A stereoselective synthesis of the C(3)-C(13) and C(14)-C(24) fragments of macrolactin A

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Synthetic studies towards the C(3)-C(13) and C(14)-C(24) segments (3, 4) of the potent antiviral and antitumor compound macrolactin A (1) are presented. Compound 3 was constructed *via* a convergent and facile approach, exploiting Wittig olefination to generate the sensitive *E*, *Z*-diene moiety. Compound 4 was synthesized from the chiral-pool derived sulfone 39a *via* an α-alkylation-desulfonation reaction sequence. Cu(II)-catalyzed coupling of a Grignard reagent with an allylic bromide and Julia olefination were also investigated for the preparation of compound 4.

Keywords Macrolactin A, antiviral, stereoselective synthesis, Wittig reaction, sulfone alkylation, Julia olefination

Introduction

Macrolactin A (**1**) is the parent aglycone of a novel family of bioactive 24-membered polyene macrolides isolated by Fenical *et al.*[1] from a taxonomically-unidentified deep sea bacterium. This compound shows a unique structure that contains three sets of conjugated dienes and four chiral centers. Its stereochemistry has also been established as 7*S*, 13*S*, 15*R*, 23*R* by NMR analysis, chemical degradation and segment synthesis.[2] Macrolactin A exhibits significant antiviral and cancer cell cytotoxic properties in preliminary assays *in vitro*. It inhibits B16-F10 murine melanoma cancer cells and mammalian *Herpes simplex* virus I and II, and protects human T-lymphoblasts against HIV replication. Unfortunately, this compound is no longer readily available from culture of bacterium.[2] Further research of pharmacology and action mechanism has to depend on its synthetic samples.

Macrolactin A (**1**) has been a focus of synthetic endeavors because of its novel structure, wide range of biological activities as well as the scarcity of the natural resource. Several research groups have reported their efforts towards the synthesis of macrolactin A,[3] but only two groups reached the goal.[4] In the reported syntheses, a similar strategy was adopted, namely, constructing the conjugated double bond structure by palladium-catalyzed sp^2-sp^2 cross-coupling reactions.

We are also engaged in the synthetic venture of macrolactin A, but our approach is totally different.[5] As depicted in Scheme 1, disconnections at the lactone linkage and C(2)-C(3) double bond give the precursor **2**, which was envisioned to be formed from dithiane **3** with iodide **4**. It was further expected that dithiane **3** and iodide **4** could be derived from the enantiopure starting materials (*S*)-malic acid and poly[(*R*)-3-hydroxybutyric acid], respectively. Herein, we wish to report the synthesis of the two segments **3** and **4** of macrolactin A (**1**) in detail.

Results and discussion

The synthesis of fragment **3** started from the known protected triol **5** which was prepared in two steps from (*S*)-malic acid.[6] Oxidation of **5** under Swern conditions[7] followed by Wittig olefination with carbethoxymethylene-

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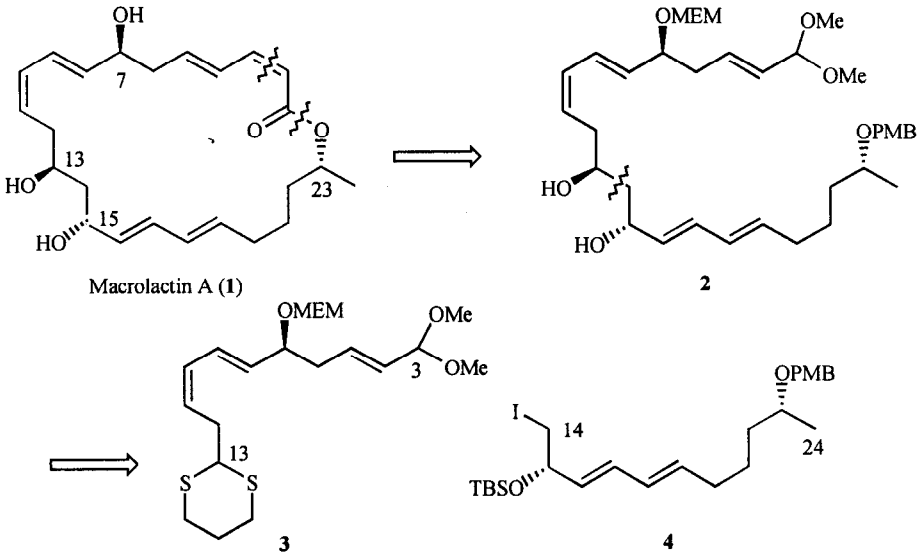
triphenylphosphorane gave the corresponding E-α,β-unsaturated ester **6** in 74% yield. It was hydrolyzed in the presence of p-toluene sulfonic acid to yield the corresponding diol, and a following selective tritylation of the primary hydroxy group afforded the trityl ether **7** in 98% yield in two steps. Protection of the secondary hydroxy group in **7** as a MEM ether followed by removal of the trityl group in **8** by exposure to formic acid in ether afforded **9** smoothly. Swern oxidation of **9** furnished the corresponding aldehyde, which was subsequently subjected to Wittig condensation with formylmethylene-triphenylphosphorane[8] giving α,β-unsaturated aldehyde **10** in 92% yield in two steps. Wittig reaction of aldehyde **10** with the phosphorane derived from acetal phosphonium salt **11**[9] in the presence of t-BuOK produced E, E, Z-triene acetal **12** as a single isomer (Scheme 2). However the transformation of acetal **12** into thioacetal **14** under the routine reaction conditions was unsuccessful.[10]

Scheme 1



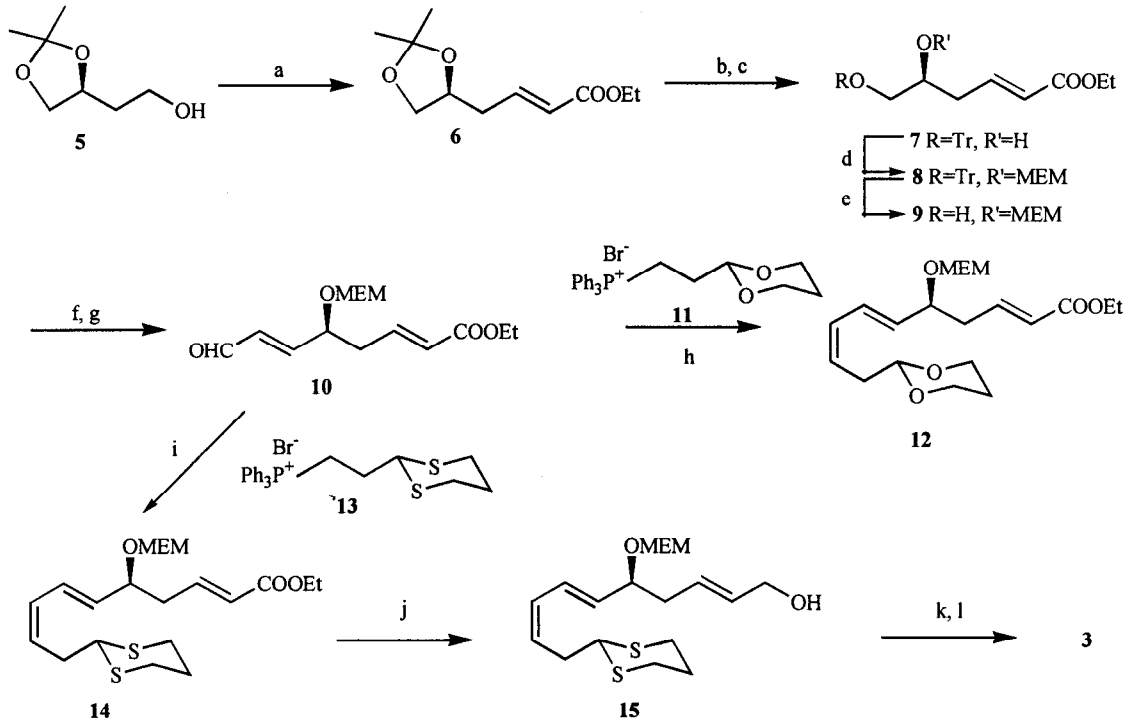
The desired 1,3-dithiane unit in ester **14** was introduced *via* Wittig reaction of aldehyde **10** and thioacetal phosphonium salt **13**[11] in ether. The solvent was critical to the success of this reaction. Among the conventional solvents (THF, benzene and toluene) tested, ether saved the best result. The E, E, Z-triene dithiane **14** was then reduced with DIBAL in methylene chloride to furnish the allylic alcohol **15**. Finally, oxidation of alcohol **15** under Swern conditions afforded the corresponding aldehyde, which was further protected as the dimethylacetal with trimethyl orthoformate in the presence of p-toluene sulfonic acid in methanol to give acetal **3** in quantitative yield.

The retrosynthetic analysis showed that a coupling reaction between Grignard reagent **16** and allylic bromide **17** seemed to be the straightforward method to build C(14)-C(24) fragment. So we proposed that a Cu(II)-catalyzed coupling of Grignard reagent **16** with allylic bromide **17** would furnish **4** (Scheme 3).

The synthesis of **17** started from aldehyde **18**[12] (Scheme 4). Condensation of **18** with triethyl 4-phosphonocrotonate[13] gave the corresponding E, E-diene ester **19** as the major product. Reduction of the latter to the corresponding primary alcohol **20** with $LiAlH_4/AlCl_3$ followed by treatment with NBS/PPh_3[14] furnished allylic bromide **17**.

