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Stereoselective preparation of trisubstituted (*Z*)-alkenes; synthesis of the C17–C27 fragment of (−)-laulimalide

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Abstract—A Ni-catalyzed cross-coupling reaction of (*Z*)-5-(*tert*-butyldiphenylsilyl)oxy-3-bromo-1-trimethylsilyl-3-penten-1-yne (**1**) with alkyl Grignard reagent gives (*Z*)-3-alkyl-5-(*tert*-butyldiphenylsilyl)oxy-1-trimethylsilyl-3-penten-1-ynes (**2**) stereospecifically in good yields. The (*Z*)-enyne **2a** is transformed in four steps to (*Z*)-3-methyl-5-silyloxy-3-pentenal (**3**), which is coupled with ketophosphonate **4** to give enone **13**. The η-hydroxyallyl methanesulfonate derived from **13** is cyclized to 3,6-dihydro[2*H*]pyran by an intramolecular SN2′ reaction stereoselectively, furnishing a C17–C27 carbon unit of (−)-laulimalide.

1. Introduction

Stereocontrolled synthesis of tricarbon-substituted (*Z*)-alkenes is important for the synthesis of organic molecules. Since the configuration of the (*Z*)-structural unit in the molecule can fix the shape, two substituted carbon branches located in the *cis* relation of olefin play a specific role either in the constitution of the macro-lactone ring structure or to fix the conformation of acyclic structure, as shown in Figure 1. In fact, a methyl substituted (*Z*)-alkenyl unit can be observed in the structures of biologically important natural products, e.g. in macrolides, such as (−)-laulimalide, (−)-zampanolide, haterumalide NA, and (+)-lasonolide A[1] as well as in acyclic marine natural products, such as (−)-discodermolide, callystatin A and (−)-ratjadone.[2]

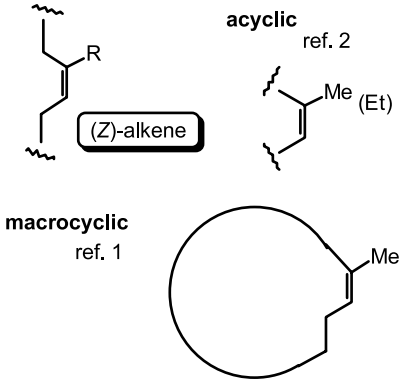
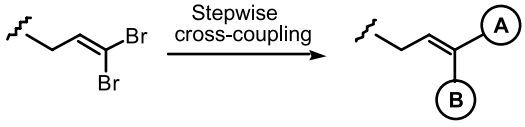


Figure 1.

Stepwise stereospecific cross-coupling of 1,1-dibromo-1-alkene, as shown in Scheme 1, is a potential method for the geometrically controlled synthesis of trisubstituted alkenes.[3] We reported carbon conjugated trisubstituted alkenes by this method.[4] More recently, we have reported that Pd-catalyzed cross-coupling reaction of 3-bromo-3-en-1-yne can afford both the (*E*)- or (*Z*)-trisubstituted alkenes stereoselectively.[5] In particular, isomerization of the (*Z*)-alkenyl–palladium complex to the (*E*)-alkenyl–palladium complex via cumulenyl–palladium complex intermediate in CH_2Cl_2 or DMF and subsequent cross-coupling in Sonogashira and Stille coupling is especially useful for the synthesis of the tricarbon-substituted conjugated (*Z*)-alkenyl unit, as shown in Scheme 2. After finding this unique isomerization, we have reinvestigated our results obtained previously by Ni-catalyzed Kumada–Tamao–Corriu coupling reaction of bromoenyne,[4a] and have found that the reaction proceeded completely with an inversion of the stereochemistry and have made a correction of the misassignment of the stereochemistry.[6] In this paper, we report the detail of this unique stereospecific synthesis of the (*Z*)-alkenyl unit by Kumada–Tamao–Corriu cross-coupling



Scheme 1.

Keywords: Bromoenyne; Trisubstituted (*Z*)-alkene; (−)-Laulimalide; SN2′ reaction; 3,6-Dihydro[2*H*]pyran.
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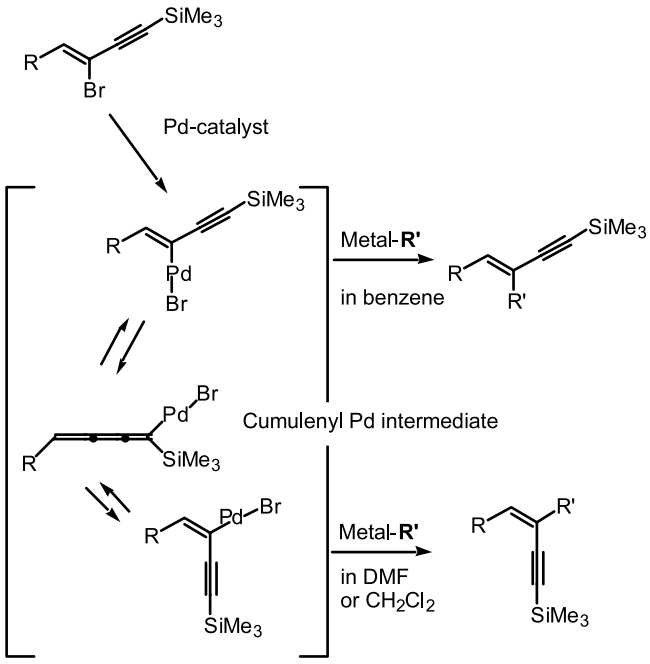


Scheme 2.

of 3-bromo-3-en-1-yne and efficient access to the C17–C27 fragment of (−)-laulimalide by means of the (*Z*)-alkenyl product.

2. Results and discussion

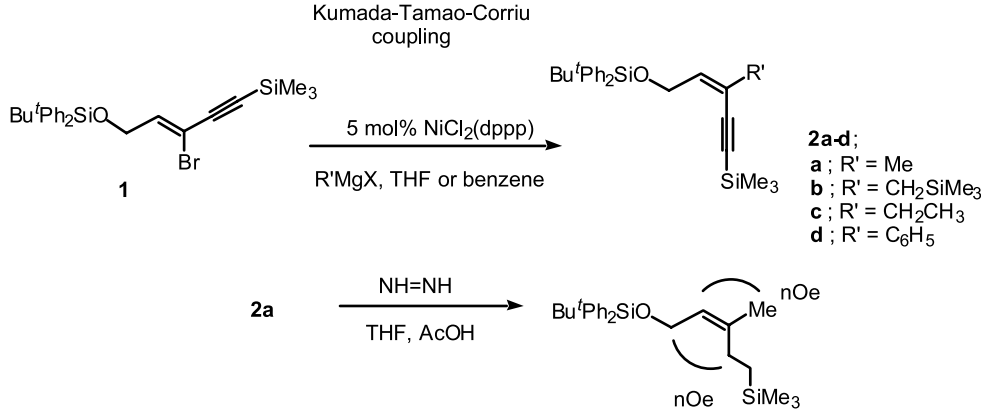
2.1. Kumada–Tamao–Corriu coupling of (*Z*)-3-bromo-1-trimethylsilyl-3-penten-1-yne

