Olefin Cross-Metathesis: Studies towards the Total Synthesis of (+)-Bitungolide F

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A stereoselective synthesis of (5*S*,6*S*)-6-[(2*S*,5*S*,7*R*,8*E*,10*E*)-5-(benzyloxy)-7-{[(*tert*-butyl)dimethylsilyl]oxy}-11-phenylundeca-8,10-dien-2-yl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (=(+)-9-*O*-benzyl-11-*O*-[(*tert*-butyl)dimethylsilyl]bitungolide F) is reported. The strategy involves *Gilman* reaction, olefin cross-metathesis, and *Horner–Wadsworth–Emmons* olefination as key steps.

Introduction. – Bitungolides A – F are α,β-unsaturated δ-lactones, isolated from *Theonella swinhoei* by *Tanaka* and co-workers, and they show remarkable phosphatase inhibition. When bitungolides were assayed against 3Y1 rat normal fibroblast cells, a cytotoxic effect was observed at a concentration of 10 μg/ml [1a]. The structures of bitungolides were elucidated by *Tanaka* through X-ray crystallography, following the spectroscopic assignments. Structurally, all bitungolides (*Fig.*) contain one aromatic ring, two conjugated olefinic C=C bonds, 1,3-dihydroxy- and 1,3-dimethyl-substituted stereogenic centres in the side chain, and an Et-substituted stereogenic center in the lactone ring as common functionalities. Bitungolides have structures similar to those of franklinolides [1b] (*Fig.*).

Bitungolide F possesses interesting biological activities as well as a unique structural complexity; these features prompted substantial synthetic efforts towards the total synthesis of (+)-bitungolide F (**1**). Previously, three total syntheses of (−)-bitungolide F and one synthesis of (−)-bitungolide E have been reported [2]. Herein, we report the first synthesis of the core skeleton of **1** by a convergent strategy that features *Gilman* reaction, more importantly, an olefin cross-metathesis reaction between two diversely substituted olefins, acid-catalyzed cyclization to access an α,β-unsaturated δ-lactone, and *Horner–Wadsworth–Emmons* olefination to generate the diene functionality.

Results and Discussion. – The retrosynthetic analysis of **1** is depicted in *Scheme 1*. The target compound **1** was envisioned to be formed from aldehyde **2** and phosphonate **3** through the LiOH-mediated *Horner–Wadsworth–Emmons* olefination. The aldehyde **2**, in turn, could be synthesized from intermediate **4** by acid-catalyzed cyclization and functional-group transformations. The ester **4** could be derived from cross-metathesis product **5** on hydrogenation, silyl deprotection, oxidation, and (*Z*)-selective *Wittig* reaction. Olefin **5**, in turn, may be derived from the coupling of olefinic

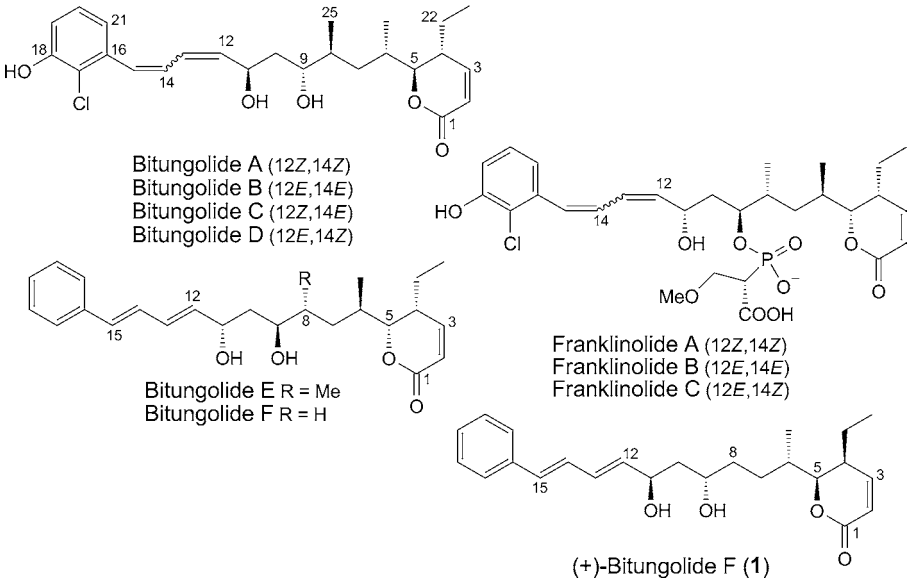


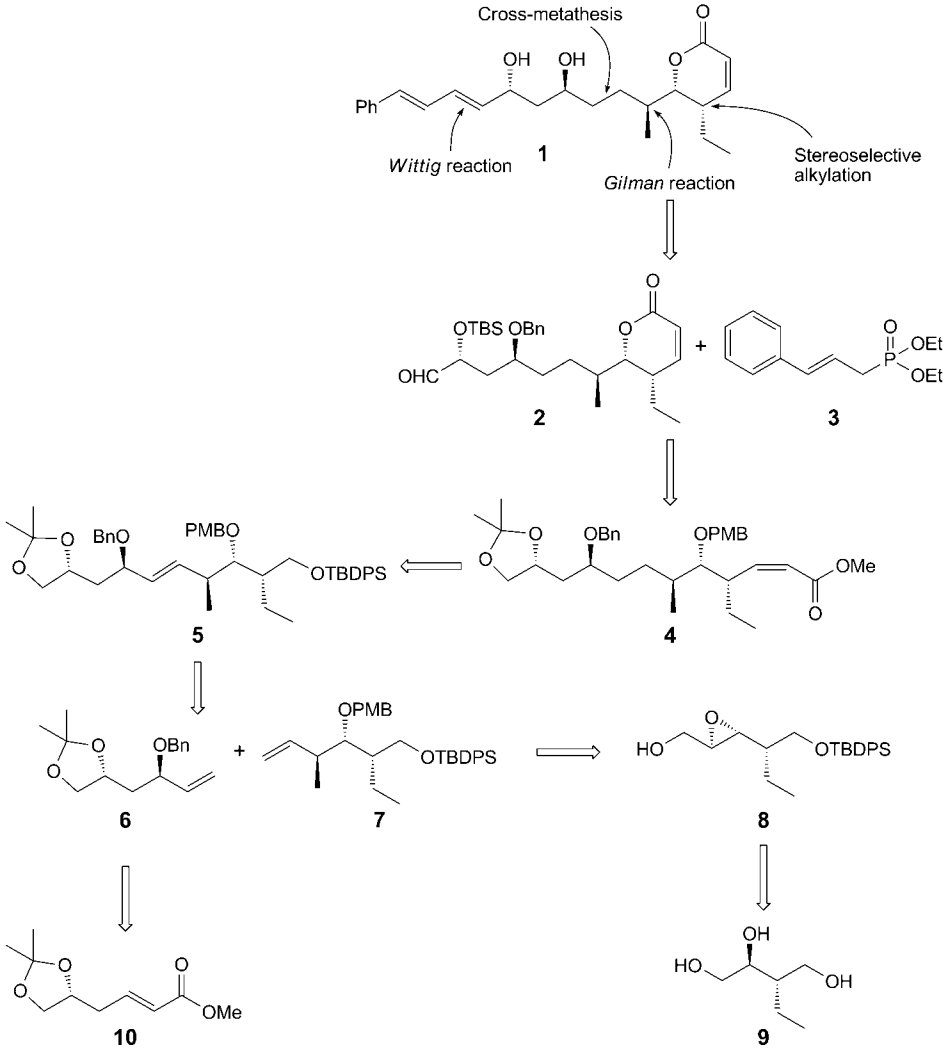
Figure. *Structures of some bitungolides and franklinolides*

fragments **6** and **7** by an olefin cross-metathesis protocol. One of the olefins, **7**, could be prepared from the epoxide **8** *via* epoxide ring opening under *Gilman* conditions, protection of the ensuing secondary alcohol as its 4-methoxybenzyl (PMB) ether, and C_1-*Wittig* olefination. The epoxide **8** was prepared from known triol **9**, and the key fragment **6** was obtained from α,β-unsaturated ester **10** *via* functional-group transformations.