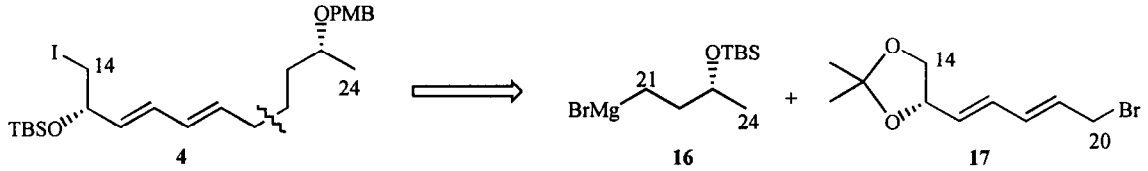
The Grignard reagent **16** was elaborated from compound **21** prepared from commercially available poly-(R)-3-hydroxybutyric acid[15] or by asymmetric synthesis.[16] Protection of the hydroxy group in **21** as TBS ether followed by reduction of the ester **22** with $LiAlH_4$ gave alcohol **23**. Alcohol **23** was then converted into the bromide **24** with PPh_3/Br_2 in 80% yield. The coupling of **16** with **17** in the presence of 0.1 eq. of Li_2CuCl_4 at −78℃ gave an inseparable mixture of the desired coupling product **25** together with the regio-isomer **26** resulting from the S_N2' reaction in 2 : 1 ratio (Scheme 5). Some other coupling conditions were also examined. However, all attempts to improve the regioselectivity of this coupling reaction were unsuccessful.

Scheme 2

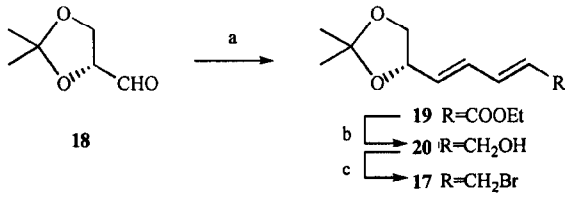


Reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78℃—r.t., 1 h, then Ph_3P=CHCOOEt, 0℃, 5 h, 74%; b) MeOH, *p*-TsOH, r.t., 2 h; c) Ph_3CCl, Et_3N, DMAP, CH_2Cl_2, reflux, 6 h, 98% (for two steps); d) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, r.t., 30 h, 91%; e) HCOOH, Et_2O, r.t., 50 min, 96%; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78℃—r.t., 1 h; g) Ph_3P=CHCHO, $CHCl_3$, r.t., 8 h, 92% (for two steps); h) **11**, *t*-BuOK, THF, 20 min, 86%; i) **13**, *t*-BuOK, Et_2O, 30 min, 90%; j) DIBAL, CH_2Cl_2, −78℃, 30 min, 91%; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78℃, 40 min, r.t., 1 h, 90%; l) MeOH, $HC(OMe)_3$, *p*-TsOH, r.t., 20 min, 100%.

Scheme 3



Scheme 4

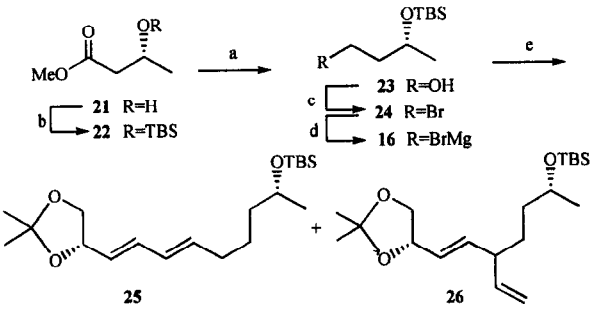


Reagents and conditions: a) ethyl diethylphosphonocrotonate, LDA, THF, 0℃, 1 h, 63%; b) $LiAlH_4$, $AlCl_3$, ether, 0℃, 1 h, 97%; c) NBS, PPh_3, DMF, r.t., 30 min, 93%.

We then turned to the Julia olefination, which had been successfully utilized in the synthesis of polyene natural products.[17] The sulfone **31** was synthesized in 4 steps and 72% overall yield from compound **27**.[18] As shown in Scheme 6, the hydroxy group in **27** was protected as the PMB ether **28**. Reduction of ester **28** followed by conversion of the resultant alcohol **29** to iodide **30**, and subsequent treatment of **30** with sodium *p*-toluenesulfinate furnished sulfone **31**. Deprotonation of **31** with *n*-BuLi in THF at −78℃ followed by addition of the *E*-unsaturated aldehyde **32**[19] resulted in a diastereomeric mixture of β-hydroxysulfones **33**. Sulfones

33 were directly treated with Na(Hg) at −20℃ to afford a 3.5:1 mixture of **25a** and **25b** based on integration of NMR signals of the vinylic hydrogens. The structures of **25a** and **25b** were determined by the chemical shifts and coupling constants of the protons in diene segments[20] (Scheme 6).

Scheme 5

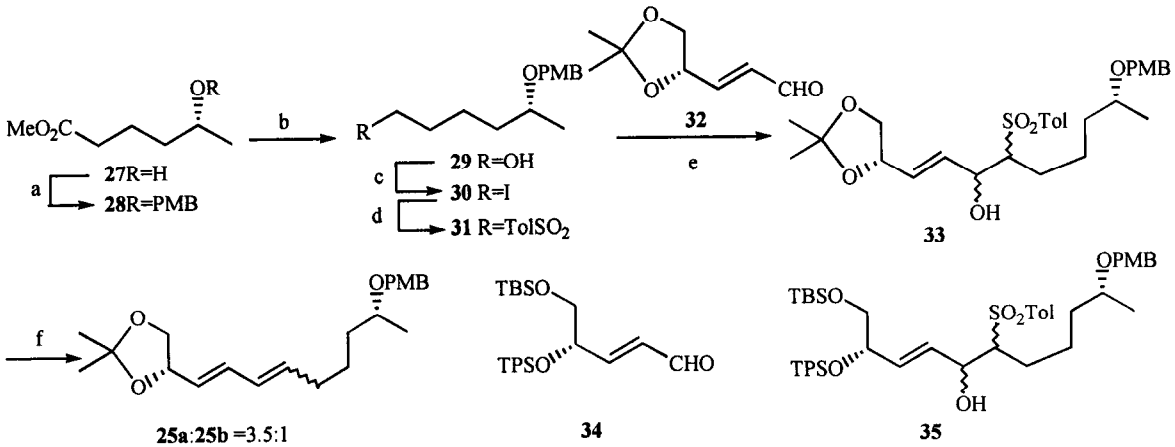


Reagents and conditions: a) TBDMSCl, imidazole, DMF, r.t., 6 h, 84%; b) $LiAlH_4$, ether, −78℃, 1 h, 98%; c) PPh_3, Br_2, $CHCl_3$, r.t., 1 h, 80%; d) Mg, THF, reflux, 15 min; e) **17**, Li_2CuCl_4(cat.), −78℃, 20 min, 0℃, 2 h, r.t., 10 h, 63%.

Further studies on this elimination by conversion of the hydroxy group of **33** into various esters such as acetate or benzoate were tested, but no improvement of the ratio of isomers was observed. Based on the knowledge that increase in steric hindrance near the site of this elimination may enhance the *E*-selectivity of the product, the α, β-unsaturated aldehyde **34** containing two bulky silyl protecting groups was thus selected instead of aldehyde **32**. Unfortunately, β-hydroxysulfones **35** obtained from coupling of aldehyde **34** and sulfone **31** offered no improvement in the ratio of two isomers.

Although the desired **25a** could be obtained in a reasonable yield and there was a possibility to separate these two isomers later, we were not yet satisfied with the results. Reinspection of the first route (Scheme 3) showed that segment **4** could be obtained by connection of C(21)-C(24) and C(14)-C(20) subunits **24** and **17** *via* regioselective alkylation of sulfone-stabilized anion with allylic bromide. Therefore, we started again the synthesis of segment **4** from ester **21** and bromide **17**, and finally the synthesis was achieved as outlined in Scheme 7. Phenylsulfone **39a** was prepared from ester **21** *via* a similar reaction sequence as that for the prepara-

Scheme 6

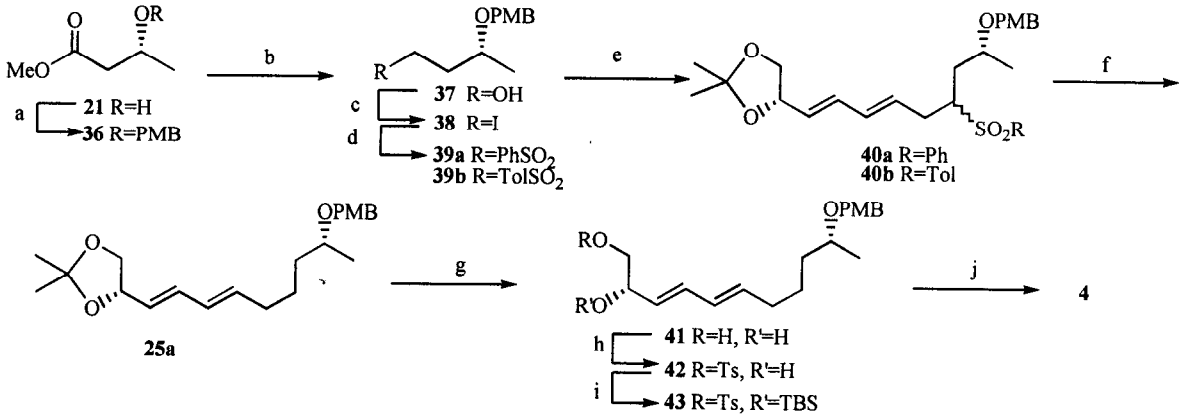


Reagents and conditions: a) PMBOC(=NH)CCl_3, CSA(cat.), CH_2Cl_2, r.t., 24 h, 92%; b) DIBAL, CH_2Cl_2, −78℃, 0.5 h, 98%; c) I_2, PPh_3, imidazole, toluene, r.t., 1 h; d) *p*-$TolSO_2Na$, *n*-Bu_4NBr (cat.), DMF, 40℃, 1 h, 80%; e) **31**, *n*-BuLi, THF, −78℃, 10 min, **32**, THF, −78℃, 1 h, 85%; f) Na(Hg) (6%), Na_2HPO_4, MeOH, EtOAc, −20℃, 30 min, 79%.