Although the Pd-catalyzed cross-coupling reactions of (*Z*)-5-(*tert*-butyldiphenylsilyl)oxy-3-bromo-1-trimethylsilyl-3-penten-1-yne (**1**) with terminal alkyne, vinylboronic acid or vinylstannane proceeded with retention of the configuration in benzene under Sonogashira, Suzuki and Stille conditions,[4,5] we have recently reported the Sonogashira and Stille reactions of **1** undergo with inversion of the configuration in CH_2Cl_2 or DMF. We have proposed this unusual isomerization mechanism by a 1,3-rearrangement of the σ-alkenyl–palladium complex through the cumulenyl–palladium intermediate shown in Scheme 2.[5] Upon careful reinvestigation of our previous results, this inversion was found to occur exclusively in the Ni-catalyzed Kumada–Tamao–Corriu coupling of **1** with ethylmagnesium bromide to give only (*Z*)-enyne. The coupling was carried out either in THF, ether or benzene with alkylmagnesium halide in the presence of 5–10 mol% of $NiCl_2$(dppp). The yields were quite good with methyl and trimethylsilylmethylmagnesium halide in 84 and 74% yields for **2a** and **2b**, respectively. With ethylmagnesium bromide, the yield of **2c** was 61% along with a small amount of enyne dimer and a reduced product by β-hydride elimination. The reaction with phenylmagnesium bromide gave **2d** poorly in less than 20% yield. The stereochemistry of **2** was confirmed by an NOE experiment after chemoselective reduction of trimethylsilylethyne to trimethylsilylethane with diimide,[7] as shown in Scheme 3, and also conversion to a dihydropyran ring in the later stage. It is interesting that the isomerization by the 1,3-rearrangement can take place depending on the solvent in the case of Pd catalyzed reactions, although the corresponding rearrangement takes place in most solvents in Ni-catalyzed cross-coupling reaction to give an isomerized alkene. Since a geometrically pure trisubstituted (*Z*)-alkene is an important functional group in organic synthesis, this method will be useful not only for the synthesis of the (*Z*)-enyne but also for that of a trisubstituted alkene. In fact, a functionalization of the trimethylsilylethynyl unit is possible such as to lead to other functional groups including ethenyl, hydroxyethyl, formylmethyl, and carboxymethyl, which can be used for the dihydropyran synthesis in Section 2.2.

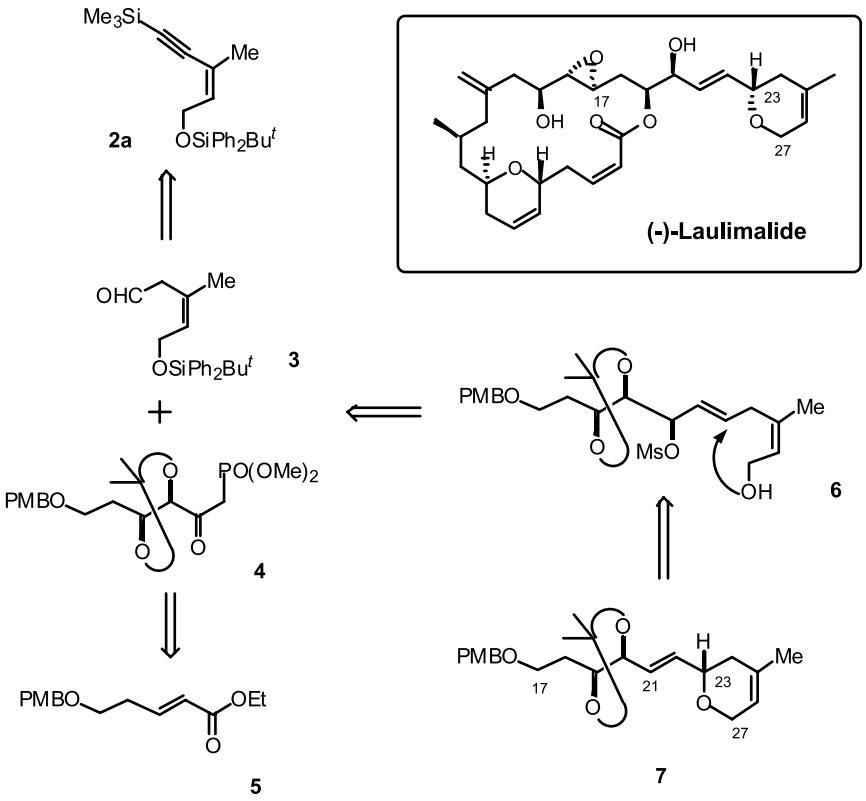
2.2. Synthetic plan for the C17–C27 fragment of (−)-laulimalide

(−)-Laulimalide is a marine natural product, possessing a high degree of cytotoxicity in a number of human cancer cell lines.[8] Although several elegant total syntheses have been achieved,[9] the 4-methyl-3,6-dihydro[2*H*]pyran ring located in the C23–C27 carbon chain, is prepared mostly by ring closing metathesis[9a,c,e–h] and/or by hetero Diels–Alder reaction.[9b,d]

We planned to use the above (*Z*)-enyne unit for the preparation of 4-methyl-3,6-dihydropyran. The structure of (−)-laulimalide and its synthetic plan for the C17–C27 carbon skeleton including the pyran ring are outlined in



Scheme 3.



Scheme 4.

Scheme 4. Reaction steps include a manipulation of aldehyde **3** from trimethylsilyethynyl alkene **2a** and the Horner–Wadsworth–Emmons reaction of ketophosphonate **4** being derived from **5** with aldehyde **3** giving the α,β-unsaturated ketone. The resultant enone will lead to dihydropyran **7** in three steps via cyclization of allyl methanesulfonate **6** by an intramolecular anti-S_N2' reaction.

2.3. Preparation of aldehyde 3

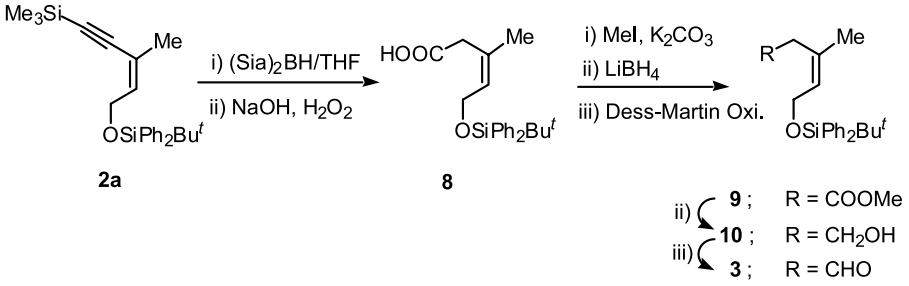
Conversion of **2a** to aldehyde **3** required four steps. First, hydroboration of the terminal alkyne and successive oxidation by Zweifel's method[10] gave carboxylic acid **8** in 72% yield. This acid was led to the methyl ester by treatment with iodomethane in the presence of K_2CO_3 to give **9** quantitatively. Reduction of the ester with $LiBH_4$ in THF afforded alcohol **10** in 79% yield. Oxidation of **10** with Dess-Martin periodinane gave aldehyde **3** quantitatively (Scheme 5).