The synthesis of **7** (*Scheme 2*) started from the known triol **9** [3]. Oxidative cleavage of triol **9** with $NaIO_4$ in CH_2Cl_2 gave the corresponding aldehyde, which, on *Wittig* olefination, afforded the α,β-unsaturated ester **11** [4]. Subsequently, ^{t}BuPh$_2$Si (TBDPS) protection of **11** and reduction of the α,β-unsaturated ester **12** with DIBAL-H afforded allylic alcohol **13**. *Sharpless* asymmetric epoxidation [5] of **13** gave epoxy alcohol **8**. The *Gilman* reaction unambiguously led to Me substitution [6]. Thus, the regioselective ring-opening reaction of epoxy alcohol **8** with Me_2CuLi in Et_2O, followed by the treatment of the crude product with $NaIO_4$ in CH_2Cl_2 to eliminate the minor 1,2-diol product, led to the required 1,3-diol **14** as a pure product. It is pertinent to mention that the Et group played a major role in defining the regioselective epoxide ring-opening. Protection of the diol **14** as its 4-methoxybenzylidene acetal and subsequent reductive opening of the acetal with DIBAL-H afforded the primary alcohol **15**. Then, oxidation of **15** under *Swern* conditions [7] gave the aldehyde, which, on *Wittig* homologation [8], furnished the fragment **7** in 80% yield.

The synthesis of olefin fragment **6** commenced from the known α,β-unsaturated ester **10** (*Scheme 3*) [9]. The ester was subjected to reduction with DIBAL-H in CH_2Cl_2 to furnish allylic alcohol **16**, which, on *Sharpless* asymmetric epoxidation [5], gave epoxy alcohol **17** (*cf.* [10]). Treatment of **17** under conventional conditions gave the epoxy chloride quantitatively, which was treated with Na in Et_2O to afford allylic

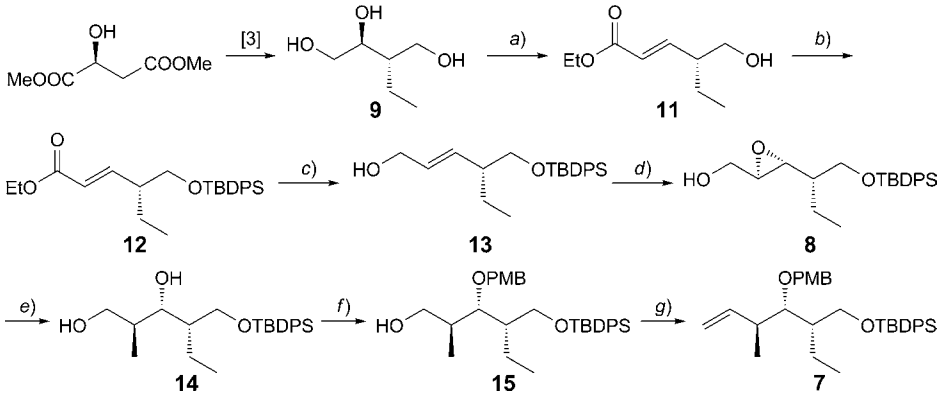
Scheme 1. *Retrosynthetic Analysis.* TBDPS, ^{t}BuPh$_2$Si; PMB, 4-Methoxybenzyl.



alcohol **18** [10]. Protection of the OH group as its Bn ether under conventional conditions gave olefin **6** [11].

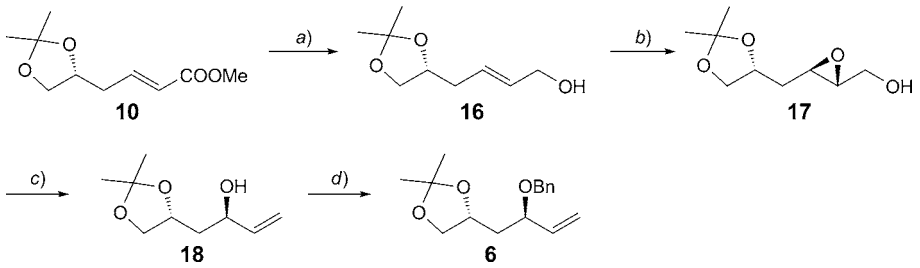
To access the functionalized C_{10} intermediate **5**, we envisaged a cross-metathesis reaction [12] as the conjunctive protocol for the union of two equally complex moieties (*Scheme 4*). The reason for invoking this reaction is twofold: our earlier experience [12f][12g] on its use in natural-product synthesis and the challenge this reaction poses when two highly substituted complex synthons are the reactants. Accordingly, in order to optimize the cross-metathesis product **5**, various reaction conditions were evaluated. The results are compiled in the *Table.* Amongst all, *Grubbs* second-generation catalyst *Gr-II*; (10 mol-%)-mediated metathesis reaction between olefin **7** (1 equiv.) and allylic

Scheme 2



a) 1. $NaIO_4$, sat. $NaHCO_3$, CH_2Cl_2, 0° to r.t.; 2. $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 0° to r.t., 75%. *b*) ^{t}BuPh$_2$SiCl (TBDPSCl), 1*H*-imidazole, CH_2Cl_2, r.t.; 95%. *c*) Diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, −78° to 0°; 98%; *d*) (−)-Diisopropyl D-tartrate ((−)-DIPT), Ti(O^{i}Pr)$_4$, cumene hydroperoxide (CHP), CH_2Cl_2, −20°; 90%. *e*) 1. Me_2CuLi, Et_2O, −20°; 2. $NaIO_4$, sat. $NaHCO_3$, CH_2Cl_2, 0° to r.t., 85%. *f*) 1. Anisaldehyde dimethyl acetal, TsOH, CH_2Cl_2, 96%; 2. DIBAL-H, CH_2Cl_2, 0°, 78%. *g*) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°; 2. $MePPh_3^+I^-$, ^{t}BuOK, THF, −5° to 0°; 80%.

Scheme 3

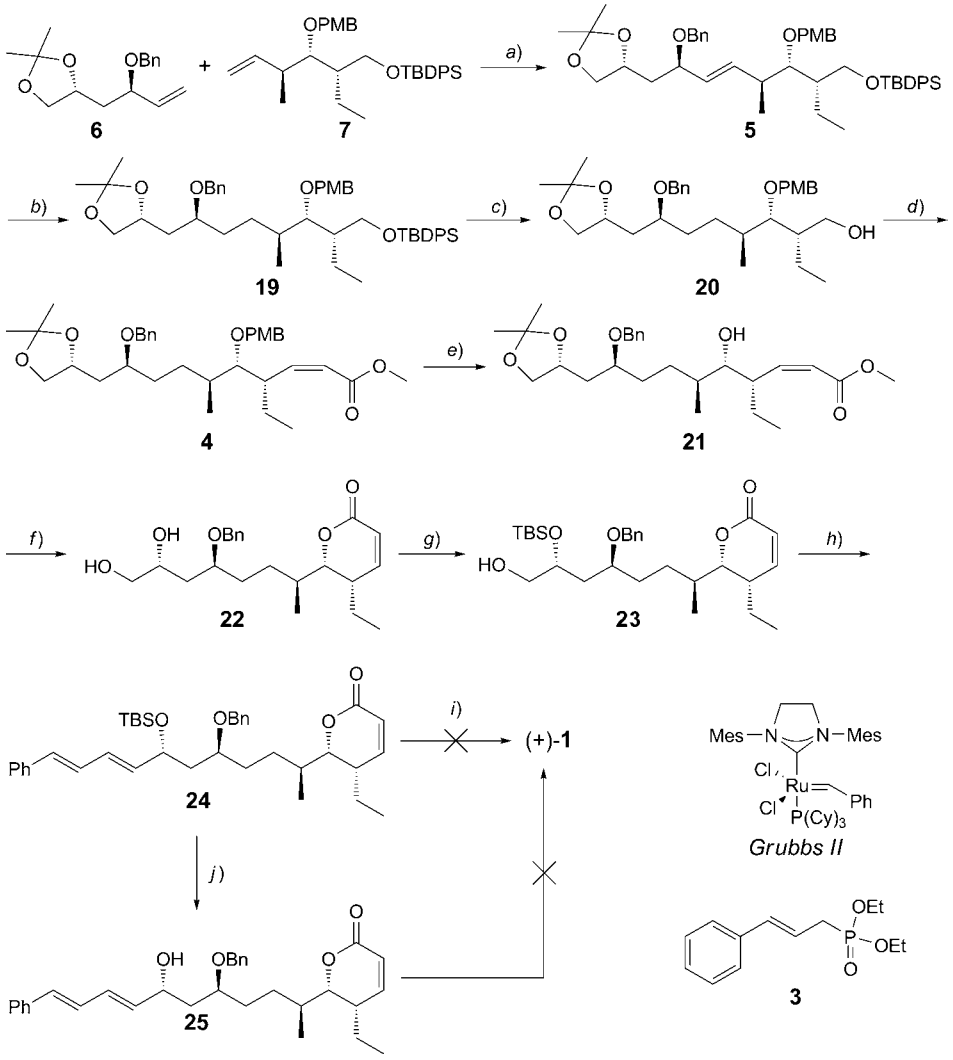


a) DIBAL-H, CH_2Cl_2, 0 °, 81%. *b*) (−)-DIPT, Ti(O^{i}Pr)$_4$, CHP, CH_2Cl_2, −20°; 90%. *c*) 1. Ph_3P, $NaHCO_3$, CCl_4, reflux; 2. Na/Et_2O, 0° to r.t., 82%. *d*) NaH, BnBr, THF, 0° to r.t., 85%.

alcohol **6** (1.5 equiv.) in CH_2Cl_2 (0.4M) at 45° afforded **5** (in an optimum yield of 47% (*E*)/(*Z*) 90:10; *Entry 4*). The ^{1}H-NMR spectrum of **5** revealed the absence terminal olefinic H-atoms in both fragments, and at the same time the appearance of two new olefinic H-atom signals at δ(H) 5.68 (*dd*, *J* = 8.2, 15.6) and 5.20 ppm (*dd*, *J* = 8.2, 15.6) indicated the formation of the cross-metathesis product.

