# Studies toward the Synthesis of Iejimalides A–D: Preparation of the C3–11 and C12–C24 Fragments

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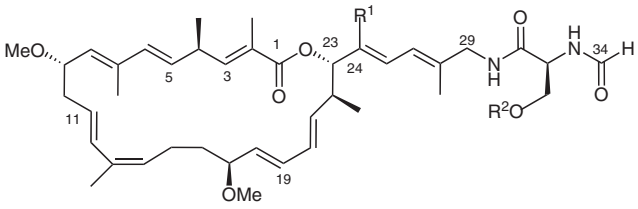
**Abstract:** The convergent synthesis of the C3–C11 and C12–C24 fragments of the iejimalides A–D is described. The C3–C11 fragment is obtained by a cross-metathesis reaction, while the C12–C24 fragment is derived from a Still–Gennari modified Horner–Wadsworth–Emmons olefination.

**Key words:** iejimalides, macrolides, cross-metathesis, Horner–Wadsworth–Emmons, fragment synthesis

Iejimalides A–D (**1a**–**d**)[1] are four novel polyene macrolides, isolated by Kobayashi and co-workers from the methanol extracts of the tunicate, *Eudistoma cf. rigida*, collected off Ie island, Okinawa province, Japan. Structurally, the iejimalides consist of a 24-membered polyene macrolide core structure containing five stereogenic centers, four conjugated diene units and an *N*-formyl-L-serine terminus (Figure 1). The iejimalides show potent growth inhibitory activity[2] against a range of human tumor cell lines, with iejimalide B being especially potent. According to the data disclosed by the National Cancer Institute (NCI), iejimalide A shows remarkable potency, with $GI_{50}$ values as low as 13 nM (MDA-MB-231/ATCC breast cancer cell line), and total growth inhibition (TGI) values as low as 40 nM (M14 melanoma cell line), whilst iejimalide B is cytostatic ($GI_{50}$) at <5 nm against 40 of the 60 standard human cancer cell lines tested.[3] In addition, the iejimalides show selective V-ATPase inhibition.[4] The overall structures of the iejimalides were first determined by Kobayashi in 1988, through degradation and NMR studies.[1a] However, the specific stereochemistry of only one of the six stereogenic centers (i.e., C32, the others being located at C4, C9, C17, C22, and C23 ) was determined. After isolation of the iejimalides in relatively large amounts from *Cystodytes* sp.,[5] Kobayashi et al. (in 2003) published revised structures for the iejimalides, with complete determination of the absolute configurations at the six stereogenic centers. They also reported a change in the olefin geometry at C13 (*Z* rather than *E*), following extensive 2D NMR investigations, distance geometry calculations and degradation studies.[6] So far, three total syntheses[7] and two syntheses of fragments[8] have been reported. The distinctive biological properties of the iejimalides and their scarcity (0.0003–0.0006% of the tunicate wet weight) in Nature, combined with their unique and intriguing molecular architecture, renders these natural products attractive synthetic targets, which has prompted us to study the synthesis of these natural products. In this connection, we herein report our preliminary studies on the synthesis of the C3–C11 and C12–C24 fragments of iejimalides A–D.




**1a**: iejimalide A; $R^1 = R^2 = H$
**1b**: iejimalide B; $R^1 = Me$, $R^2 = H$
**1c**: iejimalide C; $R^1 = H$, $R^2 = SO_3Na$
**1d**: iejimalide D; $R^1 = Me$, $R^2 = SO_3Na$

**Figure 1** The structures of iejimalides A–D

Scheme 1 outlines our retrosynthetic analysis of iejimalides A–D. The C3–C11 fragment **2** could be assembled by a cross-metathesis reaction between alkenes **4** and **5**. The subunit **4** was envisioned to originate from but-3-yn-1-ol (homopropargylic alcohol), while synthon **5** could be derived from (*S*)-Roche ester. The C12–C24 fragment could arise from a Still–Gennari modified Horner–Wadsworth–Emmons olefination reaction between phosphonate **6** and aldehyde **7**. The subunit **6**, in turn, could be prepared from γ-butyrolactone and the aldehyde **7** could be obtained from but-2-yn-1,4-diol via successive Sharpless epoxidation and Gillman reaction.

## Synthetic Strategy for the C3–C11 Fragment (2)

The synthesis of the C5–C11 conjugated diene fragment **4** began from the known epoxy alcohol **8** (Scheme 2), prepared from homopropargylic alcohol as reported previously.[9] The epoxy alcohol **8** was converted into allylic alcohol **10** by a two-step process involving initial transformation into iodide **9**, which on refluxing with activated zinc in ethanol afforded the allylic alcohol **10** (76% yield). Compound **10** was converted into the corresponding *O*-methyl ether **11** by methylation using methyl iodide in the presence of sodium hydride. Next, **11** was subjected to a one-pot dihydroxylation and oxidative cleavage of the resulting diol to furnish the corresponding aldehyde, followed by a three-carbon Wittig olefination to provide α,β-unsaturated ester **12**. This ester was converted into the

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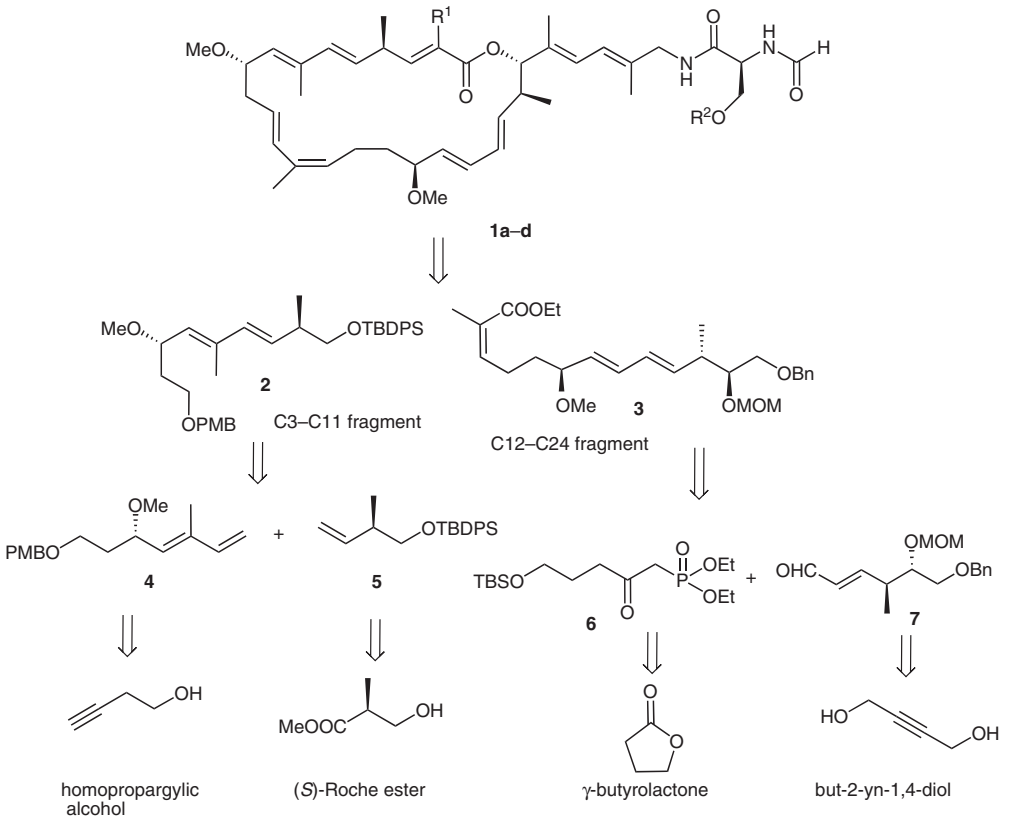
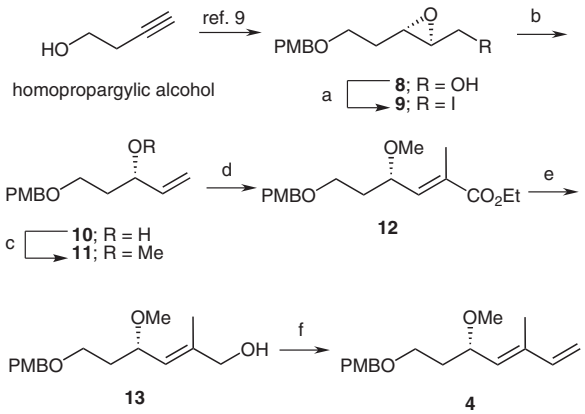