tion of **31**, including the reduction of the PMB protected ester **36** followed by conversion of the resulting alcohol **37** to iodide **38**, and treatment of **38** with sodium phenylsulfinate. Treatment of **39a** with a slight excess of lithium hexamethyldisilazane in THF gave the anion, to which was added bromide **17** in one portion. The coupling product **40a** was obtained as a mixture of diastereomers. Desulfonation of **40a** with Na(Hg) in methanol gave **25a** as a single product in 67% overall yield from **39a**. *p*-Tolylsulfone **40b** was also prepared, but the yield of desulfonation to give **25a** was much lower. Hydrolysis of acetonide **25a** and subsequent conversion of

the primary hydroxy in the resultant diol **41** to tosylate afforded compound **42**. The secondary hydroxy group in **42** was protected as TBS ether **43**. Finally, displacement of the *p*-tosyl ester in **43** with iodide completed the construction of the C(14)-C(24) fragment **4**. The ^1H NMR and ^{13}C NMR chemical shifts and coupling constants recorded for **3** and **4** were consistent with the corresponding values reported for the C(3)-C(13) and C(14)-C(24) segments in natural macrolactin A.

Scheme 7



Reagents and conditions: a) PMBOC(=NH)CCl_3, CSA (cat.), CH_2Cl_2, r.t., 36 h, 90%; b) DIBAL, CH_2Cl_2, -78℃, 0.5 h, 99%; c) I_2, PPh_3, imidazole, toluene, r.t., 1 h, 90%; d) $NaSO_2Ph$, *n*-Bu_4NBr (cat.), DMF, 40℃, 2 h, 85%; $NaSO_2Tol$, *n*-Bu_4NBr (cat.), DMF, 40℃, 2 h, 95%; e) LiHMDS, THF, -78℃, 15 min; then **17**, THF, -78℃, 15 min; f) Na(Hg) (6%), Na_2HPO_4, MeOH, 0℃, 30 min, 67%; g) CSA (cat.), MeOH, r.t., 3 h, 98%; h) TsCl, Et_3N, CH_2Cl_2, 0℃, 12 h, 69%; i) TBDMSOTf, Et_3N, CH_2Cl_2, 0℃, 15 min, 93%; j) NaI, acetone, reflux, 24 h, 60%.

Experimental

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All solvents were purified and dried by the standard procedures before use. Organic solutions of the products were dried over anhydrous sodium sulfate. All reactions involving organometallic reagents were conducted under a nitrogen or argon atmosphere. Silica gel (200—300 mesh) from Qingdao Marine Chemical Corporation was used for column chromatoghraphy unless otherwise noted. Solvents were removed by rotary evaporation. Infrared spectra were obtained on a Nicoler Magna 750. NMR spectra were measured on 400 or 300 MHz spectrometers for ^1H and 100 or 75 MHz spectrometers for ^{13}C, respectively, with tetramethylsilane as internal standard. *J* values were given in Hz. Specific rotations were measured on a Perkin-Elmer 241MC. Mass spectra and high resolution mass spectra were measured on a Varian MAT-711 and MAT-95, respectively.

(2E,5S)-Ethyl-5-hydroxy-6-trityloxyl-2-hexenoate (**7**)

To a solution of acetonide (*S*)-**6** (3.43 g, 16.03 mmol) in methanol (150 mL) was added *p*-toluenesulfonic acid (0.30 g, 1.58 mmol). The mixture was stirred at ambient temperature for 8 h, before $NaHCO_3$ (0.15 g) was added. The solution was concentrated and the residue was dissolved in ethyl acetate and filtered. The filtrate was concentrated. The crude diol thus obtained was dissolved in methylene chloride (150 mL). To the solution was added triethylamine (4.46 mL, 32.06 mmol), 4-(dimethylamino) pyridine (0.17 g, 1.40 mmol) and trityl chloride (4.52 g, 16.23 mmol) with stirring. The mixture was refluxed for 6 h, and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with ether (100 mL × 2). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried and concentrated. Purification of the residue by flash column chromatography on silica gel (petroleum ether: ethyl acetate, 5:1) gave **7** (6.53 g, 98% in two steps) as a yellowish oil. $[\alpha]_D^{22}$ + 7.92° (*c*, 0.75, $CHCl_3$). ν_{max}: 3469, 1716, 1655, 1597, 1491, 1448, 1369, 1271, 1074 cm^{-1}. δ_H

(100 MHz, $CDCl_3$): 7.53—7.35(m, 6H), 7.34—7.20(m, 9H), 6.88(dt, J = 15.7, 7.7 Hz, 1H), 5.82(d, J = 15.7 Hz, 1H), 4.15(q, J = 7.1 Hz, 2H), 3.60—4.04(m, 1H), 3.22—3.16(m, 1H), 3.12—3.05(m, 1H), 2.58—2.32(m, 2H), 2.32 (brs, 1H), 1.26(t, J = 7.0 Hz, 3H). EIMS m/z (%): 416(M^+, 0.1), 339(27), 244(23), 243 (100), 165(41). Anal. $C_{27}H_{28}O_4$. Calcd: C, 77.86; H, 6.78. Found: C, 77.77; H, 6.95.

(2E,5S)-Ethyl 5-methoxyethoxymethoxyl-6-trityloxyl-2-hexenoate (**8**)

To a solution of alcohol **7** (6.08 g, 14.61 mmol) in methylene chloride (80 mL) stirred at room temperature were added *i*-Pr_2NEt (15.26 mL, 87.67 mmol) and MEMCl (6.68 mL, 58.68 mmol). After being stirred for 48 h the reaction mixture was diluted with ether, washed with water and brine, dried and concentrated. Purification of the residue by column chromatography on silica gel (ethyl acetate:petroleum ether, 1:6) afforded **8** (6.71 g, 91%) as a colorless oil: ν_{max}: 1716, 1655, 1491, 1448, 1367, 1269, 1040 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 7.54—7.36(m, 6H), 7.34—7.18(m, 9H), 6.86(dt, J = 15.7, 7.7 Hz, 1H), 5.82(d, J = 15.6 Hz, 1H), 4.84(d, J = 7.5 Hz, 1H), 4.73(d, J = 7.1 Hz, 1H), 4.15(q, J = 7.0 Hz, 2H), 3.94—3.87(m, 1H), 3.75—3.68(m, 1H), 3.65—3.57(m, 1H), 3.54—3.43(m, 2H), 3.36(s, 3H), 3.21—3.16(m, 1H), 3.10—3.05 (m, 1H), 2.57—2.39(m, 2H), 1.27(t, J = 7.0 Hz, 3H). Anal. $C_{31}H_{36}O_6$. Calcd: C, 73.79; H, 7.19. Found: C, 73.82; H, 7.37.

(2E,5S)-Ethyl 6-hydroxy-5-methoxyethoxymethoxyl-2-hexenoate (**9**)

To a stirred solution of **8** (4.00 g, 7.94 mmol) in Et_2O (6 mL) was added formic acid (6 mL) at room temperature. The mixture was stirred at room temperature for 1.5 h and then poured into saturated aqueous $NaHCO_3$ at 0℃. The resulting mixture was extracted with Et_2O (50 mL × 2). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Purification of the residue by column chromatography (petroleum ether: ethyl acetate, 1:2) afforded alcohol **9** (2.01 g, 96%) as a colorless oil. $[\alpha]_D^{21}$ + 48.7°(*c* 1.14, $CHCl_3$). ν_{max}: 3466, 1716, 1655, 1369, 1271, 1180, 1043 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 6.91(d, J = 15.7, 7.2 Hz, 1H), 5.86(d, J = 15.7 Hz, 1H), 4.80(d, J = 7.5 Hz, 1H), 4.72 (d, J = 7.5 Hz, 1H), 4.16(q, J = 7.2 Hz, 2H), 3.86—3.78(m, 1H), 3.73—3.64(m, 3H), 3.56—3.45(m, 3H), 3.37(s, 3H), 2.50—2.35(m, 2H), 1.85(brs, 1H), 1.28(t, J = 7.2 Hz, 3H). EIMS m/z(%): 231($M^+ - CH_3$, 6), 220(6), 205(16), 187 (49), 157(31), 89(92), 59(100). Anal. $C_{12}H_{22}O_6$. Calcd: C, 54.95; H, 8.45. Found: C, 54.90; H, 8.43.

(2E,6E,5S) Ethyl 7-formyl-5-methoxyethoxymethoxylhepta-2,5-dienoate (**10**)

To a stirred solution of oxalyl chloride (0.75 mL, 8.59 mmol) in CH_2Cl_2 (15 mL) at −78℃ was added DMSO (1.06 mL, 14.96 mmol) in CH_2Cl_2 (5 mL) dropwise over 10 min. Upon complete addition, the mixture was stirred for 15 min, then **9** (1.12 g, 4.27 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min. After stirring for 1 h, triethylamine (3.00 mL, 21.56 mmol) was then added dropwise while the reaction temperature was maintained at −78℃. The stirring was continued for 5 min, then the mixture was warmed slowly to 0℃ over 1.5 h and quenched by addition of water (5 mL). The organic layer was separated and washed with water (5 mL). The aqueous layer was extracted with ether (50 mL). The organic layers were combined, washed with brine (10 mL), dried and concentrated. The residual oil was dissolved in ether (20 mL). The solution was filtered and concentrated to give a yellow oil, which was used in the next step without further purification.