2.4. Preparation of ketophosphonate 4 and Horner–Wadsworth–Emmons reaction

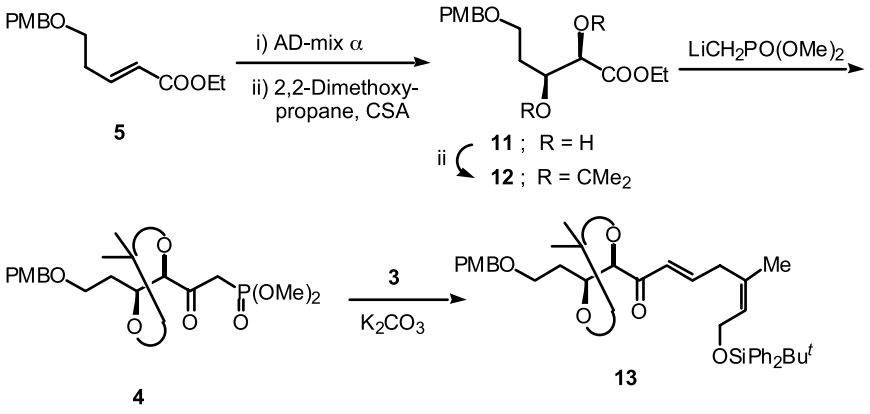
The synthesis of the C17–C20 carbon chain started from α,β-unsaturated ester **5**.[11] Sharpless asymmetric dihydroxylation of **5** using AD-mix-α gave diol **11** in 96% yield with 99% ee after recrystallization.[12] After a protection of the diol as an acetonide by 2,2-dimethoxypropane in the presence of CSA, the reaction of acetonide **12** with lithium salt of dimethyl methylphosphonate gave ketophosphonate **4** in 80% yield in two steps. Horner–Wadsworth–Emmons reaction of **4** with **3** in the presence of K_2CO_3 in THF and water[13] gave enone **13** in 70% yield (Scheme 6).

2.5. Ring formation of 3,6-dihydro[2*H*]pyran

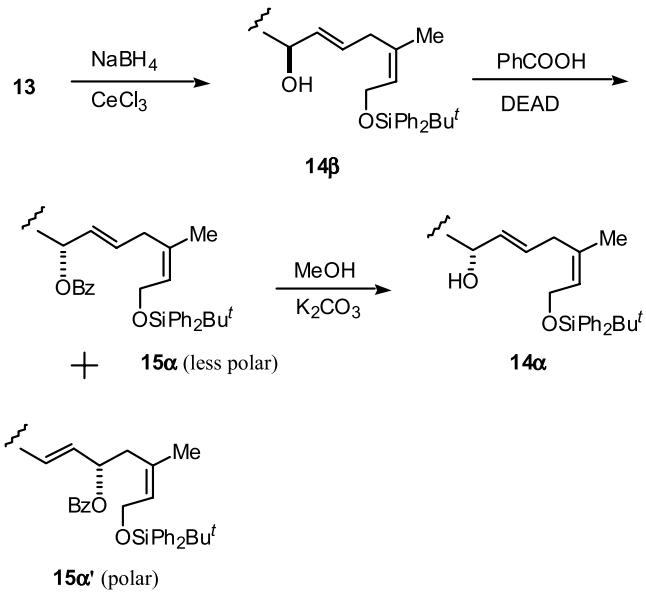
The precursors for the cyclization to 3,6-dihydro[2*H*]pyran were prepared from **13**. Although a reduction of ketone with certain hydride reagents such as $LiAl(O^tBu)_3H$ or DIBAL-H gave a lower selectivity along with the 1,4-reduction product, that with $NaBH_4$ in the presence of $CeCl_3$



Scheme 5.



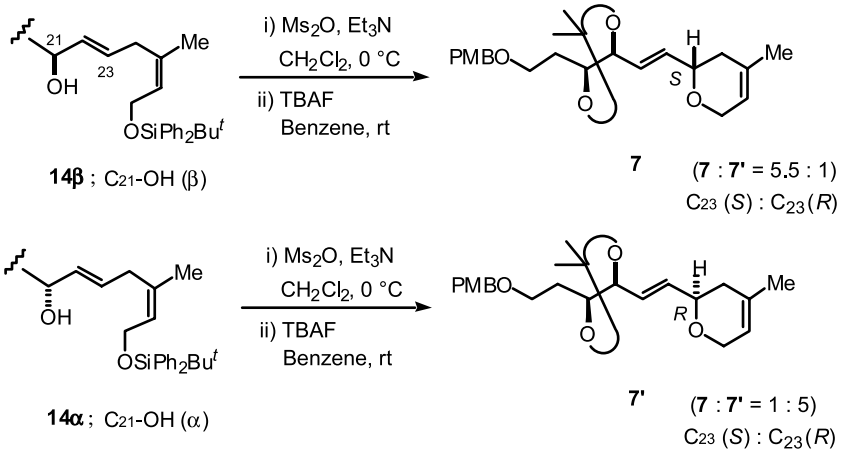
Scheme 6.



Scheme 7.

at −78 °C gave β-allylic alcohol **14**β in 80% yield selectively, with a >10:1 ratio. An β-alcohol was predominantly produced as was reported in the similar function system.[14] The other stereoisomer was prepared by an inversion of this chiral alcohol using Mitsunobu reaction. Mitsunobu reaction of **14**β with benzoic acid in the presence of diethyl diazodicarboxylate (DEAD) gave a 1:1 mixture of **15**α (C21 benzoate) and **15**α′ (C23 benzoate) in 81% yield, which were separated by HPLC. The less polar compound **15**α was obtained with a >10:1 diastereomeric ratio over the other diastereomer **15**β. Meanwhile, the regioisomer **15**α′ contained its diastereomer **15**β′ with a 20% diastereomeric ratio. Finally, methanolysis of **15**α gave **14**α in 97% yield (Scheme 7).

Treatment of **14**β with methanesulfonic anhydride in the presence of triethylamine in CH_2Cl_2 at 0 °C gave the corresponding methanesulfonate quantitatively. Without purification, it was subjected to an S_N2' reaction. When the methanesulfonate was treated with TBAF in benzene, (*S*)-dihydropyran **7** was obtained along with its diastereomer **7**′ in 60% yield with a 5.5:1 ratio. This reaction may be explained as follows. As soon as the deprotection of the silyl group with TBAF occurred, a generated oxygen nucleophile attacks the C23 carbon from *si*-face to form the pyran ring and simultaneous elimination of the methanesulfonate produces the (*E*)-alkenyl bond and (*S*)-chiral center in an anti-S_N2' fashion. The undesired (*R*)-isomer was produced via a S_N1' type reaction in a 15% diastereomeric ratio. On the other hand, the opposite stereochemistry took place in the same reaction of **14**α in which dihydropyran **7**′ was obtained for the most part along with **7** in 61% yield with a 5:1 ratio. Tosylate or nosylate of **14**α did not work well. In



Scheme 8.