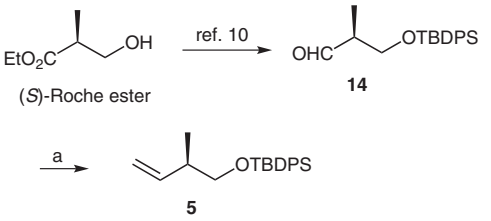

**Scheme 1** Retrosynthetic analysis of iejimalides A–D

corresponding aldehyde by reduction with diisobutylaluminum hydride (DIBAL-H), followed by pyridinium chlorochromate (PCC) oxidation. This aldehyde was subjected to one-carbon Wittig olefination (*n*-BuLi, $CH_3PPh_3I$, anhydrous THF) to produce the C5–C11 conjugated diene fragment **4**.



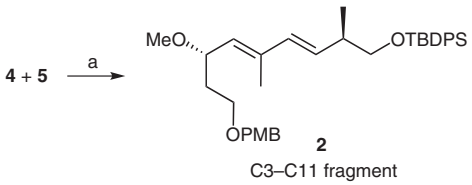

**Scheme 2** *Reagents and conditions*: (a) imidazole, $PPh_3$, $I_2$, THF, 0 °C–r.t., 30 min, 81%; (b) Zn, EtOH, reflux, 30 min, 76%; (c) MeI, NaH, THF, 2 h, 75%; (d) (i) $OsO_4$, NMO, acetone–$H_2O$ (4:1); (ii) $NaIO_4$, THF–$H_2O$ (2:1); (iii) $Ph_3P{=}C(CH_3)CO_2Et$, benzene, reflux, 4 h, 71% over 3 steps; (e) DIBAL-H, $CH_2Cl_2$, 0 °C, 1 h, 77%; (f) (i) PCC, $CH_2Cl_2$, Celite, 0 °C, 1 h, 98%; (ii) *n*-BuLi, $CH_3PPh_3I$, anhydrous THF, –50 °C to r.t., 5 h, 68%.

The synthesis of the olefinic fragment **5** began with the known aldehyde **14**[10] prepared from (*S*)-(+)-Roche ester. The aldehyde **14**, on homologation with (methylene)triphenylphosphorane in anhydrous tetrahydrofuran using *n*-butyllithium (1.6 M) produced the terminal alkene **5** in 75% yield (Scheme 3).




**Scheme 3** *Reagents and conditions*: (a) $MePPh_3I$, *n*-BuLi, anhydrous THF, –50 °C to r.t., 5 h, 75%.

With practical routes to coupling partners **4** and **5** established, we turned our attention to the key cross-metathesis coupling in the presence of Grubbs' second generation (Grubbs II) catalyst[11] (Scheme 4). Thus, cross-metathesis of alkenes **4** and **5** in the presence of Grubbs II catalyst (1 mol%) in toluene at reflux temperature gave coupled product **2** in 65% yield, without isolating any by-products. Cleavage of the *p*-methoxybenzyl (PMB) group and oxidation into the corresponding aldehyde set the stage for the Wittig olefination.



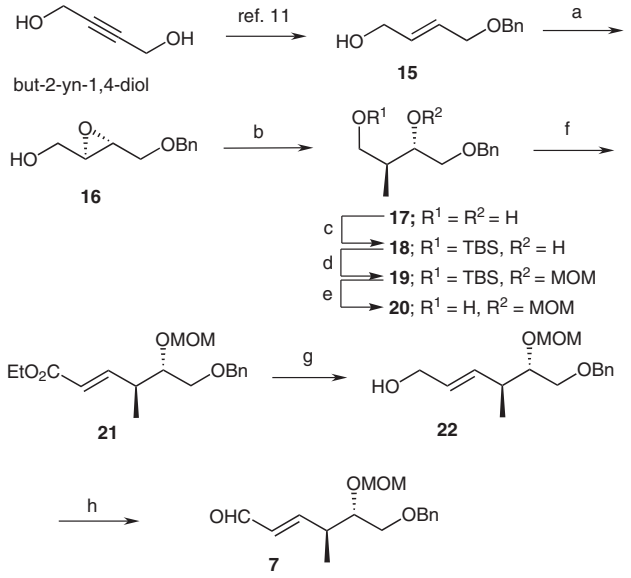

**Scheme 4** *Reagents and conditions*: (a) Grubbs II, toluene, reflux, 3 h, 65%.

## Synthetic Strategy for the C12–C24 Fragment (3)

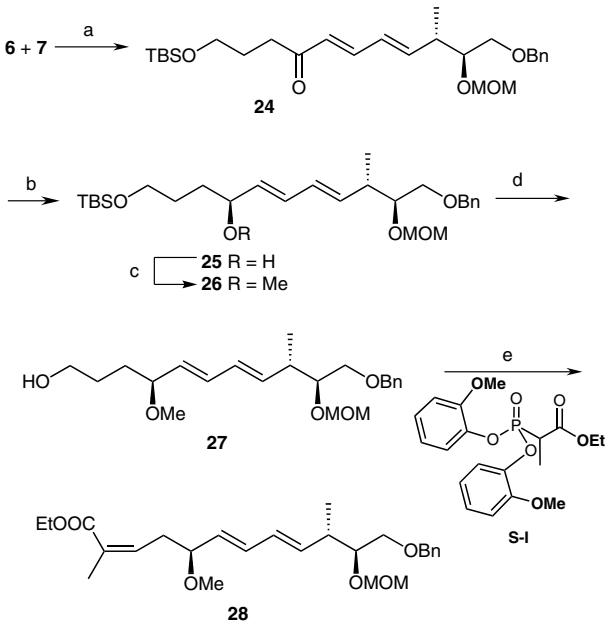
The synthesis of aldehyde **7** started with readily available but-2-yn-1,4-diol (Scheme 5). Accordingly, but-2-yn-1,4-diol was converted into the known allylic alcohol **15** as reported earlier,[12] by selective monobenzylation and partial reduction of the triple bond in a very good yield (90%). The alcohol **15** was subjected to Sharpless asymmetric epoxidation [(–)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, –25 °C, 24 h] to afford epoxy alcohol **16** in 76% yield. Epoxide opening proceeded smoothly with high regioselectivity by treatment of **16** with lithium dimethylcuprate ($Me_2CuLi$) to give the expected 1,3-diol accompanied by the undesired 1,2-diol (6:1). The minor isomer was readily removed by treating the mixture with sodium periodate to yield 1,3-diol **17** in 69% yield, possessing *anti*-stereochemistry at the two stereocenters.[13] Protection of the primary alcohol as the *tert*-butyldimethylsilyl ether **18**, followed by protection of the secondary hydroxy group with methoxymethyl chloride (MOMCl) provided methoxymethyl ether **19** in quantitative yield. Next, the *tert*-butyldimethylsilyl group was removed and the resulting alcohol **20** was oxidized into the corresponding aldehyde and subsequent Wittig olefination provided α,β-unsaturated ester **21**. Reduction of this ester provided the alcohol **22** and subsequent Swern oxidation gave the desired aldehyde **7**, which was used in the next step without purification.