To the solution of crude aldehyde in $CHCl_3$ (30 mL) was added formylmethylene-triphenylphosphorane (1.32 g, 4.34 mmol). After stirring at room temperature for 20 h, the mixture was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate, 4:1) to give **10** (1.13 g, 92%) as a pale yellow oil. $[\alpha]_D^{24}$ − 14.6°(*c* 1.28, $CHCl_3$). ν_{max}: 2928, 1720, 1693, 1657, 1456, 1456, 1369, 1317, 1269, 1180, 1109, 1040 cm^{-1}. δ_H(300 MHz, $CDCl_3$): 9.55(d, J = 7.8 Hz, 1H), 6.88(dt, J = 15.7, 7.3 Hz, 1H), 6.70(dd, J = 15.8, 1H, 5.6 Hz), 6.26(dd, J = 15.7, 7.8 Hz, 1H), 5.90

(d, J = 15.7 Hz, 1H), 4.76—4.68(m, 2H), 4.55—4.47(m, 1H), 4.15(q, J = 7.1 Hz, 2H), 3.60—3.78(m, 2H), 3.45—3.57(m, 2H), 3.35(s, 3H), 2.56—2.48(m, 2H), 1.26(t, J = 7.1 Hz, 3H). EIMS m/z(%): 255(M^+ - OMe, 9), 197(4), 151(15), 121(73), 89(100).

(2*E*,6*E*,8*Z*,5*S*) *Ethyl* 10-(1′,3′-*dithian*-2′-*yl*)-5-*methoxyethoxy-methoxyl-deca*-2,6,8-*trienoate* (**14**)

Potassium *t*-butoxide (7.50 mL, 0.5 mol/L solution in tetrahydrofuran, 3.75 mmol) was added to a stirred solution of 2-(1′, 3′-dithian-2′-yl)-ethyltriphenylphosphonium bromide (1.95 g, 3.99 mmol) in dry ether (40 mL) to give the orange phosphorane solution. Stirring was continued at room temperature for 15 min before a solution of **10** (0.52 g, 1.81 mmol) in dry ether (5 mL) was added dropwise. The mixture was stirred for 30 min and then poured into water (10 mL). The product was extracted with ethyl acetate (100 mL). The organic layer was dried and concentrated. Purification of the residue by column chromatography on silica gel (petroleum ether: ethyl acetate, 8:1) gave dithiane **14** (0.69 g, 90%) as a yellow oil. δ_H(400 MHz, $CDCl_3$): 6.97—6.85(m, 1H), 6.45(dd, J = 11.2, 14.9 Hz, 1H), 6.08(t, J = 10.8 Hz, 1H), 5.83(d, J = 15.6 Hz, 1H), 5.57—5.47(m, 2H), 4.72(d, J = 7.1 Hz, 1H), 4.60(d, J = 7.2 Hz, 1H), 4.28—4.19(m, 1H), 4.15(q, J = 7.2 Hz, 2H), 4.1—4.0(m, 1H), 3.78—3.64(m, 1H), 3.62—3.46(m, 3H), 3.34(s, 3H), 2.91—2.73(m, 4H), 2.66—2.55(m, 2H), 2.55—2.37(m, 2H), 2.13—2.03(m, 1H), 1.97—1.74(m 1H), 1.25(t, J = 7.2 Hz, 3H).

(2*E*,6*E*,8*Z*,5*S*)-10-(1′,3′-*dithian*-2′-*yl*)-5-*methoxyethoxymethoxyl-deca*-2,6,8-*trienol* (**15**)

The dithiane **14** (0.42 g, 1.01 mmol) was dissolved in methylene chloride (5 mL). The mixture was cooled to - 78℃. DIBAL (3 mL, 3 mmol, 1 mol/L solution in hexane) was added to the solution and the reaction was continued for additional 30 min. The reaction was quenched at - 78° by methanol (1 mL). Saturated aqueous sodium potassium tartrate (3 mL) was added to the mixture. After stirring for 1 h, the organic layer was separated, and the aqueous phase was extracted with methylene chloride (20 mL). The combined organic layers were washed with water (5 mL), brine (5 mL) and dried. After concentration, the residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 3:1) to obtain **15** (0.34 g, 91%) as a colorless oil. $[\alpha]_D^{21}$ - 55.7°(c 1.79, $CHCl_3$). ν_{max}: 3446, 2893, 1736, 1423, 1244, 1169, 1105, 1040 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 6.43(dd, J = 11.3, 15.0 Hz, 1H), 6.10(dd, J = 11.3, 10.8 Hz, 1H), 5.80—5.61(m, 2H), 5.60—5.44(m, 2H), 4.72(d, J = 7.0 Hz, 1H), 4.62(d, J = 7.2 Hz, 1H), 4.22—4.12(m, 1H), 4.08(brs, 2H), 3.92—3.77(m, 1H), 3.64—3.48(m, 4H), 3.38(s, 3H), 2.93—2.75(m, 4H), 2.72—2.46(m, 2H), 2.41—2.20(m, 2H), 2.16—2.04(m, 1H), 2.0—1.75(m, 1H). δ_C(300 MHz, $CDCl_3$): 133.9, 132.0, 130.2, 128.4, 127.7, 126.9, 92.4, 76.2, 71.6, 70.8, 66.7, 63.2, 58.9, 38.0, 33.4, 30.2(2C), 25.5. EIMS m/z(%): 374(M^+, 0.1), 331(6), 303(49), 259(40), 243(37), 171(31), 119(100).

(2*E*,6*E*,8*Z*,5*S*)-10-(1′,3′-*dithian*-2′-*yl*)-5-*methoxyethoxymethoxyl-deca*-2,6,8-*trienal dimethyl acetal* (**3**)

To a stirred solution of oxalyl chloride (92 μL, 1.05 mmol) in CH_2Cl_2 (5 mL) at - 78℃ was added dropwise, over 10 min, DMSO (0.148 mL, 2.09 mmol) in CH_2Cl_2 (3 mL). Upon complete addition, the mixture was stirred at - 78℃ for 15 min, then **15** (195 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 10 min. After stirring for 1h, triethylamine (0.4 mL, 2.88 mmol) was added dropwise while the reaction temperature was maintained at - 78℃. Stirring for 5 min at - 78℃, the reaction mixture was warmed slowly to 0℃ over 1.5 h. The reaction was quenched by addition of water (2 mL). The mixture was diluted with ethyl acetate (20 mL). The organic layer was separated, washed with water (2 mL) and saturated NaCl (5 mL), dried and concentrated. The purification of the residue oil by column chromatography on silica gel (petroleum ether: ethyl acetate, 5:1) gave the aldehyde (174 mg, 90%) as a yellow oil. ν_{max}: 2891, 1722, 1689, 1639, 1423, 1134, 1105, 1036 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 9.48(d, J = 7.9 Hz, 1H), 6.85(dt, J = 16.1, 7.1 Hz, 1H), 6.50(dd, J = 14.8, 11.1 Hz, 1H), 6.21—6.08(m, 2H), 5.54(dd, J = 15.2, 7.7 Hz,

2H), 4.75(d, J = 8.0 Hz, 1H), 4.64(d, J = 7.2 Hz, 1H), 4.36—4.25(m, 1H), 4.13—4.06(m, 1H), 3.79—3.71(m, 1H), 3.62—3.50(m, 3H), 3.37(s, 3H), 2.92—2.77(m, 4H), 2.70—2.47 (m, 4H), 2.18—2.07(m, 1H), 1.90—1.76(m 1H). δ_C(100 MHz, $CDCl_3$): 193.6, 153.7, 134.9, 132.7, 131.1, 129.9, 128.1, 92.7, 74.8, 71.6, 69.4, 67.1, 58.9, 47.2, 38.7, 33.5, 30.3(2C), 25.5. EIMS m/z(%): 257(5), 121(7), 119(100), 89(10).

The aldehyde (95 mg) was dissolved in methanol (5 mL). To the solution were added $HC(OMe)_3$ (5 mL) and p-toluenesulfonic acid (5 mg). The mixture was stirred for 30 min at room temperature and $NaHCO_3$ (3 mg) was added. The solution was filtered and the filtrate was concentrated. The residue oil was dissolved in ethyl acetate (20 mL). The solution was washed with aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried. After concentration, the crude product was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 8:1) to give acetal **3** (107 mg, 100%) as a pale yellow oil. $[\alpha]_D^{24}$ − 42.1°(c 0.77, $CHCl_3$). ν_{max}: 1423, 1304, 1109, 1047, 986, 906, 735, 569, 442 cm^{-1}. δ_H(400 MHz, C_6D_6): 6.55(dd, J = 15.2, 11.2 Hz, 1H), 6.12(dd, J = 11.4, 11.2 Hz, 1H), 5.89—5.79(m, 1H), 5.62(dd, J = 15.1, 7.4 Hz, 1H), 5.58—5.43(m, 2H), 4.72—4.59(m, 3H), 4.27—4.13(m, 1H), 3.77—3.67(m, 1H), 3.65—3.54(m, 1H), 3.54—3.46(m, 3H), 3.32(s, 3H), 3.25(s, 3H), 3.22(s, 3H), 2.98—2.75(m, 4H), 2.70—2.54(m, 2H), 2.42—2.25(m, 2H), 1.84—1.73(m, 1H). δ_C(300 MHz, C_6D_6): 134.7, 130.9, 130.5, 130.2, 128.3, 127.7, 102.9, 93.0, 76.0, 72.1, 67.3, 58.6, 52.1(2C), 50.6, 38.8, 33.9, 30.2(2C), 25.8. EIMS m/z(%): 418(M^+, 1), 313(2), 119(100), 89(45). HRMS Calcd for [M − OMEM]$^+$ $C_{16}H_{25}O_2S_2$: 313.1296, Found: 313.1290.