Since the geometry of the C=C is inconsequential, reduction (PtO_2/$NaHCO_3$/AcOEt) yielded the saturated compound **19**. Then, silyl deprotection gave the primary alcohol **20**, which, upon *Swern* oxidation, followed by (*Z*)-selective *Wittig* olefination [13] with the potassium salt of bis(2,2,2-trifluroethyl) [(methoxycarbonyl)methyl] phosponate, under phase-transfer conditions at −78 to 0° afforded (*Z*)-olefin **4** (66%) along with 8% of the (*E*)-olefin. Then, deprotection of the PMB ether gave the

Scheme 4



a) *Grubbs II*, 10 mol-%, CH_2Cl_2, reflux, 47%. *b*) PtO_2, $NaHCO_3$, AcOEt, r.t., 93%. *c*) Bu_4NF, THF, r.t., 94%. *d*) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78°$; 2. $(F_3CCH_2O)_2POCH_2COOMe$, Potassium bis(trimethylsilyl)amine (KHMDS), THF, $-78°$ to $0°$; 66%. *e*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O 19:1; 87%. *f*) TsOH, benzene, r.t., 80%. *g*) 1. (*tert*-Butyl)dimethylsilyl trifluoromethanesulfonate (TBDMSOTf), 2,6-lutidine, CH_2Cl_2, $-10°$, 82%; 2. HF·Pyridine, THF, $0°$ – r.t., 68%. *h*) 1. *Dess–Martin* Periodinane (DMP), $NaHCO_3$, CH_2Cl_2, $0°$ to r.t.; 2. **3**, LiOH, THF, 44%. *i*) $TiCl_4$, CH_2Cl_2, $0°$ and $-40°$ to $0°$, or BBr_3, CH_2Cl_2, $-40°$ to $0°$, or Li naphthalenide, THF, $-20°$. *j*) HF/Py, THF, $0°$ to r.t.; 50%.

Table. *Cross-Metathesis Reaction between* **6** *and* **7** *Yielding* **5**

Entry	**6**/**7** [equiv.]	Cat. (10 mol-%)	Solvent	Time [h]	Yield of **5** [%]
1	1 : 1	*Gr-I*	CH_2Cl_2	24	10
2	1 : 1	*Gr-II*	CH_2Cl_2	24	29
3	1.5 : 1	*Gr-II*	CH_2Cl_2	24	35
4	1.5 : 1	*Gr-II*	CH_2Cl_2	48	47
5	1 : 1.5	*Gr-II*	CH_2Cl_2	24	40
6	1.5 : 1	*Gr-II*	Toluene	24	32
7	1.5 : 1	*Hoveyda Gr-I*	CH_2Cl_2	24	0

corresponding hydroxy ester **21**, which, on acid-catalyzed lactonisation with concomitant deprotection of the isopropylidene group, furnished the diol **22** [13b][14].

Diol **22** was silylated (*Scheme 4*) as its ^{t}BuMe$_2$Si (TBS) ether (TBSOTf/2,6-lutidine/CH_2Cl_2/ $-10°$/20 min), and followed by selective monodeprotection [15] of the primary silyl group in the presence of HF · pyridine in THF at 0° to room temperature affording the primary alcohol **23**. The primary OH group of **23** was oxidized with *Dess–Martin* periodinane [16] to give aldehyde **2**, which, after passing through a short pad of silica gel and without any further characterization, was used for the next reaction. Thus, **2**, on LiOH-mediated *Horner–Wadsworth–Emmons* olefination [17][2a] with diethyl cinnamylphosphonate (**3**, prepared by refluxing $(EtO)_3P$ and cinnamyl bromide) in THF at reflux temperature for 12 h, furnished the (*E*)-olefin **24** (44%) along with traces of the (*Z*)-isomer. Next task was the removal of both silyl and Bn protecting groups in **24**. Initially, a one-pot deprotection of both groups was attempted, *i.e.,* the acid-catalyzed deprotection using $TiCl_4$ (*Scheme 4*). During this reaction, a total consumption of starting material was observed. The EI-MS of the crude product displayed the mass peaks at *m*/*z* 383 ($[M-H]^+$) and 384 (M^+), supporting the expected product formation. However, ^{1}H-NMR was not clean after purification. Hence, we decided to use alternate reaction conditions and attempted BBr_3-mediated one-pot deblocking strategy [18] (*Scheme 4*). Unfortunately, these reaction conditions proved too drastic and resulted in total decomposition of the starting material. Later, a stepwise deprotection was planned; first, the removal of the Bn group, followed by that of the silyl group. Accordingly, when Li napthalenide [19] in THF was used, no expected product was formed, although total consumption of starting material was observed. Alternatively, when the silyl group was removed first under conventional conditions, the expected product **25** was formed albeit in moderate yield (50%), but the removal of the 9-*O*-Bn group remained elusive as ever even under different *Lewis* acid conditions (like $TiCl_4$ or BCl_3) or under reductive conditions. Though Bn removal was reported under certain conditions such as $CrCl_2$/LiI [20a] in aqueous AcOEt or according to some other protocols [20b], herein the removal of 9-*O*-Bn proved difficult due to the sensitivity of the skeleton. Since all the above conditions proved futile, the synthetic route was abandoned.

Conclusions. – The synthesis of (5*S*,6*S*)-6-[(2*S*,5*S*,7*R*,8*E*,10*E*)-5-(benzyloxy)-7-{[(*tert*-butyl)dimethylsilyl]oxy}-11-phenylundeca-8,10-dien-2-yl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (9-*O*-benzyl-11-*O*-[(*tert*-butyl)dimethylsilyl]bitungolide F) containing

five stereogenic centers and two conjugated (*E*)-C=C was achieved involving cross-metathesis reaction as the key step.

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Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. Org. solns. were dried (anh. Na_2SO_4) and concentrated below 40° *in vacuo*. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh). Optical rotations: *JASCO DIP 300* digital polarimeter at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ^{1}H- (200, 300, and 500 MHz) and ^{13}C-NMR (50, 75, and 100 MHz) spectra: *Varian Gemini FT-200* MHz, *Bruker Avance* 300 MHz, and *Bruker Avance* 500 MHz spectrometers with TMS as internal standard for solns. in $CDCl_3$; *J* values in Hz. MS: *CEC-21-11013* or *Finnigan Mat 1210* double-focusing mass spectrometers operating at a direct inlet system or *LC/MSD Trap SL* (*Agilent Technologies*). The software ACD/Name Version 1.0, developed by M/s Advanced Chemistry Development Inc., Toronto, Canada, assisted nomenclature used in the *Exper. Part.*

*Ethyl (2*E*,4*R*)-4-(Hydroxymethyl)hex-2-enoate* (**11**). To a stirred soln. of **9** [3] (3.70 g, 27.61 mmol) in CH_2Cl_2 (40 ml) were added $NaIO_4$ (9.2 g, 43.0 mmol) and sat. aq. $NaHCO_3$ (1.5 ml) at 0°, the mixture was stirred at r.t. for 10 h, then filtered through a Na_2SO_4 pad, washed with CH_2Cl_2 (30 ml), CH_2Cl_2 was evaporated, and the crude aldehyde was used as such for the next step.