The synthesis of phosphonate ester **6** (Scheme 6) commenced from commercially available γ-butyrolactone, as reported,[14] by deprotonation of methyl diethylphosphonate with *n*-butyllithium, followed by treatment with γ-butyrolactone and protection of the resulting alcohol as a *tert*-butyldimethylsilyl ether.

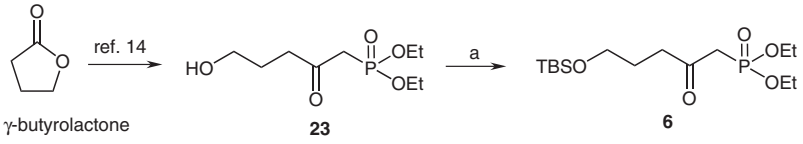
The Subsequent Horner–Wadsworth–Emmons reaction between β-ketophosphonate **6** and the aldehyde **7** (Scheme 7), using Paterson's conditions,[15] afforded **24** in 80% yield. The absolute configuration at C21 was set by a Corey–Bakshi–Shibata (CBS) reduction[16] of the enone




**Scheme 5** *Reagents and conditions*: (a) Ti(O*i*-Pr)$_4$, (–)-DIPT, TBHP, anhydrous $CH_2Cl_2$, –25 °C, 24 h, 76%; (b) CuI, MeLi, $Et_2O$, 0 °C to –40 °C, 3.5 h, 69%; (c) TBSCl, imidazole, THF, 0 °C, 30 min, 91%; (d) MOMCl, DIPEA, $CH_2Cl_2$, 0 °C–r.t., 2 h, 94%; (e) TBAF, THF, 0 °C to r.t., 1 h, 92%; (f) (i) $(COCl)_2$, $CH_2Cl_2$, DMSO, $Et_3N$, 2.5 h, –78 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, 2 h, 79%; (g) DIBAL-H, $CH_2Cl_2$, 0 °C, 1 h, 92%; (h) $(COCl)_2$, $CH_2Cl_2$, DMSO, $Et_3N$, 2.5 h, –78 °C, 94%.




**Scheme 7** *Reagents and conditions*: (a) $Ba(OH)_2{\cdot}8H_2O$, anhydrous THF, r.t., 2 h, 80%; (b) (*R*)-CBS, $BH_3{\cdot}DMS$, anhydrous THF, –40 °C, 2 h, 71%; (c) MeI, NaH, anhydrous THF, 2 h, 78%; (d) (i) TBAF, THF, 0 °C–r.t., 1 h, 67%; (e) (i) $(COCl)_2$, $CH_2Cl_2$, DMSO, $Et_3N$, –78 °C, 92%; (e) **S-I**, NaH, 18-crown-6, anhydrous THF, –78 °C, 3 h, 75%.




**Scheme 6** *Reagents and conditions*: (a) TBSCl, imidazole, $CH_2Cl_2$, 0 °C, 30 min, 94%.

**24**, which delivered the corresponding allylic alcohol **25** in 71% yield after chromatographic separation of the minor diastereomer (crude product dr = 9:1, determined by $^1$H NMR spectroscopy). Methylation of the hydroxy group provided the methyl ether **26**, which was followed by cleavage of the *tert*-butyldimethylsilyl ether and subsequent oxidation of the resulting alcohol to afford the corresponding aldehyde. This was then subjected to a Still–Gennari modified Horner–Wadsworth–Emmons[17] reaction using sodium hydride and phosphonate salt **S-I** in anhydrous tetrahydrofuran at –78 °C to afford the *cis* α,β-unsaturated ester **28** in 75% yield after column chromatography. The phosphonium bromide coupling partner could be prepared via ester reduction to give the corresponding alcohol, and then bromination.

In summary, the synthesis of the C3–C11 and C12–C24 fragments of iejimalides A–D have been accomplished in a short and convergent manner. Investigations on the assembly of the macrolactone, the preparation of the side chain and the completion of the synthesis are currently underway and will be reported in due course.

All reagents and catalysts were purchased from Sigma-Aldrich. Reactions were conducted under $N_2$ in anhydrous solvents ($CH_2Cl_2$, THF and EtOAc). All reactions were monitored by TLC (Merck 60 F-254 silica gel plates; samples were made visual under UV light). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. *n*-Hexane (bp 60–80 °C) and EtOAc (bp 76–78 °C) were used for silica gel column chromatography. Yields refer to those of chromatographically and spectroscopically ($^1$H and $^{13}$C NMR) homogeneous materials. Air-sensitive reagents were transferred via a syringe or a cannula. Evaporation of solvents was performed under reduced pressure on a Buchi rotary evaporator. Optical rotations were recorded using a JASCO DIP-370 polarimeter. IR spectra were obtained using a Perkin-Elmer Infrared-683 spectrophotometer. $^1$H and $^{13}$C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-400 MHz, Bruker UXNMR FT-300 MHz (Avance) and Avance-500 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were obtained on a Finnigan MAT1020B or micromass VG 70-70H spectrometer operating at 70 eV, using a direct inlet system.

**(*S*)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol (10)**

A stirred suspension of iodide **9** (9 g, 23.9 mmol) and Zn powder (7.8 g, 119.6 mmol) in anhydrous EtOH (75 mL) was heated at reflux temperature for 30 min. The mixture was filtered through a Celite pad, concentrated under reduced pressure, and the crude residue purified by column chromatography (EtOAc–PE, 3:7) to furnish alcohol **10** (4 g, 76%) as a light yellow liquid.

$[\alpha]_D^{25}$ +4.66 (*c* 0.1, $CHCl_3$).

IR (neat): 3443, 2934, 2861, 1612, 1512, 1246, 1092, 819 cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 5.85–5.77 (m, 1 H), 5.22 (d, *J* = 17.0 Hz, 1 H), 4.42 (s, 2 H), 4.33–4.26 (m, 1 H), 3.77 (s, 3 H), 3.66–3.60 (m, 1 H), 3.59–3.53 (m, 1 H), 3.19 (br s, 1 H), 1.85–1.71 (m, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 159.2, 140.0, 129.6, 129.3, 114.6, 113.7, 72.9, 72.0, 67.8, 55.1, 35.9.

MS (ESI): *m*/*z* = 245 $[M + Na]^+$.

**(*S*)-1-[(3-Methoxypenten-4-yloxy)methyl]-4-methoxybenzene (11)**

To a suspension of NaH (0.68 g, 28.6 mmol) in anhydrous THF, was added alcohol **10** (2.77 g, 12.4 mmol) at 0 °C. The mixture was stirred for 30 min, MeI (1 mL, 16.2 mmol) was added slowly, and the mixture was stirred at r.t. for 2 h. After completion of the reaction (monitored by TLC), it was quenched by the dropwise addition of ice-cold $H_2O$. The organic layer was separated and the aq layer extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over $Na_2SO_4$. The solvents were evaporated under vacuum and the residue was purified by column chromatography (EtOAc–hexane, 1:9) to afford methyl ether **11** (2.1 g, 75%) as a colorless oil.

$[\alpha]_D^{25}$ +6.33 (*c* 0.6, $CHCl_3$).