(2E,4E,4'R) Ethyl 5-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-penta-2,4-dienoate (**19**)

n-Butyllithium (24.10 mL, 1.45 mol/L, 35 mmol) was added dropwise to a cold solution of diisopropylamine (5.20 mL) in THF (40 mL) at 0℃. The solution was stirred for 20 min before triethyl 4-phosphonocrotonate (8.70 g, 35 mmol) was added. After stirring for 1 h, aldehyde **18** (3.10 g, 24 mmol) was added dropwise in THF (5 mL) to the mixture. Stirring was continued for 1 h at 0℃ and at room temperature for an additional hour. Saturated aqueous NH_4Cl was added to quench the reaction. The organic layer was separated. The aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined, washed with brine (5 mL), dried and concentrated. The residual oil was purified by column chromatography on silica gel (petroleum ether: ether, 25:1) to afford **19** (3.25 g, 63%) as a colorless oil. $[\alpha]_D^{20}$ + 34.6°(c 1.01, $CHCl_3$). ν_{max}: 3000, 1712, 1649, 1620, 1371, 1232, 1140, 1061 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.21(dd, J = 15.3, 11.2 Hz, 1H), 6.37(dd, J = 15.3, 11.2 Hz, 1H), 6.01(dd, J = 15.3, 6.7 Hz, 1H), 5.86(d, J = 15.4 Hz, 1H), 4.59—4.53(m, 1H), 4.15(q, J = 7.1 Hz, 2H), 4.09(dd, J = 8.2, 6.4 Hz, 1H), 3.58(t, J = 7.9 Hz, 1H), 1.43(s, 3H), 1.35(s, 3H), 1.24 (t, J = 7.1 Hz, 3H). EIMS m/z(%): 226(M^+, 18), 211(18), 196(12), 169(34), 123(40), 95 (90), 73(100).

(2E,4E,4'R)-5-[2',2'-Dimethyl-1',3'-dioxlolan-4'-yl]-penta-2,4-dienol (**20**)

To a slurry of $LiAlH_4$ (1.20 g, 31 mmol) in ether (120 mL) was added anhydrous $AlCl_3$ (1.13 g, 8.5 mmol) at 0℃. After stirring for 1 h, a solution of ester **19**(2.90 g, 13 mmol) in ether (50 mL) was added. The stirring was continued for 1 h. Ethyl acetate (15 mL) and water (1.2 mL) was successively added to destroy the excess of $LiAlH_4$. The mixture was filtered and the filtrate was washed with brine (30 mL) and dried. Purification of concentrated residue by flash chromatography on silica gel (petroleum ether: ether, 2:1) afforded **20** (2.28 g, 97%) as a colorless oil. ν_{max}: 3415, 2987, 2935, 2874, 1456, 1371, 1217, 1155, 1057 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 6.31—6.12(m, 2H), 5.84(dt, J = 14.8, 5.6 Hz, 1H), 5.66(dd, J = 14.4, 7.6 Hz, 1H), 4.53—4.48(m, 1H), 4.18(d, J = 5.6 Hz, 2H), 4.10(dd, J = 8.1, 6.3 Hz, 1H), 3.58(t, J = 8.1 Hz, 1H), 1.36(s, 3H), 1.32(s, 3H). EIMS m/z(%): 184(M^+, 6), 166(26), 81 (50), 73(100).

(S)-4-(5'-Bromo-penta-1',3'-dienyl)-2,2-dimethyl-dioxolane (**17**)

To a solution of alcohol **20** (0.96 g, 5.2 mmol) in

DMF (15 mL) was added (1.51 g, 5.7 mmol) triphenylphosphine. The solution was cooled to 0℃ and NBS (1.0 g, 5.6 mmol) was added in portions. After stirring for 30 min at room temperature, the reaction was quenched with methanol (0.5 mL). The solution was diluted with ether (50 mL), washed with water (10 mL), saturated Na_2CO_3 (10 mL) and brine (15 mL) successively. The organic layer was dried and concentrated. The residue was dissolved in hexane (60 mL) and allowed to stand in a freezer for 18 h. The solution was filtered and the filtrate was concentrated to afford the bromide **17** (1.20 g, 93%) as a colorless oil. The product was unstable on silica gel. $[\alpha]_D^{20}$ + 37.7° (*c* 1.26, $CHCl_3$). ν_{max}: 2987, 1693, 1373, 1213, 1059 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 6.34—6.20(m, 2H), 5.89(td, *J* = 15.0, 7.6 Hz, 1H), 5.70(dd, *J* = 15.1, 7.2 Hz, 1H), 4.53(dd, *J* = 14.0, 7.2 Hz, 1H), 4.08(dd, *J* = 8.0, 6.2 Hz, 1H), 4.00(d, *J* = 7.8 Hz, 2H), 3.57(t, *J* = 7.9 Hz, 1H), 1.41(s, 3H), 1.37(s, 3H). EIMS *m/z*(%): 246/248(M^+, 1), 231/233(4), 167(100), 109(42); HRMS Calcd for $C_{10}H_{15}{}^{79}BrO_2$, $C_{10}H_{15}{}^{81}BrO_2$: 246.0255, 248.0235; Found: 246.0269, 248.0217.

(R)-Methyl 3-t-butyldimethylsilyloxy-butanoate (**22**)

To a solution of alcohol **21** (0.67 g, 5.67 mmol) in DMF (10 mL) were added imidazole (0.96 g, 14.12 mmol) and TBSCl (1.27 g, 8.46 mmol) at 0℃. The mixture was stirred for 6 h and then diluted with ether (50 mL), washed with water (10 mL) and dried. After concentration, the residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate, 25:1) to give **22** (1.09 g, 84%) as a colorless oil. $[\alpha]_D^{18}$ - 32.1° (*c* 1.42, $CHCl_3$). ν_{max}: 1743, 1437, 1377, 1257, 1086 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 4.30—4.21(m, 1H), 3.64(s, 3H), 2.45(dd, *J* = 14.3, 7.8 Hz, 1H), 2.34(dd, *J* = 14.3, 5.3 Hz, 1H), 1.17(d, *J* = 6.2 Hz, 3H), 0.83(s, 9H), 0.03 (s, 3H), 0.01(s, 3H). EIMS *m/z*(%): 232(M^+), 217(3), 175(100), 133(52), 89(98). Anal. $C_{11}H_{24}O_3Si$. Calcd: C, 56.85; H, 10.40. Found: C, 56.34; H, 10.29.

(R)-3-Tert-Butyldimethylsilyloxy-butanol (**23**)

Ester **22** (1.09 g, 4.68 mmol) was added dropwise to a slurry of $LiAlH_4$ (0.40 g, 10.32 mmol) in ether (20 mL) at - 78℃. After stirring for 1 h, water (0.40 mL), 15% NaOH (0.40 mL) and water (1.20 mL) were successively added to destroy the excess of $LiAlH_4$. The mixture was filtered and the filtrate was washed with brine (5 mL) and dried. Concentration and purification of the residue by flash chromatography on silica gel (petroleum ether: ethyl acetate, 15:1) afforded **23** (0.95 g, 98%) as a colorless oil. $[\alpha]_D^{24}$ - 31.2° (*c* 0.67, $CHCl_3$). ν_{max}: 3354, 1473, 1375, 1256, 1028 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 3.99—3.91(m, 1H), 3.4—3.8(m, 2H), 3.10(brs, 1H), 1.62—1.51(m, 2H), 1.13(d, *J* = 6.2 Hz, 3H), 0.90(s, 9H), 0.05(s, 6H). EIMS *m/z*(%): 203(M^+ - 1), 189(1), 147(33), 119(100), 75(96). Anal. $C_{10}H_{24}O_2Si$. Calcd: C, 58.77; H, 11.83. Found: C, 58.68; H, 11.70.

(R)-1-Bromo-3-tert-butyldimethylsilyloxy-butane (**24**)

Bromine (0.40 g, 2.5 mmol) was added dropwise to a stirred solution of **23** (0.48 g, 2.4 mmol) and triphenylphosphine (0.66 g, 2.5 mmol) in DMF (10 mL) at 0℃. After warming to room temperature, the mixture was stirred for 1 h and diluted with ether (50 mL), washed with water (10 mL), dried and concentrated. Purification of the residue by column chromatography on silica gel (petroleum ether: ether, 50:1) gave **24** (0.51 g, 80%) as a colorless oil. $[\alpha]_D^{18}$ - 53.3° (*c* 1.22, $CHCl_3$). ν_{max}: 1471, 1257, 1130, 1072, 972 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 4.02—3.93 (m, 1H), 3.47—3.43(m, 2H), 2.0—1.83(m, 2H), 1.14(d, *J* = 6.2 Hz, 3H), 0.87(s, 9H), 0.07(s, 3H), 0.06 (s, 3H). EIMS *m/z*(%): 266/268(M^+), 251/253 (2), 209/211(61), 181/183(100).