To a soln. of the aldehyde (2.70 g, 26.47 mmol) in CH_2Cl_2 (30 ml) was added ethyl (triphenyl-λ^5-phosphanylidene)acetate (13.91 g, 31.76 mmol) at 0°. The mixture was stirred at r.t. for 3 h, then CH_2Cl_2 was evaporated, and the residue was purified by CC (SiO_2; AcOEt/hexane 1:4) to furnish **11** (3.55 g, 75% yield for two steps). Colorless liquid. $[\alpha]_D^{25} = -35.1$ ($c = 2.5$, $CHCl_3$). IR (neat): 3400, 1700, 1610, 1290. ^{1}H-NMR (200 MHz): 6.74 (*dd*, *J* = 8.8, 15.4, 1 H); 5.87 (*d*, *J* = 16.6, 1 H); 4.19 (*q*, *J* = 7.3, 2 H); 3.68–3.54 (*m*, 2 H); 2.39–2.18 (*m*, 1 H); 1.68–1.38 (*m*, 2 H); 1.30 (*t*, *J* = 7.3, 3 H); 0.92 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz): 166.7; 150.3; 123.0; 64.7; 60.4; 46.8; 23.0; 14.0; 11.4. EI-MS: 172 (M^+). Anal. calc. for $C_9H_{16}O_3$ (172.22): C 62.77, H 9.36; found: C 62.75, H 9.35. These data are consistent with those reported in [4].

*Ethyl (2*E*,4*R*)-4-({[(*tert*-Butyl)diphenylsilyl]oxy}methyl)hex-2-enoate* (**12**). To a cooled soln. of **11** (3.2 g, 18.60 mmol) and 1*H*-imidazole (3.79 g, 55.80 mmol) in CH_2Cl_2 (30 ml) was slowly added TBDPSCl (5.35 ml, 20.46 mmol) at 0°. The mixture was warmed to r.t. and stirred for 3 h, the reaction was quenched with aq. HCl (1N, 30 ml), and the layers separated. The org. phase was washed with brine (100 ml), dried (Na_2SO_4), filtered, and concentrated to afford **12** (7.20 g, 95%) after CC (SiO_2; AcOEt/hexane 4:96). White syrupy liquid. $[\alpha]_D^{25} = +0.32$ ($c = 1.3$, $CHCl_3$). IR (neat): 1750, 1610, 1210. ^{1}H-NMR (300 MHz): 7.63–7.57 (*m*, 4 H); 7.41–7.29 (*m*, 6 H); 6.78 (*dd*, *J* = 8.3, 15.8, 1 H); 5.79 (*d*, *J* = 14.3, 1 H); 4.18 (*q*, *J* = 6.7, 2 H); 3.59 (*dd*, *J* = 2.2, 6.0, 2 H); 2.33–2.21 (*m*, 1 H); 1.67–1.55 (*m*, 1 H); 1.45–1.31 (*m*, 1 H); 1.11 (*t*, *J* = 6.7, 3 H); 1.03 (*s*, 9 H); 0.86 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR (100 MHz): 166.4; 150.3; 135.4; 133.4; 129.5; 127.5; 122.2; 66.0; 60.1; 46.8; 26.8; 23.2; 19.4; 14.3; 11.5. HR-ESI-MS: 433.2190 ($[M + Na]^+$, $C_{25}H_{34}NaO_3Si^+$; calc. 433.2175).

*(2*E*,4*R*)-4-({[(*tert*-Butyl)diphenylsilyl]oxy}methyl)hex-2-en-1-ol* (**13**). To a stirred soln. of **12** (7.00 g, 17.07 mmol) in anh. CH_2Cl_2 (70 ml), DIBAL-H (34.14 ml, 34.14 mmol, 1M soln. in hexane) was added at −10°, and the mixture was stirred at 0° for 2 h. Then, MeOH (3 ml) was added, to the mixture at 0° and stirred for 10 min. Next, sat. aq. soln. of sodium potassium tartarate (10 ml) was added, and after 10 min MeOH was evaporated. The residue was diluted with H_2O (40 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined org. layers were washed with brine (100 ml), dried (Na_2SO_4), concentrated, and the residue was purified by CC (SiO_2; AcOEt/hexane 10:90) to afford **13** (6.15 g, 98%). Colorless syrup. $[\alpha]_D^{25} = -24.7$ ($c = 1.2$, $CHCl_3$). IR (neat): 3420, 3110, 1590, 1200. ^{1}H-NMR (200 MHz): 7.66–7.56 (*m*, 4 H); 7.41–7.28 (*m*, 6 H); 5.71–5.35 (*m*, 2 H); 4.04 (*d*, *J* = 5.4, 2 H); 3.57 (*d*, *J* = 6.3, 2 H); 2.20–2.00 (*m*, 1 H); 1.67–1.50 (*m*, 3 H); 1.03 (*s*, 9 H); 0.84 (*t*, *J* = 7.8, 3 H). ^{13}C-NMR (100 MHz): 135.5; 134.2;

133.8; 130.2; 129.5; 127.5; 66.9; 63.8; 46.6; 26.8; 23.6; 19.2; 11.5. HR-ESI-MS: 391.2062 ([M + Na]$^+$, $C_{23}H_{32}NaO_2Si^+$; calc. 391.2069).

*3,4-Anhydro-1-*O*-[(*tert*-butyl)diphenylsilyl]-2-deoxy-2-ethyl-*L*-arabinitol* (**8**). To a suspension of thoroughly dried molecular sieves (MS) (4 Å, 5 g) in anh. CH_2Cl_2 (60 ml) was added (−)-DIPT (2.30 g in 10 ml CH_2Cl_2, 9.82 mmol), followed by slow addition of $Ti(O^iPr)_4$ (2.40 ml, 8.45 mmol) at −20°. After stirring for 30 min, cumene hydroperoxide (CHP; 2.94 ml, 19.68 mmol) was slowly added, and the resulting soln. was stirred at −20° for a further 30 min. Allylic alcohol **13** (6.1 g, 16.50 mmol) in CH_2Cl_2 (20 ml) was then added, and the mixture was stirred at −20° for 3 h, then warmed up to 0°, and an aq. basic soln. (3M NaOH/brine 3 : 7, 30 ml) was added. After stirring for 1 h, the mixture was filtered through a pad of *Celite*, and the pad was further washed with CH_2Cl_2. The filtrate was concentrated and purified by flash CC (SiO_2; AcOEt/hexane 20 : 80) to afford **8** (5.7 g, 90%) Colorless oil. $[\alpha]_D^{25} = +37.14$ ($c = 3.7$, $CHCl_3$). IR (neat): 3415, 3010, 1240, 1140. ^{1}H-NMR (200 MHz): 7.70–7.53 (*m*, 4 H); 7.43–7.30 (*m*, 6 H); 3.83 (*d*, $J = 1.7$, 1 H); 3.72–3.49 (*m*, 3 H); 2.98–2.85 (*m*, 2 H); 1.63–1.14 (*m*, 3 H); 1.04 (*s*, 9 H); 0.91 (*t*, $J = 7.3$, 3 H). ^{13}C-NMR (100 MHz): 135.4; 133.5; 129.6; 127.6; 64.1; 61.7; 58.3; 58.0; 45.3; 26.7; 22.1; 19.0; 11.4. HR-ESI-MS: 407.2010 ([M + Na]$^+$, $C_{23}H_{32}NaO_3Si^+$; calc. 407.2018).

*1-*O*-[(*tert*-Butyl)diphenylsilyl]-2,4-dideoxy-2-ethyl-4-methyl-*L*-arabinitol* (**14**). To a stirred mixture of CuI (11.88 g, 62.40 mmol) in anh. Et_2O (100 ml), MeLi (78 ml, 124.80 mmol, 1.6M soln. in hexane) was added within 30 min at 0°. The yellow color of the mixture turned to colorless, and stirring was continued for 0.5 h. A soln. of **8** (4.80 g, 12.48 mmol) in anh. Et_2O (20 ml) was added at −20°, and the mixture was stirred for 20 h at the same temp. The reaction was quenched with aq. NH_4Cl (60 ml) and NH_3 solns. (60 ml) at 0°, and the mixture was allowed to be stirred for 15 min. Org. layer was separated, and the aq. layer was extracted with AcOEt (2 × 100 ml). The combined org. layers were washed with H_2O (2 × 100 ml) and brine (100 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was treated with $NaIO_4$ in CH_2Cl_2 for 10 h at r.t., then purified by CC (SiO_2; AcOEt/hexane, 23 : 77) to afford **14** (4.25 g, 85%). Colorless liquid. $[\alpha]_D^{25} = +30.62$ ($c = 2.65$, $CHCl_3$). IR (neat): 3450, 3090, 1240, 1140. ^{1}H-NMR (300 MHz): 7.67–7.61 (*m*, 4 H); 7.45–7.34 (*m*, 6 H); 3.84–3.76 (*m*, 3 H); 3.72–3.55 (*m*, 2 H); 1.98–1.84 (*m*, 1 H); 1.65–1.42 (*m*, 2 H); 1.37–1.31 (*m*, 1 H); 1.06 (*s*, 9 H); 0.78 (*t*, $J = 7.5$, 3 H); 0.72 (*d*, $J = 7.5$, 3 H). ^{13}C-NMR (75 MHz): 135.6; 132.6; 129.9; 127.7; 81.7; 68.8; 66.3; 43.5; 37.2; 26.8; 19.1; 15.9; 13.7; 12.1. HR-ESI-MS: 423.2315 ([M + Na]$^+$, $C_{24}H_{36}NaO_3Si^+$; calc. 423.2331).