IR (neat): 3489, 3074, 2932, 2859, 1737, 1611, 1513, 1247, 1092, 1035, 926, 821, 772, 515 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 9.0 Hz, 2 H), 5.67–5.57 (m, 1 H), 5.20–5.14 (m, 2 H), 4.38 (s, 2 H), 3.78 (s, 3 H), 3.71–3.64 (m, 1 H), 3.54–3.47 (m, 1 H), 3.46–3.39 (m, 1 H), 3.23 (s, 3 H), 1.86–1.77 (m, 1 H), 1.74–1.65 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 159.0, 138.3, 130.5, 129.2, 117.2, 113.6, 79.8, 72.5, 66.2, 56.2, 55.2, 35.5.

MS (ESI): *m*/*z* = 259 $[M + Na]^+$.

**(*S*,*E*)-Ethyl 6-(4-Methoxybenzyloxy)-4-methoxy-2-methylhex-2-enoate (12)**

NMO (1.3 g, 11.4 mmol) and the alkene **11** (2.07 g, 8.7 mmol) were dissolved in acetone–$H_2O$ (4:1, 18 mL). A solution of $OsO_4$ (0.02 M) in toluene (2 mL) was added and the mixture stirred overnight at r.t., then cooled in an ice bath. The reaction was quenched by the addition of sat. aq $Na_2SO_3$ solution (15 mL). Most of the acetone was removed by rotary evaporation, and the aq mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were concentrated under reduced pressure, and the crude diol was used in the next step without further purification. $NaIO_4$ (2.4 g, 11.4 mmol) was added to the crude diol (2.07 g, 7.6 mmol) in THF–$H_2O$ (2:1, 20 mL) at r.t. The reaction was complete within 30 min. After filtration, the two layers were separated and the aq layer was extracted with EtOAc (2 × 50 mL), dried over $Na_2SO_4$ and concentrated to give the corresponding crude aldehyde, which was used in the next step without further purification. The crude aldehyde was immediately dissolved in benzene (30 mL) and treated with $Ph_3P{=}C(CH_3)CO_2Et$ (3.8 g, 10.6 mmol). The mixture was heated at reflux temperature for 4 h, and then allowed to cool to r.t. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc–hexanes, 10–15%) to afford **12** (1.6 g, 71%) as a yellow oil.

$[\alpha]_D^{25}$ +8.80 (*c* 0.3, $CHCl_3$).

IR (neat): 2932, 1712, 1612, 1513, 1462, 1249, 1098, 1034, 822, 749, 541 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.3 Hz, 2 H), 6.81 (d, *J* = 8.3 Hz, 2 H), 6.51 (d, *J* = 9.0 Hz, 1 H), 4.38 (ABq, *J* = 11.3 Hz, 2 H), 4.23–4.13 (m, 3 H), 3.77 (s, 3 H), 3.57–3.47 (m, 1 H), 3.43–3.34 (m, 1 H), 3.23 (s, 3 H), 1.95–1.81 (m, 1 H), 1.87 (s, 3 H), 1.73–1.61 (m, 1 H), 1.31 (t, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 167.5, 159.0, 141.4, 130.4, 130.3, 129.1, 113.6, 74.5, 72.5, 65.7, 60.6, 56.5, 55.1, 34.8, 14.1, 12.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{26}O_5Na$: 345.1672; found: 345.1683.

**(*S*,*E*)-6-(4-Methoxybenzyloxy)-4-methoxy-2-methylhex-2-en-1-ol (13)**

To a solution of compound **12** (1.57 g, 4.8 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C was added DIBAL-H (6 mL, 9.7 mmol, 1.6 M in hexane). The mixture was stirred for 1 h, and was then quenched by the addition of sat. potassium sodium tartrate solution. The mixture was

warmed to r.t. and stirred for 4 h until two clear layers were observed. The layers were separated and the aq layer was extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried over $Na_2SO_4$, the solvent was evaporated, and the residue was purified by column chromatography (10–15% EtOAc–hexane) to afford allylic alcohol **13** (1 g, 77%) as a colorless oil.

$[\alpha]_D^{25}$ +0.88 (*c* 0.75, $CHCl_3$).

IR (neat): 3421, 2927, 2862, 1612, 1513, 1457, 1247, 1177, 1096, 821, 763, 517 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 9.0 Hz, 2 H), 5.24 (d, *J* = 9.0 Hz, 1 H), 4.37 (s, 2 H), 4.08 (q, *J* = 7.0 Hz, 1 H), 3.96 (s, 2 H), 3.78 (s, 3 H), 3.52–3.46 (m, 1 H), 3.44–3.36 (m, 1 H), 3.20 (s, 3 H), 1.90–1.82 (m, 1 H), 1.68 (s, 3 H), 1.66–1.59 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 159.0, 139.1, 130.5, 129.2, 125.5, 113.6, 74.1, 72.6, 68.0, 66.3, 55.9, 55.2, 35.5, 14.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{24}O_4Na$: 303.1566; found: 303.1575.

**(*S*,*E*)-1-Methoxy-4-[(3-methoxy-5-methylhepta-4,6-dienyloxy)methyl]benzene (4)**

PCC (1.15 g, 5.3 mmol) and Celite (1 g) were added to a solution of alcohol **13** (1 g, 3.5 mmol) in $CH_2Cl_2$ (30 mL). After stirring the mixture at 25 °C for 1 h, *i*-PrOH (5 mL) was added and the solvent was removed under reduced pressure. The residue was filtered through a Celite pad and the filter cake rinsed with $Et_2O$. The organic layer was washed with dil HCl (2 mL), $H_2O$ (5 mL) and brine (5 mL), and then dried ($Na_2SO_4$). Removal of the solvent afforded a gummy material, which was purified by silica gel column chromatography (EtOAc–hexane, 2:8) to afford the corresponding aldehyde (0.97 g, 54.1, 98%) as an oil.

The aldehyde (0.77 g, 2.75 mmol) was dissolved in anhydrous THF (3 mL) under $N_2$. In another round-bottomed flask, methyltriphenylphosphonium iodide (4.5 g, 11.0 mmol) in anhydrous THF (20 mL), under an $N_2$ atm, was cooled to –30 °C. *n*-BuLi (2.7 mmol, 1.6 M in hexane) was slowly added and the mixture allowed to stir for 1 h. During this time the mixture turned yellow, which indicated formation of the ylide. This yellow solution was cooled to –50 °C and treated with the above solution of the aldehyde. The resulting solution was slowly warmed to r.t. and stirred at the same temperature for 5 h. The mixture was quenched with sat. $NH_4Cl$ solution (10 mL). The organic compound was extracted with $Et_2O$ (2 × 10 mL), the combined organic layers washed with brine (3 × 10 mL), dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure. Silica gel column chromatography of the residue (8% EtOAc–hexane) afforded the desired diene **4** (0.48 g, 1.7 mmol, 68%) as a yellow liquid.

$[\alpha]_D^{25}$ +4.10 (*c* 0.19, $CHCl_3$).

IR (neat): 2927, 2859, 1714, 1610, 1248, 1175, 1100, 1035, 821 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 6.40 (dd, *J* = 17.4, 10.6 Hz, 1 H), 5.32 (d, *J* = 9.0 Hz, 1 H), 5.20 (d, *J* = 17.4 Hz, 1 H), 5.06 (d, *J* = 10.6 Hz, 1 H), 4.41 (s, 2 H), 4.21 (dt, *J* = 9.0, 6.8 Hz, 1 H), 3.80 (s, 3 H), 3.59–3.49 (m, 1 H), 3.47–3.36 (m, 1 H), 3.23 (s, 3 H), 1.99–1.88 (m, 1 H), 1.81 (d, *J* = 1.5 Hz, 3 H), 1.78–1.64 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 159.0, 140.8, 137.0, 132.8, 130.5, 129.1, 113.6, 112.6, 74.4, 72.5, 66.2, 55.9, 55.1, 35.5, 12.1.

