.50 (2H, q, *J*=6.7 Hz, C_{16}–C*H*$_2$), 2.69 (2H, m, C_{19}–C*H*$_2$), 2.89 (2H, t, *J*=7.3 Hz, C_{15}–C*H*$_2$), 3.01 (1H, m, C_{22}–C*H*), 3.03 (3H, s, C_{29}–OC*H*$_3$), 3.22 (3H, s, C_{28}–OC*H*$_3$), 3.52 (1H, m, C_6–C*H*), 3.61 (1H, d, *J*=5.2 Hz, O*H*), 3.89 (1H, m, C_4–C*H*), 4.46 (1H, dd, *J*=7.9, 6.1 Hz, C_8–C*H*), 4.95 (1H, dd, *J*=9.8, 0.9 Hz, C_{21}–C*H*), 5.34 (2H, m, C_{23} and C_{24}–C*H*), 5.41–5.56 (2H, m, C_{17} and C_{18}–C*H*), 7.98 (1H, s, C_{10}–C*H*), 8.40 (1H, s, C_{13}–C*H*); ^{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.

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References

1. (a) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T. *J. Am. Chem. Soc.* **1991**, *113*, 3173–3174. (b) Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227–2230.
2. Lindquist, N.; Fenical, W.; Van Duyne, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.
3. Nagatsu, A.; Kajitani, H.; Sakakibara, J. *Tetrahedron Lett.* **1995**, *36*, 4097–4100.
4. Linked trisoxazole units have been found in some marine macrolides. (a) ulapualides A and B: Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846–847. (b) halichondramides: Kernan, M. R.; Molinski, T. F.; Faulkner, J. D. *J. Org. Chem.* **1988**, *53*, 5014–5020. (c) kabiramides, A–E: Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M.; Noguchi, H.; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360–1363. (d) jaspisamides, A–C: Kobayashi, J.; Murata, O.; Shigemori, H. *J. Nat. Prod.* **1993**, *56*, 787–791. (e) mycalolides: Matsunaga, S.; Sugawara, T.; Fusetani, N. *J. Nat. Prod.* **1998**, *61*, 1164–1167 and references cited therein.
5. (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558–559. (b) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157–167.
6. Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924–4925.
7. (a) Yokokawa, F.; Hamada, Y.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1996**, 871–872. (b) Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Org. Lett.* **2000**, *2*, 2149–2152. (c) Wu, M.; Okino, T.; Nogle, L. M.; Marquez, B. L.; Williamson, R. T.; Sitachitta, N.; Berman, F. W.; Murray, T. F.; McGough, K.; Jacobs, R.; Colsen, K.; Asano, T.; Yokokawa, F.; Shioiri, T.; Gerwick, W. H. *J. Am. Chem. Soc.* **2000**, *122*, 12041–12042. (d) Yokokawa, F.; Sameshima, H.; Shioiri, T. *Synlett* **2001**, 986–988.
8. For our preliminary synthetic studies on hennoxazole A, see: (a) Cheng, Z.; Hamada, Y.; Shioiri, T. *Synlett* **1997**, 109–110. (b) Shioiri, T.; McFarlane, N.; Hamada *Heterocycles* **1998**, *47*, 73–76.
9. For other synthetic studies on hennoxazole A, see: (a) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415–415. (b) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177–180.
10. For a preliminary account of the total synthesis of (−)-hennoxazole A, see: Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169–4172.
11. (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408. (b) Hensel, M. J.; Fuchs, P. L. *Synth. Commun.* **1986**, 1285–1295. (c) Rathke, M. W.; Bouhlel, E. *Synth. Commun.* **1990**, *20*, 869–875.
12. (a) Ando, K. *J. Synth. Org. Chem., Jpn* **2000**, *58*, 869–876. (b) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.
13. Cheng, Z.; Nakao, R.; Hamada, Y.; Shioiri, T., unpublished results. We thank Dr Z. Cheng and Mr R. Nakao for their preliminary studies on the preparation of the triene unit.
14. Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833–4840.
15. Valle, L. D.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019–3023.
16. MOM ether **23** was prepared from the known alcohol by treatment with MOMCl and *i*-Pr_2NEt in CH_2Cl_2, see Yamada, H.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1991**, *65*, 4569–4574.
17. Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
18. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
19. Review: Negishi, E.-I.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 1–47.
20. Ester **32** is available in three steps from cinnamyl chloride and serine methyl ester hydrochloride via coupling, cyclodehydration and oxidation; see Ref. 33. Other approach, see: (a) Connell, R. D.; Tebbe, M.; Gangloff, A. R.; Helquist, P.; Åkermark, B. *Tetrahedron* **1993**, *49*, 5445–5459. (b) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496–6497.
21. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4174. (b) Nahm, S.; Weinreb, S. M.

Tetrahedron Lett. **1981**, *22*, 3815–3818. (c) Levin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.

22. The configurations of the newly formed hydroxyl stereogenic center of the aldol adducts **34** and **43** were established by NOE analysis of the corresponding *p*-methoxybenzylidene acetals, which were produced by treatment of the aldol adduct **34** and **43** under anhydrous condition with DDQ (see Section 3).[23]
23. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889–892.
24. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.
25. Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. *J. Chem. Lett.* **1987**, 1923–1926.
26. The 1,3-*syn* relationships of the acetonides **36**, **44** and **45** were supported by analysis of their ^{13}C NMR spectra. see: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.
27. Tsuji, J. *Synthesis* **1984**, 369–384.
28. Rogers, H. R.; McDermott, J. X.; Whitesides, G. M. *J. Org. Chem.* **1975**, *40*, 3577–3580.
29. (a) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6143–6146. (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033–10046.
30. Smith III, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765–8768.
31. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.
32. Takuma, S.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3147–3153 and references cited therein.
33. Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.
34. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.
35. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.