*1-*O*-[(*tert*-Butyl)diphenylsilyl]-2,4-dideoxy-2-ethyl-3,5-*O*-(4-methoxybenzylidene)-4-methyl-*L*-arabinitol*. To a soln. of **14** (3.80 g, 9.50 mmol) in anh. CH_2Cl_2 (30 ml) were added *p*-anisaldehyde dimethyl acetal (1.79 ml, 10.45 mmol) and cat. TsOH at r.t. After 2 h at r.t., anh. MeOH (1 ml) was added, and the soln. was stirred for 5 min, and then cooled to 0°. A sat. aq. soln. of $NaHCO_3$ (10 ml) and H_2O (30 ml) were added. The mixture was extracted with CH_2Cl_2 (2 × 60 ml), the extracts were washed with brine (70 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (SiO_2; AcOEt/hexane 3 : 97) to afford the cyclic acetal (4.7 g, 96%). Colorless oil. $[\alpha]_D^{25} = +59.0$ ($c = 1.0$, $CHCl_3$). IR (neat): 3070, 2900, 1260, 1140. ^{1}H-NMR (300 MHz): 7.66–7.55 (*m*, 4 H); 7.39–7.16 (*m*, 8 H); 6.79 (*d*, $J = 8.3$, 2 H); 5.32 (*s*, 1 H); 4.07 (*dd*, $J = 4.5$, 10.5, 1 H); 3.86–3.60 (*m*, 7 H); 2.11–2.00 (*m*, 1 H); 1.81–1.70 (*m*, 1 H); 1.66–1.49 (*m*, 1 H); 1.28–1.10 (*m*, 1 H); 1.04 (*s*, 9 H); 0.75 (*t*, $J = 6.7$, 3 H); 0.72 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (75 MHz): 135.5; 133.0; 129.5; 129.4; 127.5; 127.3; 113.3; 100.9; 81.5; 73.3; 62.8; 55.2; 43.3; 30.1; 29.6; 26.8; 18.0; 12.9; 12.3. HR-ESI-MS: 541.2758 ([M + Na]$^+$, $C_{32}H_{42}NaO_4Si^+$; calc. 541.2750).

*1-*O*-[(*tert*-Butyl)diphenylsilyl]-2,4-dideoxy-2-ethyl-3-*O*-(4-methoxybenzyl)-4-methyl-*L*-arabinitol* (**15**). DIBAL-H (9.55 ml, 1M soln. in hexane, 9.55 mmol) was added to a soln. of the cyclic acetal (4.50 g, 8.68 mmol) in CH_2Cl_2 (40 ml) at −20°, and the temp. was raised to 0°. After 3 h, MeOH (3 ml) was added to the mixture at 0°, and the mixture was stirred for 10 min. Sat. aq. soln. of sodium potassium tartrate (10 ml) was added, and after 10 min MeOH was evaporated. The mixture was diluted with H_2O (30 ml) and extracted with CH_2Cl_2 (2 × 60 ml). The org. layer was washed with brine (60 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; AcOEt/hexane 10 : 90) to afford **15** (3.50 g, 78%). Colorless liquid. $[\alpha]_D^{25} = +7.70$ ($c = 1.5$, $CHCl_3$). IR (neat): 3400, 3100, 1200, 1140. ^{1}H-NMR (200 MHz): 7.64–7.60 (*m*, 4 H); 7.42–7.60 (*m*, 6 H); 7.11 (*d*, $J = 8.0$, 2 H); 6.76 (*d*, $J = 8.8$, 2 H); 4.50–4.40 (*m*, 2 H); 3.77 (*s*, 3 H); 3.72–3.54 (*m*, 5 H); 1.96–1.77 (*m*, 1 H); 1.60–1.40 (*m*, 2 H); 1.32–1.13 (*m*, 1 H); 1.07 (*s*, 9 H); 0.88 (*t*, $J = 7.3$, 3 H); 0.77 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (75 MHz):

135.5; 133.1; 131.2; 129.6; 129.3; 127.6; 113.8; 84.2; 74.8; 66.8; 63.7; 55.2; 45.7; 37.8; 26.9; 18.7; 15.2; 12.6. HR-ESI-MS: 543.2899 ($[M + Na]^+$, $C_{32}H_{44}NaO_4Si^+$; calc. 543.2907).

(tert-*Butyl)({(2S,3S,4S)-2-ethyl-3-[(4-methoxybenzyl)oxy]-4-methylhex-5-en-1-yl}oxy)diphenylsilane* (**7**). A soln. of oxalyl chloride (0.57 ml, 6.63 mmol) and CH_2Cl_2 (15 ml) at $-78°$ was treated with DMSO (1.03 ml, 13.26 mmol). After 15 min, a soln. of **15** (2.30 g, 4.42 mmol) in CH_2Cl_2 (10 ml) was added dropwise. After 1 h, Et_3N (3.69 ml, 26.52 mmol) was added dropwise, and the mixture was warmed to $-30°$. Then, it was diluted with CH_2Cl_2 (20 ml), warmed to r.t., and washed sequentially with H_2O (25 ml), sat. aq. NH_4Cl (20 ml), H_2O (25 ml), and brine (25 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford aldehyde (2.30 g, 99% crude) as a clear, colorless oil. This was used without further purification.

To a soln. of (methylidene)triphenylphosphonium iodide (4.72 g, 13.32 mmol) in anh. THF (25 ml), ^{t}BuOK (1.24 g, 11.10 mmol) was added at $-5°$, and the mixture was stirred for 3 h at 0°. The aldehyde (2.30 g, 4.40 mmol) in anh. THF (10 ml) was added at 0°, and the mixture was stirred for 3 h. The reaction was quenched with sat. NH_4Cl (20 ml) soln., org. layer was separated, and the aq. layer was extracted with Et_2O (2×60 ml). The combined org. layers were washed with brine (20 ml), dried (Na_2SO_4), and concentrated to give a crude residue, which was purified by CC (SiO_2; AcOEt/hexane 2:98) to afford **7** (1.82 g, 80% over two steps). Colorless syrup. $[\alpha]_D^{25} = +40.97$ ($c = 2.2$, $CHCl_3$). IR (neat): 3100, 1610, 1190, 1140. ^{1}H-NMR (200 MHz): 7.69–7.55 (*m*, 4 H); 7.42–7.26 (*m*, 6 H); 7.17 (*d*, $J = 8.8$, 2 H); 6.79 (*d*, $J = 8.8$, 2 H); 5.98 (*m*, 1 H); 5.00–4.51 (*m*, 2 H); 4.45–4.30 (*m*, 2 H); 3.77 (*s*, 3 H); 3.61 (*d*, $J = 5.1$, 2 H); 3.50 (*t*, $J = 5.1$, 1 H); 2.48–2.27 (*m*, 1 H); 1.69–1.43 (*m*, 2 H); 1.33–1.24 (*m*, 1 H); 1.06 (*s*, 9 H); 0.98 (*t*, $J = 6.6$, 3 H); 0.76 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR (75 MHz): 158.9; 141.7; 135.6; 133.8; 131.4; 129.6; 129.1; 127.5; 114.1; 113.5; 82.7; 74.4; 62.9; 55.2; 45.2; 40.9; 26.9; 19.2; 18.7; 17.6; 12.2. HR-ESI-MS: 539.2947 ($[M + Na]^+$, $C_{33}H_{44}NaO_3Si^+$; calc. 539.2957).