MS (ESI): *m*/*z* = 299 $[M + Na]^+$.

**(*R*)-*tert*-Butyl[(2-methylbut-3-enyl)oxy]diphenylsilane (5)**

The aldehyde **14** (0.2 g, 0.6 mmol) was dissolved in anhydrous THF (2 mL) under $N_2$. In another round-bottomed flask, methyltriphenylphosphonium iodide (1.01 g, 2.4 mmol) was taken in anhydrous THF (10 mL) under an $N_2$ atm and cooled to –30 °C. *n*-BuLi (1.8 mmol, 1.6 M in hexane) was slowly added and the mixture allowed to stir for 1 h. During this time the mixture turned yellow which indicated the formation of the ylide. This yellow solution was cooled to –50 °C and the aldehyde was added. The resulting solution was slowly warmed to r.t. and stirred at the same temperature for 5 h. The mixture was quenched with sat. $NH_4Cl$ solution (5 mL). The organic compound was extracted with $Et_2O$ (2 × 10 mL) and the combined organic layer washed with brine (3 × 10 mL), dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure. Silica gel column chromatography (8% EtOAc–hexane) afforded the desired alkene **5** (0.15 g, 75%) as a colorless liquid.

$[\alpha]_D^{25}$ +4.78 (*c* 0.8, $CHCl_3$).

IR (neat): 3071, 2959, 2859, 1641, 1467, 1426, 1386, 1258, 739, 703 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.74–7.63 (m, 4 H), 7.47–7.34 (m, 6 H), 5.80 (ddd, *J* = 17.3, 10.5, 6.7 Hz, 1 H), 5.07–4.96 (m, 2 H), 3.60–3.45 (m, 2 H), 2.47–2.34 (m, 1 H), 1.11–1.01 (m, 12 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 141.3, 135.6, 133.9, 129.5, 127.5, 114.0, 68.4, 40.2, 26.8, 19.3, 16.1.

MS (ESI): *m*/*z* = 342 $[M + NH_4]^+$.

**[(2*R*,3*E*,5*E*,7*S*)-9-(4-Methoxybenzyloxy)-7-methoxy-2,5-dimethylnona-3,5-dienyloxy](*tert*-butyl)diphenylsilane (2)**

A mixture of alkene **4** (0.1 g, 0.36 mmol), alkene **5** (0.140 g, 0.43 mmol) and Grubbs-II catalyst (1 mol%) under an $N_2$ atm in toluene (10 mL) was stirred at reflux temperature. After completion of the reaction as indicated by TLC (3 h), the mixture was concentrated under reduced pressure and the residue subjected to silica gel column chromatography (EtOAc–hexane, 3:7) to give pure cross-metathesis product **2** (0.13 g, 65%), as a colorless liquid.

$[\alpha]_D^{25}$ +10.44 (*c* 0.15, $CHCl_3$).

IR (neat): 3449, 2926, 2856, 1669, 1609, 1513, 1248, 1101, 1053, 823, 704 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.5 Hz, 4 H), 7.46–7.31 (m, 6 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 6.10 (d, *J* = 15.8 Hz, 1 H), 5.61 (dd, *J* = 15.8, 7.5 Hz, 1 H), 5.21 (d, *J* = 9.8 Hz, 1 H), 4.41 (ABq, *J* = 5.2, 3.7 Hz, 2 H), 3.81–3.77 (m, 4 H), 3.60–3.38 (m, 4 H), 3.21 (s, 3 H), 2.53–2.42 (m, 1 H), 1.99–1.65 (m, 5 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 1.05 (s, 9 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 159.9, 140.8, 137.0, 135.5, 133.4, 132.8, 131.9, 130.5, 129.5, 129.4, 129.1, 127.5, 113.6, 74.4, 72.6, 66.3, 60.3, 56.0, 55.2, 35.6, 26.7, 19.7, 14.0, 12.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{48}O_4NaSi$: 595.32141; found: 595.32345.

**{(2*R*,3*R*)-3-[(Benzyloxy)methyl]oxiran-2-yl}methanol (16)**

In a two-neck 250 mL, round-bottomed flask, anhydrous $CH_2Cl_2$ (20 mL) was added to activated powdered 4 Å MS and the suspension cooled to –20 °C. Ti(O*i*-Pr)$_4$ (1.9 mL, 6.74 mmol) and (–)-DIPT (1.44 g, 6.74 mmol) in anhydrous $CH_2Cl_2$ (10 mL) were added with stirring, and the resulting mixture stirred for 30 min at –24 °C. Compound **15** (6 g, 33.7 mmol) in anhydrous $CH_2Cl_2$ (20 mL) was added and the mixture stirred for another 30 min at –24 °C. TBHP (8.0 mL, 40.4 mmol) was added and the mixture stirred at the same temperature for 24 h. After warming to 0 °C, the reaction was quenched by the addition of $H_2O$ (3.5 mL) and stirred for 1 h at r.t. Next, an aq solution of NaOH (20%) sat. with NaCl was added and the mixture was stirred vigorously for another 30 min at r.t. The resulting mixture was filtered through Celite and the residue rinsed with $CH_2Cl_2$. The organic phase was separated and the aq phase extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (EtOAc–hexane, 4:6) to afford epoxide **16** (4.8 g, 76%) as a viscous liquid.

IR (neat): 3421, 2926, 2862, 1739, 1638, 1454, 1368, 1102, 1026, 871, 745, 699, 609 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 4.58 (ABq, *J* = 11.3 Hz, 2 H), 3.92 (dd, *J* = 12.8, 2.2 Hz, 1 H), 3.77 (dd, *J* = 12.0, 3.0 Hz, 1 H), 3.72 (d, *J* = 4.5 Hz, 1 H), 3.64 (dd, *J* = 12.8, 3.7 Hz, 1 H), 3.52 (ddd, *J* = 6.0, 3.0, 1.5 Hz, 1 H), 3.23 (q, *J* = 5.2 Hz, 1 H), 3.12–3.07 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.3, 127.6, 126.8, 73.2, 69.5, 61.0, 55.8, 54.2.

**(2*S*,3*S*)-4-(Benzyloxy)-2-methylbutane-1,3-diol (17)**

To a stirred suspension of CuI (14.7 g, 74.2 mmol) in anhydrous $Et_2O$ (147 mL) at 0 °C was added slowly MeLi (92.7 mL, 0.148 mmol, 1.6 M in $Et_2O$) under an $N_2$ atm, and the resulting solution was stirred for 15 min at 0 °C. Epoxy alcohol **16** (4.8 g, 24.7 mmol) in anhydrous $Et_2O$ (20 mL) was then added dropwise at –40 °C. Once the addition was complete, the mixture was stirred at 0 °C for 3 h. The reaction was quenched by the careful addition of sat. aq $NH_4Cl$ solution. The mixture was filtered through a pad of Celite, and the salts were washed several times with $Et_2O$. The combined organic layers were washed with brine (2 × 20 mL) and dried over $Na_2SO_4$. Concentration of the $Et_2O$ extract under reduced pressure provided 4.9 g (23.4 mmol, 94%) of a pale yellow oil, which was a 6:1 mixture of the regioisomeric diols. This mixture was dissolved in THF (60 mL) and treated with $H_2O$ (30 mL) containing $NaIO_4$ (7.4 g, 34.7 mmol) with stirring to cleave the 1,2-diol. The reaction was complete in 1 h. After the layers were separated, the aq layer was extracted with $Et_2O$ (3 × 30 mL) and the combined extracts dried over $Na_2SO_4$ and concentrated in vacuo. The residue was subjected to silica gel column chromatography (EtOAc–hexane, 4:6) to afford diol **17** (3.5 g, 69%) as a pale yellow liquid.