(3E,5E,2S,10R)-1,2-Isopropylidenedioxy-10-tert-butyldimethylsilyloxy-hendeca-3,5-diene (**25**) *and (3E,2S,8R)-1,2-Isopropylidenedioxy-8-tert-butyldimethylsilyloxy-5-vinyl-3-nonene* (**26**)

To a slurry of powder magnesium (0.21 g, 8.28 mmol) in THF (12 mL) was added 1,2-dibromoethane (0.02 mL) to initiate the reaction, then bromide **24** (1.60 g, 5.99 mmol) in THF (8 mL) was added dropwise under refluxing over 15 min. After refluxing for additional 15 min, the mixture was added to a solution of

Li_2CuCl_4 (0.1 mol/L, 2.0 mL, 0.2 mmol) and bromide **16** (0.58 g, 2.35 mmol) in THF (10 mL) stirred at −78℃. After stirring at −78℃ for 20 min, the mixture was warmed to 0℃ and kept at that temperature for additional 2 h, and then at room temperature overnight. The reaction was quenched by saturated aqueous NH_4Cl (5 mL). The mixture was diluted with diethyl ether (50 mL), washed with water (10 mL) and dried. After concentration, the residue was purified by column chromatography on silica gel (petroleum ether: ether, 30:1) to afford an inseparable mixture **25** and **26** (0.52 g, 63%) as a colorless oil. GC-MS (*m/z*) **25**: **26** = 2:1; **25**: 354(M^+), 297(3), 239(6), 185(11), 159(20), 147(43), 119(48), 105(66), 75(100). **26**: 354(M^+), 239(23), 147(18), 105(27), 91(26), 75(100). δ_H(300 MHz, $CDCl_3$): 6.25(dd, J = 15.3, 10.4 Hz, **25**, 1H), 6.02(dd, J = 15.1, 10.4 Hz, **25**, 1H), 5.76—5.36(m, 4H), 5.03—4.92(m, **26**, 2H), 4.54—4.43(m, 1H), 4.10—4.02(m, 1H), 3.81—3.69(m, 1H), 3.60—3.50(m, 1H), 2.70—2.60(m, **26**, 1H), 2.10—2.02(m, **25**, 2H), 1.43(s, 3H), 1.39(s, 3H), 1.07(d, J = 6.2 Hz, 3H), 0.90(s, 9H), 0.02(s, 6H).

(R)-Methyl 5-p-methoxybenzyloxyl-hexanoate (**28**)

To a stirred solution of **27** (0.573 g, 3.92 mmol) in CH_2Cl_2 (13 mL) was added *p*-methoxybenzyl trichloroacetimidate (1.22 mL, 5.85 mmol) in CH_2Cl_2 (2 mL) and a catalytic amount of CSA (50 mg, 0.22 mmol). After stirring for 20 h, the reaction was quenched by Et_3N (35 μL). The mixture was diluted with ether (150 mL), washed with water (15 mL), aqueous $NaHCO_3$ (10 mL) and brine (20 mL) and dried. Concentration and purification of the residue by column chromatography on silica gel (petroleum ether: ether, 6:1) afforded **28** (0.96 g, 92%) as a pale yellow oil. $[\alpha]_D^{24}$ −18.3°(*c* 1.08, $CHCl_3$). ν_{max}: 1740, 1612, 1514, 1248, 1172, 1036 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.24(d, J = 8.5 Hz, 2H), 6.85(d, J = 8.6 Hz, 2H), 4.48(d, J = 11.3 Hz, 1H), 4.35(d, J = 11.2 Hz, 1H), 3.78(s, 3H), 3.65(s, 3H), 3.53—3.46(m, 1H), 2.30(t, J = 8.1 Hz, 2H), 1.4—1.8(m, 4H), 1.17(d, J = 5.9 Hz, 3H). EIMS *m/z*(%): 266(M^+, 1), 137(91), 121(100). Anal. $C_{15}H_{22}O_4$. Calcd: C, 67.65; H, 8.33. Found: C, 67.90; H, 8.40.

(R)-5-p-Methoxybenzyloxyl-hexanol (**29**)

To a solution of ester **28** (1.40 g, 5.27 mmol) in CH_2Cl_2 (50 mL) stirred at −78℃ was added DIBAL (13.1 mL, 1 mol/L solution in hexane, 13.10 mmol) over 10 min. After stirring for 30 min, the reaction was quenched by methanol (4 mL). The mixture was warmed to room temperature and saturated aqueous sodium potassium tartrate (20 mL) was added. After stirring for 1 h, the organic layer was separated and the aqueous phase was extracted with methylene chloride (50 mL). The combined organic layers were washed with water (15 mL) and brine (20 mL) and dried. Concentration and purification of the residue by column chromatography on silica gel (petroleum ether: ether, 1:1) afforded **29** (1.23 g, 98%) as a colorless oil. $[\alpha]_D^{24}$ −20.1°(*c* 1.17, $CHCl_3$). ν_{max}: 3404, 1612, 1514, 1464, 1248, 1036 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.24(d, J = 8.6 Hz, 2H), 6.86(d, J = 8.6 Hz, 2H), 4.49(d, J = 11.2 Hz, 1H), 4.35(d, J = 11.4 Hz, 1H), 3.78(s, 3H), 3.60(t, J = 6.3 Hz, 2H), 3.54—3.45(m, 1H), 1.75—1.32(m, 4H), 1.16(d, J = 6.2 Hz, 3H). EIMS *m/z*(%): 238(M^+, 7), 137(54), 121(100). Anal. $C_{14}H_{22}O_3$. Calcd: C, 70.65; H, 9.30. Found: C, 70.45; H, 9.42.

(R)-5-p-Methoxybenzyloxy-1-p-toluenesulfonyl-hexane (**31**)

To a stirred solution of **29** (1.17 g, 4.90 mmol) in toluene (100 mL) was added iodine (5.00 g, 19.60 mmol), triphenylphosphine (4.59 g, 17.50 mmol), and imidazole (1.17 g, 17.20 mmol) successively. The mixture was stirred at room temperature for 1 h. Saturated aqueous $NaHCO_3$ (25 mL) was added, stirring was continued for 1 h. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (15 mL), water (15 mL), and brine (20 mL) then dried and concentrated. To the solution of the residue in DMF (40 mL) were added sodium *p*-toluenesulfinate (1.69 g, 9.50 mmol) and *n*-tetrabutylammonium bromide (72 mg). The mixture was stirred at 40℃ for 2 h before being cooled to room temperature and diluted with ether (100 mL). The organic layer was washed with water (20 mL), dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: ether, 3:2) to give compound **31** (1.47 g, 80% for two steps) as a

colorless oil: $[\alpha]_D^{24}$ - 7.0°(*c* 1.55, $CHCl_3$). ν_{max}: 1612, 1514, 1302, 1248, 1143, 1088, 1036 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 7.74(d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.20(d, *J* = 8.5 Hz, 2H), 6.83(d, *J* = 8.5 Hz, 2H), 4.44(d, *J* = 11.3 Hz, 1H), 4.28(d, *J* = 11.3 Hz, 1H), 3.77(s, 3H), 3.47—3.38(m, 1H), 3.02(t, *J* = 8.0 Hz, 2H), 2.42(s, 3H), 1.60—1.78(m, 2H), 1.32—1.53 (m, 4H), 1.11(d, *J* = 6.2 Hz, 3H). EIMS *m/z* (%): 376(M^+, 8), 183(11), 137(57), 121(100). Anal. $C_{21}H_{28}O_4S$. Calcd: C, 66.99; H, 7.50. Found: C, 66.70; H, 7.61.

(3E,5E,2S,10R)-1,2-Isopropylidenedioxy-10-p-methoxybenzyloxyl-hendeca-3,5-diene (**25a**) *and (3E, 5Z, 2S, 10R)-1,2-isopropylidenedioxy-10-p-methoxybenzyloxyl-hendeca-3,5-diene* (**25b**)

n-BuLi (0.19 mL, 1.1 mol/L, 0.21 mmol) was added dropwise to a solution of sulfone **31** (75 mg, 0.20 mmol) in THF (3 mL) stirred at - 78° under N_2. The mixture was stirred for 10 min, then aldehyde **32** (28 mg, 0.18 mmol) in THF (1 mL) was added dropwise. After stirring for 1 h at - 78°, the reaction was quenched by the addition of saturated aqueous NH_4Cl (0.2 mL). The mixture was diluted with ether (20 mL). The organic layer was washed with brine (5 mL), dried and concentrated. Purification of the residue by column chromatography on silica gel (petroleum ether: ether, 1:2) afforded a mixture of diastereomers **33** (81 mg, 85%).

To the solution of crude mixture **33** (64 mg, 0.12 mmol) in ethyl acetate (2 mL) and methanol (0.45 mL) at - 20℃ was added Na_2HPO_4 (64 mg, 0.12 mmol) and Na/Hg (276 mg, 6%, 0.72 mmol). After stirring at - 20℃ for 30 min, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether: ether, 6:1) to afford a mixture of **25a** and **25b** (34 mg, 79%) as a colorless oil. **25a**:**25b** = 3.5:1. δ_H(400 MHz, $CDCl_3$): 7.24(d, *J* = 8.5 Hz, 4H), 6.85(d, *J* = 8.5 Hz, 4H), 6.56(dd, *J* = 15.1, 11.1 Hz, 1H, 25b), 6.26(dd, *J* = 15.1, 10.4 Hz, 1H, **25a**), 6.03—5.94(m, 2H, **25a** and **25b** overlap), 5.70(td, 1H, *J* = 15.1, 6.8 Hz, **25a**), 5.59(dd, *J* = 15.1, 7.9 Hz, 1H, **25b**), 5.53—5.42(m, 2H, **25a** and **25b** overlap), 4.54—4.48(m, 4H), 4.35(d, *J* = 11.3 Hz, 2H), 4.09—4.02(m, 2H), 3.78(s, 6H), 3.60—3.53(m, 2H), 3.51—3.42(m, 2H), 2.19—2.12(m, 1H, **25b**), 2.09—1.98(m, 1H, **25a**), 1.3—1.6(m, 8H), 1.41(s, 6H), 1.38(s, 6H), 1.15(d, *J* = 6.2 Hz, 6H).