*(2*E*)-4-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]but-2-en-1-ol* (**16**). To a stirred soln. of **10** (6.82 g, 34.1 mmol) in anh. CH_2Cl_2 (20 ml), DIBAL-H (68.2 ml, 68.2 mmol, 1M soln. in hexane) was added at 0°, and the mixture was stirred at the same temp. for 2 h. MeOH (2 ml) was added to the mixture at 0° and stirred for 10 min., sat. aq. soln. of sodium potassium tartrate (5 ml) was added, and, after 10 min, MeOH was evaporated. The residue was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (2×25 ml). The combined org. layers were washed with brine (10 ml), dried (Na_2SO_4), concentrated, and the residue was purified by CC (SiO_2; AcOEt/hexane 2:8) to afford **16** (4.75 g, 81%). Colorless syrup. $[\alpha]_D^{25} = +42.0$ ($c = 0.50$). IR (neat): 3400, 1610, 1220, 1160. ^{1}H-NMR (300 MHz): 5.79–5.58 (*m*, 2 H); 4.18–4.06 (*m*, 3 H); 3.98 (*dd*, $J = 6.0, 8.3$, 1 H), 3.80 (*dd*, $J = 6.0, 8.3$, 1 H), 2.41–2.21 (*m*, 2 H); 1.73–1.51 (br. *s*, 1 H); 1.38 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (75 MHz): 132.1; 127.1; 108.9; 75.1; 68.7; 63.1; 36.4; 26.7; 25.4. EI-MS: 172 (M^+). Anal. calc. for $C_9H_{16}O_3$ (172.22): C 62.77, H 9.36; found: C 62.79, H 9.34. Spectroscopic data are consistent with those reported in [10].

*4,5-Anhydro-3-deoxy-1,2-*O*-(1-methylethylidene)-*D*-xylo-hexitol* (**17**). To a suspension of thoroughly dried MS (4 Å, 3.0 g) in anh. CH_2Cl_2 (60 ml) was added (−)-DIPT (0.59 ml, 2.52 mmol), followed by slow addition of $Ti(O^iPr)_4$ (0.37 ml, 1.26 mmol) at $-20°$. After stirring for 30 min, CHP (1.94 ml, 12.60 mmol) was slowly added, and the mixture was stirred at $-20°$ for a further 30 min. Allylic alcohol **16** (4.3 g, 25.00 mmol) in CH_2Cl_2 (20 ml) was then added, and the mixture was stirred at $-20°$ for 12 h, then warmed up to 0°, and an aq. basic soln. (3M NaOH/brine 3:7, 100 ml) was added. After stirring for 1 h, the mixture was filtered through a pad of *Celite*, and the pad was further washed with CH_2Cl_2. The filtrate was concentrated and purified by flash CC (SiO_2; AcOEt/hexane 25:75) to afford **17** (4.23 g, 90%). Colorless oil. $[\alpha]_D^{25} = +79.92$ ($c = 0.85$, $CHCl_3$). IR (neat): 3410, 1200, 1110. ^{1}H-NMR (200 MHz): 4.31–4.14 (*m*, 1 H); 4.05 (*dd*, $J = 5.4, 7.8$, 1 H); 3.83 (*dd*, $J = 2.3, 12.5$, 1 H); 3.66–3.48 (*m*, 2 H); 3.09–2.99 (*m*, 1 H); 2.91–2.87 (*m*, 1 H); 2.03–1.83 (*m*, 1 H); 1.69–1.50 (*m*, 1 H); 1.38 (*s*, 3 H); 1.34 (*s*, 3 H). ^{13}C-NMR (75 MHz): 108.9; 73.3; 69.1; 61.4; 58.6; 52.9; 36.3; 26.7; 25.4. EI-MS: 188 (M^+). Anal. calc. for $C_9H_{16}O_4$ (188.22): C 57.43, H 8.57; found: C 57.45, H 8.59. Spectroscopic data are consistent with those reported in [10].

*(2*R*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]but-3-en-2-ol* (**18**). To a stirred soln. of **17** (4.0 g, 21.27 mmol) in anh. CCl_4 (25 ml), Ph_3P (11.1 g, 42.55 mmol) and $NaHCO_3$ (0.178 g, 2.17 mmol) were added, and the mixture was heated reflux for 4 h. CCl_4 was evaporated under reduced pressure, and the

residue was purified by CC (SiO_2; AcOEt/hexane, 0.5:9.5) to afford epoxy chloride quantitatively as a colorless syrup.

A soln. of epoxy chloride (4.30 g, 20.87 mmol) in anh. Et_2O (15 ml) was added dropwise to a stirred suspension of freshly prepared Na sand (0.96 g, 41.7 mmol) in anh. Et_2O (20 ml) under N_2 at r.t. during 20 min. After complete addition, the mixture was stirred for further 8 h. Then, the reaction was carefully quenched with MeOH (10 ml) at 0°, and the mixture was diluted with brine (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC (SiO_2; AcOEt/hexane 2:8) to give **18** (3.0 g, 82% over two steps). Colorless syrup. $[\alpha]_D^{25} = -25.84$ ($c = 1.1$, $CHCl_3$). IR (neat): 3420, 3010, 1610, 1220, 1110. ^{1}H-NMR (300 MHz): 5.92–5.80 (*m*, 1 H); 5.33–5.06 (*m*, 2 H); 4.37–4.20 (*m*, 2 H); 4.03 (*dd*, $J = 6.0, 8.3$, 1 H); 3.53 (*t*, $J = 7.5$, 1 H); 2.36–2.10 (br. *s*, 1 H); 1.85–1.62 (*m*, 2 H); 1.39 (*s*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR (75 MHz): 140.5; 114.3; 108.8; 73.2; 69.8; 69.4; 39.8; 26.8; 25.6. EI-MS: 172 (M^+). Anal. calc. for $C_9H_{16}O_3$ (172.22): C 62.77, H 9.36; found: C 62.76, H 9.33. Spectroscopic data are consistent with reported ones [12].

*(4*R*)-4-[(2*R*)-2-(Benzyloxy)but-3-en-1-yl]-2,2-dimethyl-1,3-dioxolane* (**6**). To a cooled (0°) suspension of NaH (0.837 g, 34.8 mmol, 60% (*w*/*w*) dispersion in paraffin oil) in THF (15 ml), a soln. of **18** (3.0 g, 17.4 mmol) in THF (10 ml) was added dropwise. After 15 min, BnBr (3.28 g, 17.4 mmol) was added dropwise at 0° and stirred for 6 h at r.t. The reaction was quenched with sat. aq. NH_4Cl soln. (30 ml), and the mixture was extracted with AcOEt (2 × 100 ml). The combined org. layers were washed with H_2O (100 ml) and brine (50 ml), dried (Na_2SO_4), and evaporated. The crude product was purified by CC (SiO_2; AcOEt/hexane, 1:9) to afford **6** (3.87 g, 85%). Light-yellow syrup. $[\alpha]_D^{25} = +59.81$ ($c = 0.9$, $CHCl_3$). IR (neat): 2990, 1610, 1190, 1100. ^{1}H-NMR (300 MHz): 7.37–7.17 (*m*, 5 H); 5.85–5.65 (*m*, 1 H); 5.28–5.15 (*m*, 2 H); 4.60–4.10 (*m*, 3 H); 4.05–3.80 (*m*, 2 H); 3.47 (*t*, $J = 7.8$, 1 H); 1.75 (*t*, $J = 6.2$, 2 H); 1.35 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (75 MHz): 138.5; 138.0; 128.3; 127.7; 127.4; 117.4; 108.3; 77.7; 73.3; 70.4; 69.9; 40.0; 26.9; 25.8. HR-ESI-MS: 285.1458 ($[M + Na]^+$, $C_{16}H_{22}NaO_3^+$; calc. 285.1467). Spectroscopic data are consistent with those reported in [11].

*({(2*S*,3*S*,4*S*,5*E*,7*R*)-7-(Benzyloxy)-8-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-ethyl-3-[(4-methoxybenzyl)oxy]-4-methyloct-5-en-1-yl}oxy)*(tert-*butyl)diphenylsilane* (**5**). To a soln. of **7** (0.882 g, 1.71 mmol) in anh. CH_2Cl_2 (0.4M) were added **6** (0.673 g, 2.57 mmol) and *Grubbs II* catalyst (10 mol-%) under N_2 at r.t., then temp. was raised to reflux, and the mixture was stirred for 48 h. The mixture was directly adsorbed on SiO_2 to perform the CC (SiO_2; AcOEt/hexane 4:96) to afford **5** (0.60 g, 47%). Colorless syrup. $[\alpha]_D^{25} = +32.99$ ($c = 2.0$, $CHCl_3$). IR (neat): 3010, 2940, 1610, 1190, 1100. ^{1}H-NMR (200 MHz): 7.73–7.54 (*m*, 4 H); 7.49–7.08 (*m*, 13 H); 6.78 (*d*, $J = 8.5$, 2 H); 5.68 (*dd*, $J = 8.2, 15.6$, 1 H); 5.20 (*dd*, $J = 8.2, 15.6$, 1 H); 4.57–4.37 (*m*, 4 H); 4.30–4.09 (*m*, 2 H); 3.94 (*dd*, $J = 5.8, 7.8$, 1 H); 3.76 (*s*, 3 H); 3.61–3.45 (*m*, 2 H); 3.39 (*t*, $J = 7.8$, 1 H); 2.50–2.29 (*m*, 1 H); 1.67–1.24 (*m*, 14 H); 1.07 (*s*, 9 H); 0.78 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (75 MHz): 158.5; 139.0; 136.8; 135.3; 133.5; 131.1; 129.6; 129.3; 128.6; 127.9; 127.4; 127.3; 127.1; 113.3; 108.5; 82.5; 76.3; 74.3; 73.1; 69.7; 69.6; 62.5; 54.9; 45.3; 39.9; 39.6; 29.2; 26.6; 25.5; 19.0; 18.6; 18.3; 12.0. HR-ESI-MS: 773.4215 ($[M + Na]^+$, $C_{47}H_{62}NaO_6Si^+$; calc. 773.4213).