$[\alpha]_D^{25}$ –6.78 (*c* 0.55, $CHCl_3$).

IR (neat): 3386, 3030, 2923, 2829, 1636, 1454, 1098, 1024, 771, 697, 602 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 5 H), 4.57 (ABq, *J* = 11.8 Hz, 2 H), 3.75 (td, *J* = 7.0, 3.2 Hz, 1 H), 3.67 (d, *J* = 5.6 Hz, 2 H), 3.61 (dd, *J* = 9.4, 3.0 Hz, 1 H), 3.49–3.42 (m, 2 H), 2.91 (br s, 2 H), 0.87 (d, *J* = 6.7 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 137.6, 128.4, 127.8, 127.7, 75.3, 73.3, 72.8, 67.0, 37.3, 13.5.

MS (ESI): *m*/*z* = 233 $[M + Na]^+$.

**(2*S*,3*S*)-1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-3-methylbutan-2-ol (18)**

To a stirred solution of the diol **17** (3.47 g, 16.5 mmol) in $CH_2Cl_2$ (30 mL), imidazole (2.24 g, 32.9 mmol) was added at 0 °C, and the resulting mixture stirred for 15 min. TBSCl (2.23 g, 14.87 mmol) was added to the mixture at 0 °C, which was stirred for a further 1 h. After completion of the reaction as indicated by TLC, the mixture was concentrated under reduced pressure and the residue subjected to column chromatography (EtOAc–hexane, 1:9) to yield pure product **18** (4.8 g, 91%) as a colorless liquid.

$[\alpha]_D^{25}$ +4.88 (*c* 0.3, $CHCl_3$).

IR (neat): 3469, 3065, 3037, 2955, 2930, 2857, 1635, 1467, 1362, 1253, 1097, 1028, 837, 766, 698, 603 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 4.57 (ABq, *J* = 11.8 Hz, 2 H), 3.79 (dd, *J* = 9.8, 4.5 Hz, 2 H), 3.64–3.47 (m, 3 H), 2.62 (s, 1 H), 1.94–1.82 (m, 1 H), 0.92–0.87 (m, 12 H), 0.06 (s, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.3, 127.7, 127.6, 74.3, 73.3, 72.7, 66.8, 37.1, 25.8, 18.1, 13.3, –5.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{33}O_3Si$: 325.2193; found: 325.2204.

**[(2*S*,3*S*)-4-(Benzyloxy)-3-(methoxymethoxy)-2-methylbutoxy](*tert*-butyl)dimethylsilane (19)**

To a solution of the alcohol **18** (4.77 g, 14.7 mmol) in $CH_2Cl_2$ (35 mL) was added DIPEA (6.33 mL, 36.8 mmol). After 1 h, the solution was cooled to 0 °C and MOMCl (1.77 mL, 22.07 mmol) was added under $N_2$ using a syringe. The resulting mixture was stirred at r.t. for 6 h and then quenched by adding sat. $NaHCO_3$ solution. The product was extracted with $CH_2Cl_2$ (2 × 100 mL) and the combined organic layers concentrated under reduced pressure. The residue was purified on a silica gel column using (10% EtOAc–hexane) to yield **19** (5 g, 94%) as a bright yellow oil.

$[\alpha]_D^{25}$ = +9.74 (*c* 0.65, $CHCl_3$).

IR (neat): 2954, 2930, 2887, 2858, 2212, 1709, 1464, 1253, 1102, 1037, 838, 775, 738, 697 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 4.83–4.68 (m, 2 H), 4.54 (ABq, *J* = 12.0 Hz, 2 H), 3.76–3.67 (m, 1 H), 3.66–3.51 (m, 4 H), 3.37 (s, 3 H), 2.06–1.92 (m, 1 H), 0.93–0.87 (m, 12 H), 0.02 (s, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.6, 127.4, 96.6, 78.1, 73.2, 71.1, 64.5, 55.5, 37.7, 25.8, 18.2, 13.3, –5.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{36}O_4NaSi$: 391.2275; found: 391.2288.

**(2*S*,3*S*)-4-(Benzyloxy)-3-(methoxymethoxy)-2-methylbutan-1-ol (20)**

To a stirred solution of compound **19** (4.97 g, 13.5 mmol) in anhydrous THF (20 mL), TBAF (16.2 mL, 16.2 mmol, 1 M solution in THF) was added slowly at 0 °C. After completion of the reaction as indicated by TLC, the mixture was concentrated under reduced pressure and the residue purified by column chromatography (EtOAc–hexane, 3:7) to yield alcohol **20** (3.15 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$ +62.80 (*c* 0.5, $CHCl_3$).

IR (neat): 3440, 3030, 2922, 1651, 1453, 1366, 1201, 1101, 1032, 916, 739, 699, 605 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 4.81 (d, *J* = 6.6 Hz, 1 H), 4.65 (d, *J* = 6.6 Hz, 1 H), 4.55 (ABq, *J* = 12.0 Hz, 2 H), 3.78–3.51 (m, 5 H), 3.40 (s, 3 H), 2.04–1.90 (m, 1 H), 1.81 (br s, 1 H), 0.97 (d, *J* = 6.9 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 137.8, 128.3, 127.6, 127.5, 96.6, 79.8, 73.5, 70.9, 64.9, 55.7, 37.0, 13.8.

MS (ESI): *m*/*z* = 254 $[M]^+$.

**(*E*,4*S*,5*S*)-Ethyl 6-(Benzyloxy)-5-(methoxymethoxy)-4-methylhex-2-enoate (21)**

Oxalyl chloride (1.54 mL, 17.8 mmol) was added dropwise at –78 °C to a solution of DMSO (2.5 mL, 35.7 mmol) in anhydrous $CH_2Cl_2$ (20 mL). The mixture was stirred for 25 min at this temperature and then a solution of alcohol **20** (2.28 g, 8.93 mmol) in anhydrous $CH_2Cl_2$ (2 mL) was added. The mixture was stirred for 1 h at –78 °C. After addition of $Et_3N$ (7.4 mL, 53.6 mmol), the mixture was stirred for 15 min at –78 °C and then for 20 min at 0 °C. The reaction mixture was then diluted with $H_2O$ (15 mL) and $CH_2Cl_2$ (30 mL). The organic layer was separated and washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo to afford a crude aldehyde, which was used in the next step without purification. The crude aldehyde was immediately dissolved in benzene (15 mL) and treated with $Ph_3P{=}CHCO_2Et$ (2.28 g, 9.0 mmol). The mixture was heated at reflux temperature for 1 h, and then allowed to cool to r.t. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to afford alkene **21** (2.2 g, 79%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +50.86 (*c* 0.5, $CHCl_3$).

IR (neat): 2932, 1718, 1653, 1453, 1368, 1265, 1103, 1036, 918, 863, 739, 699 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 6.98 (dd, *J* = 15.6, 8.1 Hz, 1 H), 5.83 (dd, *J* = 15.8, 1.1 Hz, 1 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.63 (d, *J* = 6.7 Hz, 1 H), 4.52 (s, 2 H), 4.18 (q, *J* = 6.9 Hz, 2 H), 3.69 (q, *J* = 5.0 Hz, 1 H), 3.57–3.45 (m, 2 H), 3.37 (s, 3 H), 2.78–2.65 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.10 (d, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 166.5, 150.2, 137.9, 128.4, 128.3, 127.5, 121.6, 96.4, 79.2, 73.3, 70.6, 60.1, 55.7, 38.4, 15.8, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}O_5Na$: 345.1672; found: 345.1681.