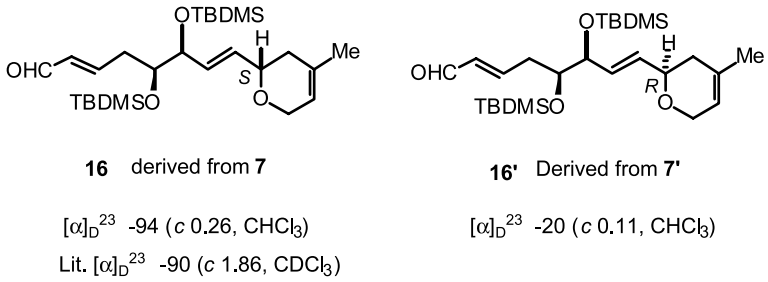


Figure 2.

both cases, substitutions proceeded well in benzene in about 5:1 ratio but gave a lower ratio in THF (Scheme 8).

The stereochemistry of 3,6-dihydro[2*H*]pyran was confirmed after a conversion to the fragment that Wender et al. used for their total synthesis of (−)-laulimalide.[9d] Functionalization and two-carbon extension by seven-step reactions from **7** reached α,β-unsaturated aldehyde **16**.[15] The proton NMR of the Wender's α,β-unsaturated aldehyde **16** was exactly matched with that of the major isomer being derived from **7**. Its specific degree −94 (*c* 0.26, $CHCl_3$) was quite close to that of the Wender's intermediate [−90 (*c* 1.86, $CDCl_3$)]. On the other hand, the specific degree of its diastereomer **16′** derived from **7′** was found to be −20 (*c* 0.11, $CHCl_3$) (Fig. 2).

3. Conclusion

A Ni-catalyzed cross-coupling reaction of **1** with alkyl Grignard reagent gave alkylated (*Z*)-enyne **2** with inversion of the initial configuration stereospecifically. A ring construction of 3,6-dihydro[2*H*]pyran was achieved by an intramolecular S_N2' reaction of η-hydroxyallyl methanesulfonate. The substitution reaction accompanied with chirality transfer effectively gave the C17–C27 carbon unit of (−)-laulimalide.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded at 300 or 400 MHz and at 75 or 100 MHz, respectively. Melting points were obtained on a melting point apparatus and were uncorrected. Mass spectra were recorded using electron impact (EI) ionization at 70 or 20 eV or chemical ionization (CI) with isobutene gas. Silica gel (70–230 mesh) was used for flash chromatography. Analytical thin-layer chromatography (TLC) was performed on glass pre-coated with silica gel (0.25 mm thickness). High performance liquid chromatography (HPLC) was carried out on a UV spectrophotomeric detector (254 nm) to which a 20×250 mm size column packed with silica gel was attached. All experiments were carried out under an argon atmosphere. THF and ether were dried over sodium/benzophenone ketyl, and CH_2Cl_2 was dried over P_2O_5, and they were distilled prior to use. The solvent extracts were dried over $MgSO_4$, and the solutions were evaporated under reduced pressure. AD-mix-α was purchased from Sigma-Aldrich chemical company.

4.2. Kumada–Tamao–Corriu coupling of bromoenyne with Grignard reagents

To a mixture of bromoenyne **1** (1.42 g, 3 mmol) and $NiCl_2$(dppp) (81 mg, 5 mol%) in THF (7.5 mL) was dropped a THF solution of MeMgBr (0.93 M, 9.6 mL) at 0 °C. Then the cooling bath was removed and the mixture was stirred at room temperature. After 1–4 h, the mixture was quenched with water and extracted with hexane (two times). The combined extracts were washed with satd NH_4Cl, water, and brine. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography to give **2** as an oil. Reaction time; 4 h for **2a**, 1 h for **2b**, 1.5 h for **2c** and 1.0 h for **2d**. Eluents for chromatography; 5% benzene in hexane for **2a**, 3% EtOAc in hexane for **2b**, 2% EtOAc in hexane for **2c** and 10% benzene in hexane for **2c**.

4.2.1. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-3-methyl-1-trimethylsilyl-3-penten-1-yne (2a). Oil, 84% yield. R_f=0.5 (20% benzene in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (9H, s), 1.06 (9H, s), 1.83 (3H, q, *J*=1.3 Hz), 4.42 (2H, dq, *J*=6.2, 1.3 Hz), 5.88 (1H, td, *J*=6.2, 1.3 Hz), 7.34–7.42 (6H, m), 7.67–7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.13, 19.2, 22.7, 26.9, 63.2, 103.4, 118.7, 127.6, 127.7, 129.5, 133.9, 135.5, 137.8. IR (film) cm^{-1}: 2137. MS (EI) *m/z*: 406 (M^+). HR-MS (EI) *m/z*: 406.2144 (calcd for $C_{25}H_{34}OSi_2$: 406.2148).

4.2.2. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-5-trimethylsilyl-1-(trimethylsilyl)methyl-3-penten-1-yne (2b). Oil, 74% yield. R_f=0.53 (3% ^{t}BuOMe in hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (9H, s), 0.05 (9H, s), 1.05 (9H, s), 1.60 (2H, s), 4.43 (2H, d, *J*=6.3 Hz), 5.70 (1H, t, *J*=6.3 Hz), 7.34–7.41 (6H, m), 7.67–7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5, −0.2, 19.3, 26.9, 27.3, 63.3, 104.2, 121.1, 127.6, 128.3, 129.5, 134.0, 134.8, 135.5. MS (EI) *m/z*: 478 (M^+). HR-MS (EI) *m/z*: 478.2539 (calcd for $C_{28}H_{42}OSi_3$: 478.2544).

4.2.3. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-3-ethyl-1-trimethylsilyl-3-penten-1-yne (2c). Oil, 61% yield. R_f=0.53 (20% benzene in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (9H, s), 1.06 (9H, s), 1.06 (3H, t, *J*=7.7 Hz), 2.11 (2H, q, *J*=7.3 Hz), 4.46 (2H, d, *J*=6.2 Hz), 5.88 (1H, t, *J*=6.2 Hz), 7.37–7.42 (6H, m), 7.67–7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0, 12.9, 19.3, 27.0, 29.8, 63.3, 99.8, 125.2, 128.0, 128.4, 129.6, 134.0, 135.7, 136.3. IR (film) cm^{-1}: 2141. MS (EI) *m/z*: 420 (M^+). HR-MS (EI) *m/z*: 420.2300 (calcd for $C_{26}H_{36}OSi_2$: 420.2305).