*({(2*S*,3*S*,4*S*,7*S*)-7-(Benzyloxy)-8-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-ethyl-3-[(4-methoxybenzyl)oxy]-4-methyloctyl}oxy)*(tert-*butyl)diphenylsilane* (**19**). To a stirred soln. of **5** (1.4 g, 1.86 mmol) in AcOEt (6 ml), a cat. amount of PtO_2 was added, and the mixture was stirred for 8 h at r.t. under H_2. The mixture was filtered through a pad of *Celite*; and the filtrate was concentrated under reduced pressure and adsorbed on SiO_2 for the CC (SiO_2; AcOEt/hexane 4:96) to furnish **19** (1.30 g, 93%). Colorless syrup. $[\alpha]_D^{25} = +23.95$ ($c = 0.35$, $CHCl_3$). IR (neat): 3020, 2990, 1290, 1120. ^{1}H-NMR (200 MHz): 7.62–7.59 (*m*, 4 H); 7.36–7.23 (*m*, 11 H); 7.13 (*d*, $J = 8.2$, 2 H); 6.75 (*d*, $J = 8.2$, 2 H); 4.57–4.32 (*m*, 4 H); 4.29–4.07 (*m*, 1 H); 4.03–3.89 (*m*, 1 H); 3.75 (*s*, 3 H); 3.62–3.38 (*m*, 5 H); 1.17–1.08 (*m*, 16 H); 1.07 (*s*, 9 H); 0.85 (*d*, $J = 6.6$, 3 H); 0.74 (*t*, $J = 7.4$, 3 H). ^{13}C-NMR (75 MHz): 135.6; 133.2; 130.9; 129.6; 129.0; 128.3; 127.8; 127.6; 127.5; 113.6; 108.3; 83.2; 76.9; 74.7; 73.7; 71.5; 70.1; 63.6; 55.2; 44.9; 39.5; 39.0; 36.1; 32.0; 27.0; 25.9; 19.3; 19.0; 18.4; 16.7; 12.6. HR-ESI-MS: 775.4386 ($[M + Na]^+$, $C_{47}H_{64}NaO_6Si^+$; calc. 775.4370).

*(2*S*,3*S*,4*S*,7*S*)-7-(Benzyloxy)-8-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-ethyl-3-[(4-methoxybenzyl)oxy]-4-methyloctan-1-ol* (**20**). To a soln. of **19** (1.25 g, 1.66 mmol) in anh. THF (10 ml), Bu_4NF (2 ml, 1.99 mmol, 1M soln. in THF) was added at 0° under N_2 atmosphere, and the mixture was stirred for 12 h at r.t. THF was evaporated to furnish a crude residue, which was purified by CC (SiO_2; AcOEt/hexane

16:84) to afford **20** (0.80 g, 94%). Colorless syrup. $[\alpha]_D^{25} = +27.9$ ($c = 0.4$, $CHCl_3$). IR (neat): 3400, 3010, 2920, 1190, 1100. ^{1}H-NMR (200 MHz): 7.32–7.23 (*m*, 5 H); 7.18 (*d*, *J* = 8.3, 2 H); 6.75 (*d*, *J* = 8.3, 2 H); 4.58–4.41 (*m*, 4 H); 4.22–4.00 (*m*, 1 H); 3.98 (*dd*, *J* = 6.0, 7.9, 1 H); 3.75 (*s*, 3 H); 3.67–3.56 (*m*, 3 H); 3.44 (*t*, *J* = 7.9, 1 H); 3.34 (*dd*, *J* = 2.6, 6.7, 1 H); 1.78–1.62 (*m*, 8 H); 1.53–1.43 (*m*, 2 H); 1.36 (*s*, 3 H); 1.30 (*s*, 3 H); 0.88 (*m*, 6 H). ^{13}C-NMR (75 MHz): 130.7; 129.2; 128.2; 127.7; 127.4; 113.7; 108.3; 84.3; 76.7; 73.8; 73.5; 71.4; 69.9; 63.4; 55.1; 44.0; 38.9; 35.6; 32.0; 27.6; 26.9; 25.7; 18.7; 16.7; 12.5. HR-ESI-MS: 537.3184 ($[M + Na]^+$, $C_{31}H_{46}NaO_6^+$; calc. 537.3192).

*Methyl (2Z,4*S*,5*S*,6*S*,9*S*)-9-(Benzyloxy)-10-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-ethyl-5-[(4-methoxybenzyl)oxy]-6-methyldec-2-enoate* (**4**). To a stirred soln. of oxalyl chloride (0.20 ml, 2.33 mmol) in CH_2Cl_2 (7 ml) at $-78°$, DMSO (0.36 ml, 4.66 mmol) was added. After 15 min, a soln. of **20** (0.80 g, 1.55 mmol) in CH_2Cl_2 (5 ml) was added dropwise. After 1 h, Et_3N (1.30 ml, 9.32 mmol) was added dropwise, and the mixture was warmed to $-30°$. It was diluted with CH_2Cl_2 (15 ml), warmed to r.t., and washed sequentially with H_2O (20 ml) and brine (20 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford 0.80 g (99% crude yield) of aldehyde as a light yellow syrup. This was used as such for further reaction.

To a stirred soln. of $(F_3CCH_2O)_2POCH_2COOMe$ (0.66 ml, 3.12 mmol), 18-crown-6 (2.46 g, 9.36 mmol) in anh. THF (8 ml) was added KHMDS (5.86 ml, 2.93 mmol, 0.5M soln. in toluene) at $-78°$, and the temp. was raised to 0°, and the mixture was stirred for further 30 min. To the mixture, aldehyde (0.80 g, 1.55 mmol) dissolved in THF (5 ml) was added at $-78°$. The mixture was stirred for 2 h at $-78°$, then temp. was gradually increased to 0° in 6 h. Later, the reaction was quenched with aq. NH_4Cl (10 ml), and the mixture was extracted with AcOEt (2 × 30 ml). The combined org. layers were washed with brine (1 × 30 ml), dried (Na_2SO_4), and concentrated, and the residue was purified by CC (SiO_2; AcOEt/hexane 6:94) to give **4** (0.58 g, 66%). Colorless syrup. $[\alpha]_D^{25} = +118.3$ ($c = 0.5$, $CHCl_3$). IR (neat): 3030, 2910, 1740, 1220. ^{1}H-NMR (200 MHz): 7.26–7.20 (*m*, 5 H); 7.14 (*d*, *J* = 8.4, 2 H); 6.78 (*d*, *J* = 8.8, 2 H); 6.07 (*t*, *J* = 11.3, 1 H); 5.79 (*d*, *J* = 11.3, 1 H); 4.61–4.33 (*m*, 4 H); 4.26–4.08 (*m*, 1 H); 3.96 (*dd*, *J* = 5.8, 7.7, 1 H); 3.76 (*s*, 3 H); 3.67 (*s*, 3 H); 3.60–3.49 (*m*, 1 H); 3.42 (*t*, *J* = 7.7, 1 H); 3.12 (*t*, *J* = 5.5, 1 H); 1.78–1.56 (*m*, 6 H); 1.40–1.15 (*m*, 10 H); 0.94 (*d*, *J* = 6.6, 3 H); 0.82 (*d*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz): 166.6; 152.9; 128.5; 128.0; 127.8; 121.0; 120.1; 113.7; 108.2; 87.4; 76.8; 74.8; 73.6; 71.4; 70.0; 55.2; 51.0; 42.5; 38.9; 36.8; 32.2; 27.3; 27.0; 25.8; 22.1; 16.6; 11.7. HR-ESI-MS: 591.3285 ($[M + Na]^+$, $C_{34}H_{48}NaO_7^+$; calc. 591.3298).