(R)-Methyl 3-p-methoxybenzyloxyl-butanoate (**36**)

To a stirred solution of **21** (6.42 g, 54.40 mmol) in CH_2Cl_2 (100 mL) was added *p*-methoxybenzyl trichloroacetimidate (17.1 mL, 82.00 mmol) in CH_2Cl_2 (100 mL) and a catalytic amount of CSA (0.63 g, 2.72 mmol). After stirring for 24 h, the reaction was quenched by the addition of Et_3N (0.4 mL). The mixture was diluted with ether (150 mL), washed with water (10 mL), $NaHCO_3$ (10 mL) and brine (20 mL) and dried. Concentration and purification of the residue by column chromatography on silica gel (petroleum ether: ether, 6:1) afforded **36** (11.60 g, 90%) as a pale yellow oil. $[\alpha]_D^{22}$ - 22.3°(*c* 1.05, $CHCl_3$). ν_{max}: 1740, 1614, 1514, 1302, 1248, 1174, 1086 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.23(d, *J* = 8.6 Hz, 2H), 6.85(d, *J* = 8.6 Hz, 2H), 4.48(d, *J* = 11.1 Hz, 1H), 4.41 (d, *J* = 11.1 Hz, 1H), 4.0—3.95(m, 1H), 3.78 (s, 3H), 3.66(s, 3H), 2.62(dd, *J* = 15.4, 7.1 Hz, 1H), 2.40(dd, *J* = 15.5, 6.6 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H). EIMS *m/z*(%): 238(M^+, 3), 137(100), 121(54), 109(10), 84(12). Anal. $C_{13}H_{18}O_4$. Calcd: C, 65.55; H, 7.56. Found: C, 66.14; H, 7.59.

(R)-3-p-Methoxybenzyloxyl-butanol (**37**)

To a solution of ester **36** (3.10 g, 13.00 mmol) in CH_2Cl_2 (50 mL) stirred at - 78℃ was added DIBAL (32.00 mL, 1 mol/L solution in hexane, 32.00 mmol) over 10 min. The mixture was stirred for 30 min and then quenched by the addition of methanol (12 mL). Saturated aqueous sodium potassium tartrate (15 mL) was added. After stirring for 1 h, the organic layer was separated and the aqueous phase was extracted with methylene chloride (100 mL). The combined organic layers were washed with water (10 mL) and brine (15 mL) and dried. Concentration and purification of the residue by column chromatography on silica gel (petroleum ether: ether, 2:1) afforded **37** (2.71 g,

99%) as a colorless oil. $[\alpha]_D^{22}$ - 51.8°(*c* 0.84, $CHCl_3$). ν_{max}: 3380, 1612, 1514, 1248, 1036 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.24(d, *J* = 8.6 Hz, 2H), 6.86(d, *J* = 8.6 Hz, 2H), 4.55(d, *J* = 11.1 Hz, 1H), 4.35(d, *J* = 11.1 Hz, 1H), 3.78(s, 3H), 3.65—3.58(m, 1H), 3.31—3.22(m, 2H), 2.08—1.87(m, 2H), 1.22(d, *J* = 6.2 Hz, 3H). EIMS *m/z*(%): 210(M^+, 7), 137(99), 121(100), 84(50). Anal. $C_{12}H_{18}O_3$. Calcd: C, 68.55; H, 8.63. Found: C, 68.05; H, 8.44.

(*R*)-1-*Iodo*-3-*p*-*methoxybenzyloxyl*-*butane* (**38**)

To a stirred solution of **37** (2.71 g, 12.90 mmol) in toluene (260 mL) were added iodine (13.60 g, 53.30 mmol), triphenylphosphine (12.50 g, 47.70 mmol) and imidazole (3.18 g, 46.70 mmol) successively. The mixture was stirred at room temperature for 1 h. Saturated aqueous $NaHCO_3$ (50 mL) was added. Stirring was continued for an additional 20 min. The organic layer was separated, washed with saturated aqueous $Na_2S_2O_3$ (50 mL), water (20 mL), and brine (50 mL), dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: ether, 7:1) to afford **38** (3.70 g, 90%) as a colorless oil: $[\alpha]_D^{18}$ -69.6°(*c* 1.22, $CHCl_3$). ν_{max}: 1612, 1514, 1248, 1036 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.26(d, *J* = 8.6 Hz, 2H), 6.87(d, *J* = 8.6 Hz, 2H), 4.53(d, *J* = 11.0 Hz, 1H), 4.37(d, *J* = 11.0 Hz, 1H), 3.79(s, 3H), 3.78—3.68(m, 3H), 1.76—1.71(m, 2H), 1.20(d, *J* = 5.9 Hz, 3H). EIMS *m/z*(%): 320(M^+, 22), 121 (100). Anal. $C_{12}H_{17}IO_2$. Calcd: C, 45.02; H, 5.35. Found: C, 44.99; H, 5.46.

(*R*)-3-*p*-*Methoxybenzyloxyl*-1-*phenylsulfonyl*-*butane* (**39a**)

To a solution of compound **38** (1.22 g, 3.81 mmol) in DMF (22 mL) were added sodium phenylsulfinate (0.94 g, 5.73 mmol) and *n*-tetrabutylammonium bromide (0.07 g). After stirring at 40℃ for 3.5 h, the mixture was cooled to room temperature, diluted with ether (100 mL), washed with water (15 mL), dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: ether, 3:2) to afford compound **39a** (1.08 g, 85%) as a colorless oil. $[\alpha]_D^{22}$ - 9.26°(*c* 1.08, $CHCl_3$). ν_{max}: 3063, 2970, 1612, 1585, 1514, 1446, 1306, 1248, 1175, 1148, 1086, 1034 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.86 (d, *J* = 8.8 Hz, 2H), 7.69—7.58(m, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.16(d, *J* = 8.6 Hz, 2H), 6.83(d, *J* = 8.7 Hz, 2H), 4.42(d, *J* = 11.2 Hz, 1H), 4.24(d, *J* = 11.1 Hz, 1H), 3.77(s, 3H), 3.62—3.52(m, 1H), 3.30—3.18(m, 1H), 3.15—3.03(m, 1H), 2.0—1.89(m, 1H), 1.88—1.73(m, 1H), 1.14(d, *J* = 6.2 Hz, 3H). δ_C: 159.1, 139.0, 133.5, 130.2, 129.1, 127.8, 113.7, 72.1, 69.9, 55.1, 52.6, 29.3, 19.2. EIMS *m/z*(%): 334(M^+, 5), 262(5), 197(1), 143(8), 137(100), 121(54). HRMS Cacld. for $C_{18}H_{22}O_4S$: 334.1239, Found: 334.1240.

(3*E*, 5*E*, 2*S*, 10*R*)-1, 2-*Isopropylidenedioxy*-10-*p*-*methoxybenzyoxyl*-*undeca*-3,5-*diene* (**25a**)

To a solution of **39a** (1.05 g, 3.14 mmol) in THF (25 mL) was added dropwise LiHMDS (6.31 mL, 6.31 mmol, 1 mol/L solution in hexane) stirred at -78℃. After stirring for 20 min, the bromide **17** (0.80 g, 3.24 mmol) was added. The reaction mixture was stirred at -78℃ for 30 min. Saturated aqueous NH_4Cl (5 mL) was added. The mixture was diluted with ether (100 mL). The organic layer was washed with water (10 mL) and brine (15 mL), dried and concentrated. Purification of the residue by column chromatography on silica gel (petroleum ether: ether, 3:1) afforded **40a** (1.54 g) as a mixture of diastereomers. To the solution of the mixture in MeOH (45 mL) were added Na_2HPO_4 (6.54 g, 46.06 mmol) and Na/Hg (11.8 g, 6%, 30.78 mmol) at 0℃. The mixture was stirred at 0℃ for 1.5 h, diluted with ether (100 mL) and filtered through a short silica gel column. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether: ether, 6:1) to afford **25a** (0.76 g, 67%) as a colorless oil. $[\alpha]_D^{15}$ - 3.1°(*c* 0.84, $CHCl_3$). ν_{max}: 1614, 1514, 1371, 1248, 1059, 991 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.26(d, *J* = 8.6 Hz, 2H), 6.87(d, *J* = 18.6 Hz, 2H), 6.26(dd, *J* = 15.4, 10.4 Hz, 1H), 6.02(dd, *J* = 15.0, 10.3 Hz, 1H), 5.70(dt, *J* = 15.2, 7.5 Hz, 1H), 5.52(dd, *J* = 15.4, 7.9 Hz, 1H), 4.53—4.46(m, 2H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.07(dd, *J* = 7.9, 6.1 Hz, 1H), 3.80(s, 3H), 3.58(t, *J* = 7.9 Hz, 1H),

3.50—3.42(m, 1H), 2.10—2.01(m, 2H), 1.60—1.34(m, 4H), 1.43(s, 3H), 1.39(s, 3H), 1.17 (d, J = 6.1 Hz, 3H). δ_C(75 MHz, $CDCl_3$): 159.0, 136.3, 134.1, 131.1, 129.3, 129.2, 127.5, 113.7, 109.2, 77.3, 74.2, 69.9, 69.5, 55.2, 36.2, 32.6, 26.7, 25.9, 25.0, 19.6. EIMS *m/z* (%): 360(M^+, 3), 302(1), 284(1), 149(6), 121 (100), 79(10). HRMS Cacld. for $C_{22}H_{32}O_4$: 360.2301, Found: 360.2318.