4.2.4. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-3-phenyl-1-trimethylsilyl-3-penten-1-yne (2d). Oil, 17% yield. R_f= 0.34 (2% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (9H, s), 1.09 (9H, s), 4.68 (2H, d, J=6.2 Hz), 6.58 (1H, t, J=6.2 Hz), 7.25–7.45 (9H, m), 7.53–7.59 (2H, m), 7.68–7.75 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.10, 19.3, 26.8, 63.9, 101.0, 123.0, 126.1, 127.7, 127.9, 128.3, 129.6, 133.7, 135.6, 137.0, 137.9. IR (film) cm^{-1}: 2141. MS (EI) *m*/*z*: 468 (M^+). HR-MS (EI) *m*/*z*: 468.2298 (calcd for $C_{30}H_{36}OSi_2$: 468.2305).

4.3. Preparation of the C23–C27 carbon chain

4.3.1. (*Z*)-5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-pentenoic acid (8). To a THF solution of borane (70 mmol) in THF (75 mL) was added 2-methyl-2-butene (14.8 mL, 140 mmol) dropwise at −15 °C and the mixture was stirred at 0 °C for 2 h. This mixture was recooled to −40 °C, and a THF (20 mL) solution of **2a** (9.43 g, 23.2 mmol) was dropped. The mixture was allowed to warm up to −3 °C gradually during 3 h, and then quenched with MeOH (30 mL) carefully at −10 °C. The whole mixture was further stirred for an additional 30 min at −10 °C. Aq sodium hydroxide (70 mL of 3 M solution) and hydrogen peroxide (24 mL of 30% solution) were added to the mixture at the same temperature. After stirring for 30 min, the mixture was acidified with aq HCl (1 M solution) at the same temperature and allowed to warm up to room temperature. The reaction mixture was extracted with EtOAc three times, and the extracts were washed with aq sodium thiosulfate, water, and brine successively. After drying over $MgSO_4$, the extract was condensed and the residual oil was purified by column chromatography on silica gel eluted with EtOAc to give carboxylic acid **8** (6.15 g) in 72% yield as a colorless oil. R_f=0.61 (40% EtOAc in hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.80 (3H, d, J= 1.3 Hz), 2.93 (2H, s), 4.19 (2H, dd, J=6.4, 1.1 Hz), 5.63 (1H, t, J=6.4 Hz), 7.36–7.44 (6H, m), 7.66–7.70 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.9, 26.8, 37.8, 60.7, 127.7, 128.4, 129.7, 130.6, 133.5, 135.6, 176.0. IR (neat) cm^{-1}: 3071, 3049, 2931, 2858, 1712, 1428, 1111, 1057. CI-MS (CI) *m*/*z*: 369 (M^++H), 367, 311, 233, 199, 189, 113. HR-MS (CI): *m*/*z* 369.1877 (calcd for $C_{22}H_{29}O_3Si$: 369.1886).

4.3.2. Methyl (*Z*)-5-(*tert*-butyldimethylsilyl)oxy-3-methyl-3-pentenoate (9). To a mixture of **8** (6.79 g, 18.4 mmol) and iodomethane (3.44 mL, 55.3 mmol) in anhydrous acetone (100 mL) was added anhydrous powdered potassium carbonate (12.7 g, 92 mmol), and the mixture was stirred for 5 h at room temperature. Then, it was quenched with satd NH_4Cl (10 mL) and the whole was condensed to a half volume under a reduced pressure. The mixture was extracted with ether and the extract was washed with brine, and dried over $MgSO_4$. Solvent was removed and the residual oil was chromatographed on silica gel eluted with 5% EtOAc in hexane to give **9** (7.0 g) as a colorless oil in quantitative yield. R_f=0.22 (5% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.77 (3H, d, J=1.3 Hz), 2.87 (2H, s), 3.59 (3H, s), 4.21 (2H, d, J=6.4 Hz), 5.58 (1H, td, J=6.4, 1.3 Hz), 7.35–7.44 (6H, m), 7.64–7.70 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.9, 26.8, 37.5, 51.8, 60.8, 127.6, 128.4, 129.6, 130.0, 133.8, 135.6, 171.5. IR (neat) cm^{-1}: 3071, 3049, 2932, 2857, 1741, 1429, 1110, 1057. MS (EI) *m*/*z*: 382 (M^+), 325, 213, 199, 105, 95. HR-MS (EI): *m*/*z* 382.1967 (calcd for $C_{23}H_{30}O_3Si$: 382.1964).

4.3.3. (*Z*)-5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-penten-1-ol (10). $LiBH_4$ (1.25 g, 57 mmol) was added to a solution of **9** (7.28 g, 19 mmol) in THF (100 mL) at 0 °C by several portions, and the reaction was continued for 15 h at room temperature. Then, water was added and the mixture was extracted with ether several times. The combined extracts were washed with water, brine and dried over $MgSO_4$, and concentrated. The residual oil was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give **10** (5.36 g) in 79% yield. Colorless oil, R_f=0.60 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.74–1.76 (3H, m), 2.24 (2H, t, J= 6.2 Hz), 3.61 (2H, t, J=6.2 Hz), 4.15 (2H, d, J=7.1 Hz), 5.58 (1H, t, J=7.1 Hz), 7.36–7.44 (6H, m), 7.68–7.72 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.5, 26.8, 35.2, 59.9, 60.1, 126.8, 127.7, 128.3, 129.7, 133.6, 135.6. IR (neat) cm^{-1}: 3392, 3071, 3048, 2931, 2857, 1472, 1428, 1112, 1062. MS (EI) *m*/*z*: 354 (M^+), 297, 267, 219, 199, 152, 78. HR-MS (EI): *m*/*z* 354.2020 (calcd for $C_{22}H_{30}O_2Si$: 354.2015).

4.3.4. (*Z*)-5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-penten-1-al (3). To a solution of **10** (2.76 g, 7.75 mmol) in CH_2Cl_2 (75 mL) was added Dess-Martin periodinate (4.94 g, 11.65 mmol) in an ice bath. After the addition, the bath was removed and the mixture was stirred for 30 min at room temperature. Then the mixture was quenched with satd sodium thiosulfate and satd $NaHCO_3$, and the whole mixture was extracted with ether three times. The combined extracts were washed with water and brine and dried over $MgSO_4$. Solvent was removed under a reduced pressure to give a crude aldehyde **3** which was used for the next Hornor–Wadsworth–Emonns reaction without further purification. R_f=0.86 (20% EtOAc in hexane). ^{1}H NMR (300 MHz, C_6D_6) δ 1.26 (9H, s), 1.55 (3H, s), 2.54 (2H, d, J=2.0 Hz), 4.23 (2H, d, J=6.3 Hz), 5.73 (1H, t, J= 6.3 Hz), 7.30–7.40 (6H, m), 7.85–7.92 (4H, m), 9.10 (1H, t, J=2.0 Hz).