**(*E*,4*S*,5*S*)-6-(Benzyloxy)-5-(methoxymethoxy)-4-methylhex-2-en-1-ol (22)**

To a solution of compound **21** (2.17 g, 6.7 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C was added DIBAL-H (8.4 mL, 13.4 mmol, 1.6 M in hexane). The solution was stirred for 1 h, and was then quenched by addition of sat. potassium sodium tartrate solution. The resulting solution was warmed to r.t. and then stirred for 4 h until two clear layers were observed. The layers were separated and the aq layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were dried over $Na_2SO_4$, the solvent was evaporated, and the residue purified by column chromatography (10–15% EtOAc–hexane) to afford allylic alcohol **22** (1.8 g, 92%) as a colorless oil.

$[\alpha]_D^{25}$ +37.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3421, 3030, 2888, 1664, 1453, 1102, 1036, 741, 699 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 5.68–5.63 (m, 2 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.65 (d, *J* = 6.7 Hz, 1 H), 4.51 (ABq, *J* = 13.2, 12.2 Hz, 2 H), 4.08 (d, *J* = 3.0 Hz, 2 H), 3.66–3.63 (m, 1 H), 3.52–3.48 (m, 2 H), 3.38 (s, 3 H), 2.60–2.48 (m, 1 H), 1.06 (d, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 138.0, 133.6, 129.7, 128.2, 127.6, 127.5, 96.5, 79.8, 73.1, 70.9, 63.4, 55.5, 38.2, 16.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}O_4Na$: 303.1566; found: 303.1575.

**(4*S*,5*S*,*E*)-6-(Benzyloxy)-5-(methoxymethoxy)-4-methylhex-2-enal (7)**

Oxalyl chloride (1.0 mL, 12.0 mmol) was added dropwise at –78 °C to a solution of DMSO (1.7 mL, 24.0 mmol) in anhydrous $CH_2Cl_2$ (20 mL). The mixture was stirred for 25 min at this temperature and then a solution of **22** (1.77 g, 6.0 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was added. The mixture was stirred for 1 h at –78 °C. After addition of $Et_3N$ (5.0 mL, 36.1 mmol), the mixture was stirred for 15 min at –78 °C and then for 20 min at 0 °C. The reaction mixture was then diluted with $H_2O$ (10 mL) and $CH_2Cl_2$ (25 mL). The organic layer was separated and washed with brine (15 mL), dried over $Na_2SO_4$, and concentrated in vacuo to afford a crude aldehyde **7**, which was used in the next step without further purification.

**Diethyl {5-[(*tert*-Butyldimethylsilyl)oxy]-2-oxopentyl}phosphonate (6)**

To a stirred solution of alcohol **23** (1.7 g, 7.1 mmol) in $CH_2Cl_2$ (15 mL), imidazole (0.97 g, 14.2 mmol) was added at 0 °C, and the resulting mixture stirred for 15 min. TBSCl (1.6 g, 10.7 mmol) was added to the mixture at 0 °C, which was then stirred for 1 h. After completion of the reaction as indicated by TLC, the mixture was concentrated under reduced pressure and the residue subjected to column chromatography (EtOAc–hexane, 1:9) to yield the pure product **6** (2.35 g, 94%) as a colorless liquid.

IR (neat): 3446, 2928, 2836, 1715, 1254, 1099, 1027, 835, 776 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.19–4.06 (m, 4 H), 3.60 (t, *J* = 6.0 Hz, 2 H), 3.11 (s, 1 H), 3.04 (s, 1 H), 2.68 (t, *J* = 7.1 Hz, 2 H), 1.88–1.73 (m, 2 H), 1.32 (t, *J* = 6.9 Hz, 6 H), 0.86 (s, 9 H), 0.02 (s, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 202.0, 62.5, 62.4, 61.9, 41.5, 40.5, 26.6, 25.8, 18.2, 16.3, 16.2, 5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{33}O_5PNaSi$: 375.1727; found: 375.1741.

**(5*S*,6*S*,7*E*,9*E*)-5-[(Benzyloxy)methyl]-6,16,16,17,17-pentamethyl-2,4,15-trioxa-16-silaoctadeca-7,9-dien-11-one (24)**

To a solution of β-ketophosphonate **6** (2.3 g, 6.5 mmol) in THF (30 mL) was added $Ba(OH)_2·8H_2O$ (1.0 g, 6.0 mmol) at r.t., which had been preactivated by heating at 110 °C for 1 h and dried under vacuum. The mixture was stirred for 30 min, then crude aldehyde **7** (1.6 g, 5.4 mmol) in THF–$H_2O$ (9:1, 15 mL) was added. The mixture was stirred for 1.5 h and then quenched with sat. $NH_4Cl$ solution (15 mL). The organic compound was extracted with EtOAc (2 × 30 mL) and the combined organic layer washed with brine (3 × 15 mL), dried over anhydrous $Na_2SO_4$, and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (8% EtOAc–hexane) to afford the desired ketone **24** (1.3 g, 80%) as a pale yellow oil.

$[\alpha]_D^{25}$ +28.53 (*c* 0.5, $CHCl_3$).

IR (neat): 3448, 2922, 2853, 1637, 1460, 1099, 762 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 6 H), 7.18–7.08 (m, 1 H), 6.19–6.14 (m, 1 H), 6.09 (d, *J* = 15.1 Hz, 1 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.63 (d, *J* = 6.7 Hz, 1 H), 4.51 (s, 2 H), 3.76–3.58 (m, 3 H), 3.56–3.43 (m, 2 H), 3.37 (s, 3 H), 2.80–2.60 (m, 2 H), 2.58–2.50 (m, 1 H), 1.96–1.74 (m, 2 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.89 (m, 9 H), 0.05 (s, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 200.6, 146.0, 142.6, 137.9, 129.1, 128.5, 128.2, 127.7, 127.5, 96.5, 79.5, 74.9, 73.2, 70.7, 55.6, 39.2, 36.5, 27.3, 25.8, 18.2, 16.3, –5.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{45}O_5Si$: 477.3030; found: 477.3039.

**(5*S*,6*S*,7*E*,9*E*,11*S*)-5-[(Benzyloxy)methyl]-6,16,16,17,17-pentamethyl-2,4,15-trioxa-16-silaoctadeca-7,9-dien-11-ol (25)**

A flame-dried round-bottomed flask (100 mL) was charged with ketone **24** (1.27 g, 2.6 mmol) and anhydrous THF (5 mL), the vessel was cooled to –20 °C and (*R*)-methyl-CBS-oxazaborolidine (2.6 mL, 2.6 mmol) was added. $BH_3$·DMS complex (0.75 mL, 8.0 mmol) was slowly added over 10 min, and the mixture was stirred for 50 min at this temperature before being slowly quenched with MeOH over a period of about 15 min. The mixture was warmed to r.t. and after the majority of gas evolution had subsided, the solvents were evaporated under vacuum and the residue was purified by column chromatography (EtOAc–hexane, 1:9) to afford alcohol **25** (0.9 g, 71%) as a colorless oil.

$[\alpha]_D^{25}$ +9.75 (*c* 0.2, $CHCl_3$).