(3*E*, 5*E*, 2*S*, 10*R*)-2-*Hydroxy*-10-*p*-*methoxybenzyloxyl*-*undeca*-3,5-*dienol* (**41**)

To a solution of **25a** (755 mg, 2.10 mmol) in MeOH (60 mL) was added a catalytic amount of CSA (30 mg, 0.13 mmol). After stirring for 2 h, $NaHCO_3$ (11 mg) was added. The mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: ether, 1:5) to give **41** (660 mg, 98%) as a colorless oil: $[\alpha]_D^{15}$ −13.3°(*c* 1.42, $CHCl_3$). ν_{max}: 3383, 1659, 1612, 1514, 1248, 1070, 1036 cm^{-1}. δ_H(300 MHz, $CDCl_3$): 7.24(d, J = 8.0 Hz, 2H), 6.85(d, J = 8.0 Hz, 2H), 6.23(dd, J = 15.1, 10.4 Hz, 1H), 5.98(dd, J = 15.1, 10.4 Hz, 1H), 5.67(dt, J = 15.1, 7.4 Hz, 1H), 5.49(dd, J = 15.3, 6.3 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.34(d, J = 11.3 Hz, 1H), 4.25—4.15(m, 1H), 3.77(s, 3H), 3.35—3.62 (m, 3H), 2.86—3.20(m, 2H), 2.15—1.99(m, 2H), 1.31—1.60(m, 4H), 1.15(d, J = 6.1 Hz, 3H). δ_C(100 MHz, $CDCl_3$): 159.0, 135.7, 132.5, 131.0, 129.5, 129.2, 128.9, 113.7, 74.3, 72.9, 69.9, 66.4, 55.3, 36.2, 32.6, 25.1, 19.6. EIMS *m/z*(%): 320(M^+, 1), 260(2), 242(1), 204(1), 121(100). HRMS Cacld. for $C_{19}H_{28}O_4$: 320.1987, Found: 320.1986.

(3*E*, 5*E*, 2*S*, 10*R*)-2-*Hydroxy*-10-*p*-*methoxybenzyloxyl*-1-*p*-*toluenesulfonyloxy*-*undeca*-3,5-*diene* (**42**)

To a solution of diol **41** (55 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) stirred at 0℃ were added triethylamine (42 μL, 0.30 mmol) and *p*-toluenesulfonyl chloride (35 mg, 0.18 mmol). After stirring at 0℃ for 5 h, water (0.3 mL) was added. The mixture was stirred at room temperature for 1h, diluted with Et_2O (20 mL). The organic layer was washed with water (2 mL) and brine (5 mL), dried and concentrated. The residual oil was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 4:1) to give **42** (56 mg, 69%) as a colorless oil: $[\alpha]_D^{18}$ −5.9°(*c* 0.60, MeOH). ν_{max}: 3400, 1612, 1514, 1362, 1248, 1176 cm^{-1}. δ_H(300 MHz, $CDCl_3$): 7.82(d, J = 8.5 Hz, 2H), 7.34(d, J = 8.5 Hz, 2H), 7.25(d, J = 8.5 Hz, 2H), 6.86(d, J = 8.5 Hz, 2H), 6.25(dd, J = 15.7, 10.2 Hz, 1H), 5.94(dd, J = 15.1, 10.2 Hz, 1H), 5.70(dt, J = 15.1, 7.1 Hz, 1H), 5.40(dd, J = 15.1, 6.3 Hz, 1H), 4.48(d, J = 11.2 Hz, 1H), 4.35—4.45(m, 1H), 4.35(d, J = 11.2 Hz, 1H) 4.06—3.99(m, 1H), 3.92—3.84(m, 1H), 3.79(s, 3H), 3.52—3.40(m, 1H), 2.44(s, 3H), 2.1—2.0(m, 2H), 1.55—1.30(m, 4H), 1.16(d, J = 6.2 Hz, 3H). δ_C(100 MHz, $CDCl_3$): 159.0, 144.9, 136.8, 133.6, 132.7, 131.1, 129.9, 129.13, 127.9, 126.3, 113.7, 74.2, 73.1, 70.0, 69.9, 55.2, 36.1, 32.5, 25.0, 21.6, 19.5.

(3*E*,5*E*,2*S*,10*R*)-2-*tert*-*Butyldimethylsilyloxy*-10-*p*-*methoxybenzyloxyl*-1-*p*-*toluenesulfonyloxy*-*undeca*-3,5-*diene* (**43**)

Alcohol **42** (150 mg, 0.32 mmol) and triethylamine (0.26 mL, 1.87 mmol) were dissolved in CH_2Cl_2(9 mL) at 0℃, then *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.22 mL, 0.96 mmol) was added dropwise. The mixture was stirred at 0℃ for 30 min before being quenched by saturated aqueous NH_4Cl (0.5 mL). The mixture was diluted with ether (20 mL), washed successively with water (5 mL) and brine (5 mL). The organic layer was dried and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether: ether, 10:1) to yield silyl ether **43** (173 mg, 93% yield) as a colorless oil. $[\alpha]_D^8$ +2.4°(*c* 1.84, MeOH). ν_{max}: 1614, 1514, 1464, 1363, 1250, 1178, 1097 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.75(d, J = 8.1 Hz, 2H), 7.31(d, J = 8.1 Hz, 2H), 7.24(d, J = 8.6 Hz, 2H), 6.85(d, J = 8.5 Hz, 2H), 6.15(dd, J = 15.2, 10.5 Hz, 1H), 5.92 (dd, J = 15.1, 10.5 Hz, 1H), 5.69—5.58 (m, 1H), 5.34(dd, J = 15.3, 6.1 Hz, 1H), 4.47(d, J = 11.3 Hz, 1H), 4.40—4.31(m, 2H), 3.86(dd, J = 10.0, 4.5 Hz, 1H), 3.89—3.76(m, 4H), 3.50—3.44(m, 1H), 2.42(s, 3H), 2.1—2.0(m, 2H), 1.3—1.6(m, 4H), 1.15(d, J = 6.2 Hz,

3H), 0.84(s, 9H), 0.09(s, 3H), 0.03(s, 3H). δ_C ($CDCl_3$): 159.0, 144.6, 135.9, 133.0, 132.6, 131.1, 129.7 (2C), 129.2, 129.1 (2C), 128.1, 127.9 (2C), 113.7 (2C), 74.2, 73.2, 70.9, 69.9, 55.2, 36.2, 32.6, 25.7 (3C), 25.0, 21.6, 18.1, -4.7, -4.9. Anal. $C_{32}H_{48}O_6SSi$. Calcd: C, 65.27; H, 8.22. Found: C, 65.41; H, 8.36.

(3E,5E,2S,10R)-2-tert-Butyldimethylsilyloxy-1-iodo-10-p-methoxybenzyloxyl-undeca-3,5-diene (**4**)

To a stirred solution of **43** (154 mg, 0.26 mmol) in acetone (8 mL) were added NaI (79 mg, 0.52 mmol) and *i*-Pr_2NEt (91 μL, 0.52 mmol). The reaction mixture was heated to reflux for 24 h. After being cooled to room temperature, the mixture was diluted with Et_2O (20 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried and concentrated. The residual oil was purified by flash column chromatography on silica gel (petroleum ether: ether, 25:1) to give **4** (86 mg, 60%) as a colorless oil: $[\alpha]_D^{18}$ -27.6° (*c* 0.72, MeOH). ν_{max}: 614, 1514, 1248, 1097, 1040, 991 cm^{-1}. δ_H(400 MHz, $CDCl_3$): 7.76(d, *J* = 8.7 Hz, 2H), 6.87(d, *J* = 8.7 Hz, 2H), 6.16(dd, *J* = 15.1, 10.4 Hz, 1H), 6.00(dd, *J* = 15.1, 10.4 Hz, 1H), 5.69(dt, *J* = 15.0, 7.0 Hz, 1H), 5.50 (dd, *J* = 15.1, 6.6 Hz, 1H), 4.49(d, *J* = 11.2 Hz, 1H), 4.37(d, *J* = 11.2 Hz, 1H), 4.25—4.16(m, 1H), 3.80(s, 3H), 3.56—3.43(m, 1H), 3.16(d, *J* = 6.0 Hz, 2H), 2.15—2.0(m, 2H), 1.3—1.7 (m, 4H), 1.17(d, *J* = 6.1 Hz, 3H), 0.91(s, 9H), 0.08(s, 3H), 0.03(s, 3H). δ_C(100 MHz, $CDCl_3$): 159.0, 135.8, 131.9, 131.5, 131.2, 129.4, 129.2 (2C), 113.7, 74.3, 73.2, 69.9, 55.3, 36.2, 32.7, 25.9, 25.1, 19.6, 18.2, 13.6, -4.3, -4.7; Anal. $C_{25}H_{41}IO_3Si$. Calcd: C, 55.14; H, 7.59. Found: C, 55.47; H, 7.70.

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20. Chemical shifts and coupling constants of the diene segments in compounds **25a** and **25b**:**25a** δ 16-H 5.50, 17-H 6.26, 18-H 6.01, 19-H 5.70, 20-H 2.05, $J_{16,17}$ = 15.1 Hz, $J_{17,18}$ = 10.4 Hz, $J_{18,19}$ = 15.1 Hz, $J_{19,20}$ = 6.8 Hz; **25b** 16-H 5.59, 17-H 6.56, 18-H 5.98, 19-H 5.45, 20-H 2.14, $J_{16,17}$ = 15.1 Hz, $J_{17,18}$ = 11.1 Hz, $J_{18,19}$ = 11.3 Hz, $J_{19,20}$ = 6.8 Hz.

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