4.4. Preparation of the C17–C27 ketophosphonate

4.4.1. Ethyl (2*R*,3*S*)-2,3-dihydroxy-5-(4-methoxybenzyl) oxypentanoate (11). A suspension of AD-mix-α (25.1 g, 1.40 g/mol) in a 1:1 mixture of ^{t}BuOH and water (180 mL) was stirred for 15 min at room temperature, and then $MeSO_2NH_2$ (1.70 g, 17.9 mmol) and unsaturated ester **5** (4.73 g, 17.9 mmol) were added to the mixture at 0 °C. After being stirred for 1 day at the same temperature, the reaction mixture was quenched with satd sodium thiosulfate and extracted with EtOAc three times. The extracts were combined and washed with dil. HCl, water and brine. The organic extract was dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel eluted with 40% EtOAc in hexane to give **11** (5.14 g) in 96% yield which was recrystallized by isopropyl ether to give pure colorless crystals over 99% ee.

Mp 39–40 °C (from diisopropyl ether) lit. mp 40 °C.[12] R_f= 0.22 (50% EtOAc in hexane). $[\alpha]_D^{22}$ −2.0 (*c* 1.19, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, *J*=7.1 Hz), 1.79–1.87 (1H, m), 1.99–2.07 (1H, m), 2.90–3.02 (1H, br), 3.18–3.24 (1H, br), 3.62–3.74 (2H, m), 3.80 (3H, s), 4.06 (1H, brs), 4.14–4.19 (1H, m), 4.24–4.32 (2H, m), 4.46 (2H, s), 6.88 (2H, d, *J*=6.6 Hz), 7.25 (2H, d, *J*=6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 33.2, 55.3, 61.9, 67.8, 71.6, 73.0, 73.6, 113.8, 129.4, 129.9, 159.3, 173.2.

4.4.2. Ethyl (4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl) oxyethyl]-[1,3]dioxolan-4-carboxylate (12). A mixture of diol **11** (4.4 g, 14.7 mmol) and CSA (1.13 g, 4.42 mmol) was stirred in 2,2-dimethoxypropane at rt for 3 h. After an addition of aq $NaHCO_3$, the reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residual oil was chromatographed on silica gel eluted with 10% EtOAc in hexane to give acetonide **12** (4.03 g) in 80% yield. A colorless oil, R_f=0.48 (20% EtOAc in hexane). $[\alpha]_D^{25}$ −19.1 (*c* 1.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*=7.1 Hz), 1.44 (3H, s), 1.46 (3H, s), 1.96 (1H, dddd, *J*=14.1, 7.7, 5.9, 5.7 Hz), 2.10 (1H, dddd, *J*=14.1, 7.7, 6.6, 4.4 Hz), 3.54–3.66 (2H, m), 3.80 (3H, s), 4.13–4.32 (4H, m), 4.43 (2H, s), 6.87 (2H, d, *J*=8.8 Hz), 7.25 (2H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 25.7, 27.1, 33.6, 55.3, 61.3, 66.3, 72.6, 76.5, 79.1, 110.7, 113.7, 129.2, 130.4, 159.1, 170.7. IR (neat) cm^{-1}: 2988, 2936, 2866, 1757, 1736, 1613, 1586, 1513, 1372, 1249, 1099, 1036. MS (EI) *m/z*: 338 (M^+), 323, 280, 262, 233, 177, 189, 136. HR-MS (EI): *m/z* 338.1727 (calcd for $C_{18}H_{26}O_6$: 338.1729).

4.4.3. Dimethyl 2-{(4*R*,5*S*)-2,2-dimethyl-5-(4-methoxybenzyl)oxyethyl-[1,3]dioxolan-4-yl}-2-oxo-ethyl-1-phosphonate (4). To a solution of lithium salt of dimethyl methylphosphonate generated from dimethyl methylphosphonate (3.40 g, 27.4 mmol) with ^{n}BuLi (1.57 M in hexane solution, 15.1 mL) at −78 °C in anhydrous THF (100 mL), a THF (20 mL) solution of ester **12** (4.03 g, 11.9 mmol) was added dropwise at −78 °C and the mixture was stirred for 30 min at the same temperature. Satd NH_4Cl was added to the mixture and it was extracted with EtOAc. The organic extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc to give **4** (4.96 g) with a quantitative yield. A colorless oil. R_f=0.65 (EtOAc). $[\alpha]_D^{25}$ +22.2 (*c* 1.54, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.44 (3H, s), 1.88–1.99 (1H, m), 2.02–2.11 (1H, m), 3.25 (1H, dd, *J*=21.8, 14.5 Hz), 3.44 (1H, dd, *J*=22.5, 14.5 Hz), 3.53–3.64 (2H, m), 3.77 (3H, d, *J*=6.0 Hz), 3.79 (3H, d, *J*=6.0 Hz), 3.80 (3H, s), 4.17 (1H, d, *J*=7.7 Hz), 4.22 (1H, ddd, *J*=11.7, 7.7, 7.5 Hz), 4.42 (2H, s), 6.86 (2H, d, *J*=8.8 Hz), 7.24 (2H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.1, 33.6, 35.8, 37.2, 52.9, 53.0 (d, *J*=6.5 Hz), 53.2 (*J*=6.1 Hz), 66.2, 72.6, 75.1, 84.8, 84.8, 110.5, 113.6, 113.7, 129.3, 130.4, 159.1, 201.6 (d, *J*=7.2 Hz). IR (neat) cm^{-1}: 3473, 2988, 2955, 2856, 1717, 1613, 1514, 1250, 1033. MS (EI) *m/z*: 416 (M^+), 350, 340, 272, 237, 222, 176. HR-MS (EI): *m/z* 416.1601 (calcd for $C_{19}H_{29}O_8P$: 416.1600).

4.5. Preparation of the C17–C27 carbon chain

4.5.1. (2*E*,5*Z*)-7-(*tert*-Butyldiphenylsilyl)oxy-1-{(4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl)oxyethyl]-[1,3]-dioxolan-4-yl}-5-methyl-hepta-2,5-dien-1-one (13). A mixture of ketophosphonate **4** (1.94 g, 4.66 mmol), crude aldehyde **3** (3.1 mmol), and anhydrous powdered K_2CO_3 (856 mg, 6.2 mmol) was stirred in a 1:1 mixture of THF–water (40 mL) at room temperature. After 3 h, the reaction was quenched with satd NH_4Cl, and extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give **13** (1.4 g) in 70% yield. A colorless oil. R_f=0.30 (15% EtOAc in hexane). $[\alpha]_D^{29}$ 2.6 (*c* 1.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.34 (3H, s), 1.43 (3H, s), 1.68 (3H, d, *J*=1.3 Hz), 1.87–1.96 (1H, m), 1.98–2.07 (1H, m), 2.74 (2H, d, *J*=6.8 Hz), 3.49–3.62 (2H, m), 3.78 (3H, s), 4.15–4.18 (4H, m), 4.39 (2H, s), 5.54 (1H, td, *J*=6.4, 1.3 Hz), 6.44 (1H, dt, *J*=15.8, 1.6 Hz), 6.83 (1H, dt, *J*=15.8, 6.8 Hz), 6.84 (2H, d, *J*=8.8 Hz), 7.21 (2H, d, *J*=8.8 Hz), 7.35–7.44 (6H, m), 7.65–7.69 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.5, 26.1, 26.8, 27.2, 33.6, 35.4, 55.3, 60.6, 66.3, 72.5, 75.7, 84.1, 110.2, 113.7, 125.7, 127.2, 127.7, 129.2, 129.6, 130.4, 133.0, 133.7, 135.6, 146.7, 159.1, 197.5. IR (neat) cm^{-1}: 3070, 2932, 2857, 1692, 1617, 1587, 1513, 1248, 1110. MS (EI) *m/z*: 642 (M^+), 585, 459, 433, 199, 143. HR-MS (EI): *m/z* 642.3380 (calcd for $C_{39}H_{50}O_6Si$: 642.3376).