IR (neat): 3447, 2922, 2852, 1638, 1462, 1253, 1098, 1035, 835, 775, 698 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 6.30–5.98 (m, 2 H), 5.78–5.44 (m, 2 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.73–4.63 (m, 1 H), 4.51 (s, 2 H), 4.60–4.46 (m, 1 H), 3.71–3.57 (m, 3 H), 3.56–3.45 (m, 2 H), 3.42–3.32 (m, 4 H), 2.63–2.50 (m, 1 H), 1.18–1.11 (m, 2 H), 1.06 (d, *J* = 6.7 Hz, 3 H), 0.95–0.87 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 138.2, 135.7, 134.4, 130.4, 130.1, 128.2, 127.5, 127.4, 96.6, 79.9, 73.3, 73.2, 72.2, 63.3, 55.6, 38.8, 34.6, 28.8, 25.9, 18.3, 16.6, –5.3.

MS (ESI): *m*/*z* = 479 [M + H]$^+$.

**(4*S*,5*E*,7*E*,9*S*,10*S*)-[11-(Benzyloxy)-4-methoxy-10-(methoxymethoxy)-9-methylundeca-5,7-dienyloxy](*tert*-butyl)dimethylsilane (26)**

To a suspension of NaH (0.1 g, 4.1 mmol) in anhydrous THF, was added alcohol **25** (0.87 g, 1.8 mmol) at 0 °C. After stirring for 30 min, MeI (0.14 mL, 2.3 mmol) was added slowly and the mixture stirred for a further 2 h at r.t. Following completion of the reaction (monitored by TLC), it was quenched by the addition of ice-cold

$H_2O$ dropwise. The organic layer was separated and the aq layer extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvents were evaporated under vacuum. The residue was purified by column chromatography (EtOAc–hexane, 1:9) to afford methyl ether **26** (0.7 g, 78%) as a colorless oil.

IR (neat): 3450, 2927, 1636, 1456, 1257, 1097, 1033, 699 $cm^{-1}$.

$[\alpha]_D^{25}$ –0.47 (*c* 0.35, $CHCl_3$).

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 6.26–5.99 (m, 2 H), 5.72–5.35 (m, 2 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.65 (d, *J* = 6.7 Hz, 1 H), 4.61–4.45 (m, 1 H), 4.52 (s, 2 H), 4.03–3.79 (m, 2 H), 3.77–3.48 (m, 3 H), 3.38 (s, 3 H), 3.24 (s, 3 H), 2.63–2.51 (m, 1 H), 1.68–1.49 (m, 4 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.05 (d, *J* = 1.5 Hz, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 138.2, 135.8, 132.0, 130.0, 128.4, 128.2, 127.8, 127.5, 96.6, 82.0, 79.9, 78.3, 73.2, 63.2, 56.8, 55.6, 40.7, 31.9, 29.6, 25.9, 16.5, 14.1, –5.3.

MS (ESI): *m*/*z* = 516 $[M + Na]^+$.

**(4*S*,5*E*,7*E*,9*S*,10*S*)-11-(Benzyloxy)-4-methoxy-10-(methoxymethoxy)-9-methylundeca-5,7-dien-1-ol (27)**

To a stirred solution of compound **26** (0.67 g, 1.36 mmol) in anhydrous THF, TBAF (1.63 mL, 1.6 mmol, 1 M in THF) was added slowly at 0 °C. After completion of the reaction as indicated by TLC, the mixture was concentrated under reduced pressure and the residue subjected to column chromatography (EtOAc–hexane, 3:7) to yield the pure product **27** (0.34 g, 67%) as a colorless liquid.

$[\alpha]_D^{25}$ –48.66 (*c* 0.15, $CHCl_3$).

IR (neat): 3445, 2923, 2856, 1728, 1632, 1452, 1367, 1147, 1097, 1032, 994, 916, 741, 698 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 6.26–6.01 (m, 2 H), 5.72–5.39 (m, 2 H), 4.78 (d, *J* = 6.6 Hz, 1 H), 4.70–4.60 (m, 1 H), 4.56–4.48 (m, 3 H), 3.69–3.46 (m, 5 H), 3.38 (s, 3 H), 3.24 (s, 3 H), 2.64–2.49 (m, 1 H), 1.19–1.11 (m, 2 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 0.98–0.86 (m, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 138.2, 136.2, 132.9, 129.8, 128.3, 128.2, 127.5, 127.4, 96.6, 81.8, 79.9, 73.5, 73.2, 62.7, 56.0, 55.6, 38.8, 32.5, 28.8, 16.5.

MS (ESI): *m*/*z* = 401 $[M + Na]^+$.

**Ethyl (2*Z*,6*S*,7*E*,9*E*,11*S*,12*S*)-13-(Benzyloxy)-6-methoxy-12-(methoxymethoxy)-2,11-dimethyltrideca-2,7,9-trienoate (28)**

Oxalyl chloride (1.3 mL, 1.6 mmol) was added dropwise at –78 °C to a solution of DMSO (0.23 mL, 3.2 mmol) in anhydrous $CH_2Cl_2$ (10 mL). The mixture was stirred for 25 min at this temperature and then a solution of **27** (0.31 g, 0.8 mmol) in anhydrous $CH_2Cl_2$ (3 mL) was added. The mixture was stirred for 1 h at –78 °C. After addition of $Et_3N$ (0.68 mL, 4.9 mmol), the mixture was stirred for 15 min at –78 °C and then for 20 min at 0 °C. The reaction mixture was then diluted with $H_2O$ (10 mL) and $CH_2Cl_2$ (20 mL). The organic layer was separated and washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo to afford a crude aldehyde, which was used in the next step without further purification.

A solution of the phosphonate **S-I** (0.09 g, 0.23 mmol) in anhydrous THF (5 mL) was added to an ice-cold suspension of NaH (0.015 g, 0.66 mmol) in THF (5 mL). After the mixture had been stirred for 30 min at 0 °C, it was cooled to –78 °C, and then a solution of the above aldehyde (0.1 g, 0.26 mmol) in anhydrous THF (6 mL) was added dropwise along with a catalytic amount of 18-crown-6. The mixture was stirred for 1 h, diluted with $Et_2O$ (5 mL) and quenched by the slow addition of $H_2O$ (4 mL). The layers were separated, and the aq phase extracted with $Et_2O$ (2 × 10 mL). The organic extract was washed with brine (5 mL), dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (EtOAc–PE, 0.3:9.7) to give α,β-unsaturated ester **28** (0.09 g, 75%) as a viscous liquid.

$[\alpha]_D^{25}$ –7.52 (*c* 0.35, $CHCl_3$).

IR (neat): 3452, 2924, 2853, 1711, 1457, 1372, 1224, 1102, 1037, 945, 757, 669 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 7.22–6.98 (m, 1 H), 6.26–5.90 (m, 1 H), 5.91 (t, *J* = 7.5 Hz, 1 H), 5.72–5.58 (m, 1 H), 5.55–5.35 (m, 1 H), 4.79 (d, *J* = 6.7 Hz, 1 H), 4.65 (d, *J* = 6.7 Hz, 1 H), 4.52 (s, 2 H), 4.59–4.47 (m, 1 H), 4.19 (q, *J* = 7.5 Hz, 2 H), 3.70–3.46 (m, 3 H), 3.38 (s, 3 H), 3.24 (s, 3 H), 2.61–2.41 (m, 3 H), 1.89 (s, 3 H), 1.29 (t, *J* = 7.5 Hz, 3 H), 1.18–1.13 (m, 2 H), 1.07 (d, *J* = 6.7 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 159.1, 140.9, 138.5, 137.0, 135.5, 132.9, 130.6, 129.1, 128.2, 127.5, 126.9, 96.6, 86.0, 74.4, 72.6, 66.3, 60.0, 56.0, 55.2, 39.5, 35.6, 31.9, 29.6, 22.6, 14.2, 12.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{40}O_6Na$: 483.2717; found: 483.2716.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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