4.5.2. (2*E*,5*Z*)-(1*R*)-7-(*tert*-Butyldiphenylsilyl)oxy-1-{(4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl)oxyethyl]-[1,3]dioxolan-4-yl}-5-methyl-hepta-2,5-dien-1-ol (14β). To a stirred mixture of **13** (1.75 g, 2.72 mmol) and $CeCl_3$ heptahydrate (1.52 g, 4.08 mmol) in methanol (28 mL), $NaBH_4$ (154 mg, 4.08 mmol) was added at −78 °C by several portions during 1 h. Then, the cooling bath was removed and the mixture was allowed to warm up to room temperature. Water was added and the mixture was extracted with EtOAc. The organic extract was washed with water and brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane. Alcohol **14**β (1.41 g) was obtained in 80% yield with a >10:1 diastereomeric ratio. A colorless oil, R_f=0.29 (20% EtOAc in hexane). $[\alpha]_D^{24}$ −9.4 (*c* 1.56, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.39 (6H, s), 1.67 (3H, d, *J*=1.1 Hz), 1.73–1.91 (2H, m), 2.59 (2H, t, *J*=6.5 Hz), 3.48–3.58 (2H, m), 3.63 (1H, dd, *J*=7.7, 4.8 Hz), 3.80 (3H, s), 3.97 (1H, dd, *J*=7.9, 4.0 Hz), 3.98 (1H, dd, *J*=7.9, 4.8 Hz), 4.20 (2H, d, *J*=6.4 Hz), 4.41 (2H, s), 5.37 (1H, dd, *J*=15.3, 6.8, 1.1 Hz), 5.46 (1H, t, *J*=6.4 Hz), 5.54 (1H, dtd, *J*=15.3, 6.5, 1.1 Hz), 6.87 (2H, d, *J*=8.8 Hz), 7.23 (2H, d, *J*=8.8 Hz), 7.36–7.42 (6H, m), 7.67–7.71 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.4, 26.8, 27.1, 27.4, 33.6, 35.1, 55.2, 60.6, 66.8, 72.3, 72.7, 75.0, 83.7, 108.9, 113.7, 125.7, 127.6, 129.2, 129.6, 129.7, 130.4, 131.1, 133.9, 135.1, 135.6, 159.1. IR (neat) cm^{-1}: 3466, 3070, 2932, 2857, 1613, 1514, 1248, 1109, 1039. MS (EI) *m/z*: 644 (M^+), 629, 587, 443, 388, 313, 295, 213, 199. HR-MS (EI): *m/z* 644.3541 (calcd for $C_{39}H_{52}O_6Si$: 644.3533).

4.6. Mitsunobu reaction of 14β with benzoic acid; preparation of 15α and 15α′

To a mixture of **14**β (926 mg, 1.44 mmol), benzoic acid (352 mg, 2.88 mmol), and triphenylphosphine (755 mg, 2.88 mmol) in benzene, diethyl diazodicarboxylate (1.25 mL, 40% in toluene solution) was dropped in an ice bath. After the mixture was stirred for 1 h at the same temperature, water was added and the mixture was extracted with ether. The ethereal extract was washed with water, and brine and dried over $MgSO_4$. After the solvent was removed, the crude product was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane. A 1:1 mixture of C21 and C23 benzoates, **15**α and **15**α′ (871 mg) were obtained in 81% yield. They were separated by HPLC with 15% EtOAc in hexane as an eluent (12 mL/min).

4.6.1. Compound 15α. Colorless oil (less polar isomer, retention time 11.9 min), R_f=0.57 (20% EtOAc in hexane) $[\alpha]_D^{25}$ −18.6 (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s), 1.30 (3H, s), 1.38 (3H, s), 1.63 (3H, d, *J*= 1.1 Hz), 1.90–2.00 (2H, m), 2.60 (2H, d, *J*=6.4 Hz), 3.50–3.62 (2H, m), 3.77 (3H, s), 3.93 (1H, dd, *J*=8.0, 3.5 Hz), 4.04 (1H, td, *J*=8.0, 3.7 Hz), 4.17 (2H, dd, *J*=6.4, 1.1 Hz), 4.39 (2H, s), 5.44 (1H, t, *J*=6.4 Hz), 5.52–5.67 (3H, m), 6.82 (2H, d, *J*=8.8 Hz), 7.19 (2H, d, *J*=8.8 Hz), 7.33–7.44 (8H, m), 7.53–7.59 (1H, m), 7.64–7.68 (4H, m), 8.02–8.05 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.3, 26.8, 26.9, 27.4, 34.0, 35.1, 55.2, 60.6, 66.6, 72.5, 74.4, 75.2, 82.0, 109.3, 113.7, 125.3, 125.9, 127.6, 128.4, 129.1, 129.5, 129.7, 130.2, 130.5, 133.0, 133.6, 133.9, 134.8, 135.6, 159.1, 165.4. IR (neat) cm^{-1}: 2932, 2857, 1722, 1613, 1514, 1249, 1110. MS (EI) *m/z*: 748 (M^+), 733, 691, 634, 615, 313, 295, 199. HR-MS (EI): *m/z* 748.3788 (calcd for $C_{46}H_{56}O_7Si$: 748.3795).

4.6.2. Compound 15α′. Colorless oil (polar isomer, retention time 13.5 min), R_f=0.57 (20% EtOAc in hexane). The diastereomeric ratio of (*S*)- and (*R*)-benzoates was 4:1. The spectral data are described for only the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.37 (3H, s), 1.38 (3H, s), 1.76 (3H, d, *J*=1.1 Hz), 1.75–1.85 (2H, m), 2.13 (1H, dd, *J*=13.9, 4.8 Hz), 2.45 (1H, dd, *J*=13.9, 9.0 Hz), 3.44–3.57 (2H, m), 3.70–3.78 (1H, m), 3.79 (3H, s), 4.01 (1H, dd, *J*=8.2, 6.4 Hz), 4.11 (1H, dd, *J*=12.8, 5.7 Hz), 4.28 (1H, dd, *J*=12.8, 7.3 Hz), 4.35 (2H, s), 5.47 (1H, dd, *J*=7.3, 5.7 Hz), 5.54–5.60 (1H, m), 5.70 (1H, dd, *J*=15.5, 6.4 Hz), 5.77 (1H, dd, *J*=15.5, 6.2 Hz), 6.84 (2H, d, *J*=8.8 Hz), 7.19 (2H, d, *J*=8.8 Hz), 7.31–7.44 (8H, m), 7.47–7.53 (1H, m), 7.64–7.69 (4H, m), 7.88–7.93 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 24.0, 26.8, 26.9, 27.2, 32.0, 37.2, 55.3, 60.8, 66.6, 72.2, 72.6, 77.9, 81.3, 108.7, 113.7, 127.6, 128.3, 128.3, 129.2, 129.5, 129.6, 129.6, 130.1, 130.4, 132.2, 132.3, 132.9, 133.9, 135.6, 159.1, 165.4. IR (neat) cm^{-1}: 3070, 2932, 2858, 1720, 1613, 1514, 1269, 1249, 1110. MS (EI) *m/z*: 748 (M^+), 733, 691, 633, 615, 313, 295, 213. HR-MS (EI): *m/z* 748.3790 (calcd for $C_{46}H_{56}O_7Si$: 748.3795).

4.6.3. (2*E*,5*Z*)-(1*S*)-7-(*tert*-Butyldiphenylsilyl)oxy-1-{(4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl)oxyethyl]-[1,3]dioxolan-4-yl}-5-methyl-hepta-2,5-dien-1-ol (14α). A mixture of benzoate **15**α (120 mg, 0.16 mmol) and powdered K_2CO_3 (111 mg, 0.8 mmol) in methanol (1.6 mL) was stirred for 2 h at room temperature. The mixture was poured into cold water and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. After solvent was removed, the residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane to give alcohol **14**α (100 mg) in 97% yield. Colorless oil, R_f=0.52 (30% EtOAc in hexane). $[\alpha]_D^{23}$ −8.3 (*c* 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.36 (3H, s), 1.37 (3H, s), 1.67 (3H, d, *J*=1.5 Hz), 1.75–1.84 (1H, m), 1.86–1.95 (1H, m), 2.59 (2H, d, *J*=6.4 Hz), 3.50–3.60 (2H, m), 3.68 (1H, dd, *J*=8.1, 4.6 Hz), 3.79 (3H, s), 4.00 (1H, td, *J*=8.1, 3.7 Hz), 4.15 (1H, td, *J*=6.1, 0.9 Hz), 4.20 (2H, dd, *J*=6.6, 1.2 Hz), 4.41 (2H, s), 5.39–5.48 (2H, m), 5.54 (1H, dtd, *J*=15.4, 6.6, 1.1 Hz), 6.86 (2H, d, *J*= 8.6 Hz), 7.23 (2H, d, *J*=8.6 Hz), 7.36–7.44 (6H, m), 7.66–7.70 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.4, 26.8, 27.0, 27.3, 34.2, 35.1, 55.3, 60.7, 66.9, 71.8, 72.7, 74.8, 83.2, 108.6, 113.8, 125.7, 127.6, 128.9, 129.3, 129.6, 130.4, 130.7, 133.9, 135.2, 135.6, 159.2. IR (neat) cm^{-1}: 3450, 3033, 2932, 2857, 1613, 1514, 1428, 1249, 1110, 1040. MS (EI) *m/z*: 644 (M^+), 629, 587, 388, 313, 295, 213, 199. HR-MS (EI): *m/z* 644.3528 (calcd for $C_{39}H_{52}O_6Si$: 644.3533).

4.6.4. Stereoselective dihydropyran ring formation by SN2′ reaction; preparation of 7 and 7′. A mixture of alcohol **14** (α or β, 0.2 mmol), triethylamine (1.4 mmol) and methanesulfonic anhydride (1 mmol) was stirred in CH_2Cl_2 (2 mL) at 0 °C for 1 h. A cold water was added to the mixture, and it was extracted with ether. The ethereal layer was quickly washed with aq $NaHCO_3$, water, and brine and dried over $MgSO_4$. Evaporation of solvent and residue was dissolved in benzene (1 mL). To this solution a THF solution of tetrabutylammonium fluoride (1 M, 1 mL) was added and the mixture was stirred for overnight at room temperature. Then, the mixture was quenched with water and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane to give a colorless oil. A 5.5:1 mixture of **7** and **7′** was obtained from **14**β in 60% yield, and a 1:5 mixture was obtained from **14**α in 61% yield. The mixture of **7** and **7′** were not separable by column chromatography, TLC, and HPLC. A mixture of **7** and **7′**. Colorless oil, R_f=0.36 (20% EtOAc in hexane). IR (neat) cm^{-1}: 2933, 2853, 1613, 1514, 1247, 1091, 1037. MS (EI) *m/z*: 388 (M^+), 370, 330, 312, 267, 209, 160, 136. HR-MS (EI): *m/z* $[M]^+$ 388.2251 (calcd for $C_{23}H_{32}O_5$: 388.2250). ^{1}H NMR and ^{13}C NMR are following; **7**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.40 (3H, s), 1.69 (3H, brs), 1.77–1.95 (3H, m), 1.99–2.08 (1H, m), 3.51–3.63 (2H, m), 3.80 (3H, s), 3.83 (1H, td, *J*=8.2, 4.0 Hz), 4.00–4.06 (1H, m), 4.06 (1H, dd, *J*=8.2, 7.5 Hz), 4.11–4.22 (2H, m), 4.43 (2H, s), 5.41 (1H, brs), 5.70 (1H, ddd, *J*=15.6, 7.5, 1.3 Hz), 5.87 (1H, ddd, *J*=15.6, 5.4, 0.5 Hz), 6.86 (2H, d, *J*=8.8 Hz), 7.25 (2H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 26.9, 27.2, 32.0, 35.6, 55.2, 65.6, 66.7, 72.6, 73.1, 77.8, 81.9, 108.6, 113.7, 119.6, 127.4, 129.2, 130.5, 131.3, 135.4, 159.1. **7′**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.40 (3H, s), 1.69 (3H, brs), 1.78–1.94 (3H, m), 2.01–2.11 (1H, m), 3.51–3.64 (2H, m), 3.80 (3H, s), 3.79–

3.84 (1H, m), 3.98–4.03 (1H, m), 4.07 (1H, t, $J=7.7$ Hz), 4.12–4.23 (2H, m), 4.43 (2H, s), 5.41 (1H, brs), 5.69 (1H, ddd, $J=15.7$, 7.2, 1.5 Hz), 5.90 (1H, ddd, $J=15.7$, 5.1, 0.9 Hz), 6.87 (2H, d, $J=8.8$ Hz), 7.25 (2H, d, $J=8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 27.0, 27.3, 32.1, 35.6, 55.3, 65.7, 66.8, 72.7, 72.9, 78.0, 81.8, 108.6, 113.8, 119.7, 127.1, 129.3, 130.5, 131.4, 135.0, 159.1.

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