*Methyl (2Z,4*S*,5*S*,6*S*,9*S*)-9-(Benzyloxy)-10-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-ethyl-5-hydroxy-6-methyldec-2-enoate* (**21**). To a stirred soln. of **4** (0.56 g, 0.984 mmol) in CH_2Cl_2/H_2O 19:1 (8 ml) was added DDQ (0.16 g, 1.18 mmol) at 0°, and the mixture was stirred at r.t. for 20 min. Then, sat. aq. $NaHCO_3$ (8 ml) was added, the mixture was and extracted with CH_2Cl_2 (2 × 20 ml), the combined org. layers were washed with H_2O (20 ml) and brine (10 ml), dried (Na_2SO_4), concentrated, and the crude residue was purified by CC (SiO_2; AcOEt/hexane 12:88) to afford **21** (0.385 g, 87%). Colorless syrup $[\alpha]_D^{25} = +198.0$ ($c = 1.4$, $CHCl_3$). IR (neat): 3400, 3030, 1720, 1220. ^{1}H-NMR (200 MHz): 7.56–7.15 (*m*, 5 H); 6.05 (*t*, *J* = 11.3, 1 H); 5.80 (*d*, *J* = 11.8, 1 H); 4.56–4.50 (*m*, 2 H); 4.28–4.07 (*m*, 1 H); 3.97 (*dd*, *J* = 5.8, 8.0, 1 H); 3.66 (*s*, 3 H); 3.62–3.49 (*m*, 1 H); 3.43 (*t*, *J* = 7.7, 1 H); 3.29 (*t*, *J* = 5.5, 1 H); 1.86–1.17 (*m*, 17 H); 0.93 (*d*, *J* = 6.6, 3 H); 0.84 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz): 166.8; 152.3; 128.3; 127.8; 127.4; 120.9; 120.1; 108.4; 84.2; 79.2; 76.8; 73.6; 71.4; 70.0; 51.0; 42.9; 38.6; 36.7; 31.6; 27.2; 26.9; 22.0; 16.6; 11.5. HR-ESI-MS: 471.2741 ($[M + Na]^+$, $C_{26}H_{40}NaO_6^+$; calc. 471.2723).

*(5*R*,6*R*)-6-[(2*S*,5*S*,7*R*)-5-(Benzyloxy)-7,8-dihydroxyoctan-2-yl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one* (**22**). To a soln. of **21** (0.30 g, 0.66 mmol) in benzene (3 ml) was added cat. TsOH at r.t., and the was stirred for 3 h. The mixture was treated with Et_3N, and the solvent was removed under reduced pressure, and the residue was adsorbed on SiO_2 for CC (SiO_2; AcOEt/hexane 60:40) to afford **22** (0.20 g, 80%). Colorless syrup. $[\alpha]_D^{25} = +272.2$ ($c = 0.3$, $CHCl_3$). IR (neat): 3410, 2990, 1700, 1210, 1100. ^{1}H-NMR (500 MHz): 7.27–7.19 (*m*, 5 H); 6.99 (*dd*, *J* = 6.7, 9.6, 1 H); 5.98 (*d*, *J* = 9.6, 1 H); 4.61–4.40 (*m*, 2 H); 3.93–3.91 (*m*, 2 H); 3.71–3.65 (*m*, 1 H); 3.52 (*dd*, *J* = 3.3, 10.6, 1 H); 3.38 (*dd*, *J* = 6.7, 11.1, 1 H); 2.42 (br. *s*, 2 H); 2.26–2.23 (*m*, 1 H); 1.89–1.36 (*m*, 7 H); 1.23–1.18 (*m*, 2 H); 0.89 (*t*, *J* = 7.7, 3 H); 0.82 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz): 164.8; 151.1; 138.5; 128.3; 127.8; 127.6; 120.7; 84.2; 76.9; 71.4; 69.1; 66.8; 36.4; 33.6; 30.5; 28.1; 20.0; 14.8; 10.8. HR-ESI-MS: 399.2140 ($[M + Na]^+$, $C_{22}H_{32}NaO_5^+$; calc. 399.2147).

*(5*R*,6*R*)-6-[(2*S*,5*S*,7*R*)-5-(Benzyloxy)-7,8-bis{[(*tert*-butyl)dimethylsilyl]oxy}octan-2-yl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one.* A soln. of **22** (0.16 g, 0.42 mmol), 2,6-lutidine (0.29 ml, 2.54 mmol), and (*tert*-butyl)dimethylsilyl trifluoromethanesulfonate (TBDMSOTf; 0.214 ml, 0.93 mmol) was stirred at $-10°$ for 20 min under N_2, the reaction was quenched with sat. $NaHCO_3$ (5 ml), and the mixture was extracted with CH_2Cl_2 (2 × 15 ml). The org. layer was washed with sat. $CuSO_4$ soln. (2 × 15 ml), brine (1 × 15 ml), dried (Na_2SO_4), concentrated and the residue was purified by CC (AcOEt/hexane, 6 : 94) to give the title compound (0.210 g, 82%). Colorless syrup. $[\alpha]_D^{25} = +232.60$ ($c = 1.5$, $CHCl_3$). IR (neat): 3020, 2990, 1720, 1190. ^{1}H-NMR (500 MHz): 7.35–7.19 (*m*, 5 H); 7.02 (*dd*, *J* = 6.1, 9.2, 1 H); 6.04 (*d*, *J* = 9.7, 1 H); 4.61–4.42 (*m*, 2 H); 3.98 (*dd*, *J* = 2.5, 10.2, 1 H); 3.90–3.81 (*m*, 1 H); 3.68–3.59 (*m*, 1 H); 3.56–3.38 (*m*, 2 H); 2.34–2.24 (*m*, 1 H); 2.00–1.20 (*m*, 9 H); 0.98 (*t*, *J* = 7.1, 3 H); 0.90–0.88 (*m*, 21 H); 0.05–0.04 (*m*, 12 H). ^{13}C-NMR (75 MHz): 165.1; 150.9; 138.2; 128.2; 127.5; 127.2; 120.9; 84.3; 76.1; 70.7; 70.3; 67.9; 39.8; 36.5; 33.6; 31.3; 27.9; 25.9; 20.0; 18.4; 17.1; 14.8; 10.9; −3.9; −4.7; −5.3. HR-ESI-MS: 627.3868 ($[M + Na]^+$, $C_{34}H_{60}NaO_5Si_2^+$; calc. 627.3877).

*(5*R*,6*R*)-6-[(2*S*,5*S*,7*R*)-5-(Benzyloxy)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-8-hydroxyoctan-2-yl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one* (**23**). A soln. of the compound (0.20 g, 0.33 mmol) obtained in the previous step in anh. THF (2 ml) were added HF · pyridine (41 µl) at 0°, and the mixture was stirred at r.t. for 12 h. Later, the mixture was poured into sat. $NaHCO_3$ soln. (10 ml), extracted with AcOEt (2 × 30 ml), org. layer was washed with sat. $CuSO_4$ soln. (2 × 15 ml) and brine (1 × 15 ml), dried (Na_2SO_4), concentrated, and the residue was purified by CC (SiO_2; AcOEt/hexane 20 : 80) to give **23** (0.11 g, 68%). Colorless syrup. $[\alpha]_D^{25} = +230.36$ ($c = 1.5$, $CHCl_3$). IR (neat): 3410, 3020, 2980, 1720, 1190. ^{1}H-NMR (500 MHz): 7.36–7.24 (*m*, 5 H); 7.06 (*dd*, *J* = 6.3, 9.7, 1 H); 6.03 (*d*, *J* = 9.7, 1 H); 4.60–4.44 (*m*, 2 H); 4.00 (*dd*, *J* = 2.9, 10.2, 1 H); 3.96–3.88 (*m*, 1 H); 3.65–3.41 (*m*, 3 H); 2.37–2.27 (*m*, 1 H); 1.99–1.23 (*m*, 9 H); 0.96 (*t*, *J* = 7.8, 3 H); 0.92–0.85 (*m*, 12 H); 0.07 (*s*, 6 H). ^{13}C-NMR (75 MHz): 164.7; 150.9; 138.7; 128.3; 127.6; 127.4; 120.8; 84.2; 76.1; 70.4; 67.0; 39.5; 36.5; 33.6; 30.7; 27.7; 25.8; 20.0; 18.0; 16.5; 14.9; 10.9; −4.3; −4.5. HR-ESI-MS: 513.3031 ($[M + Na]^+$, $C_{28}H_{46}NaO_5Si^+$; calc. 513.3012).

*(5*R*,6*R*)-6-[(2*S*,5*S*,7*R*,8*E*,10*E*)-5-(Benzyloxy)-7-{[(*tert*-butyl)dimethylsilyl]oxy}-11-phenylundeca-8,10-dien-2-yl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one* (**24**). To a stirred soln. of **23** (0.05 g, 0.102 mmol) in anh. CH_2Cl_2 (2 ml) were added $NaHCO_3$ (0.017 g, 0.204 mmol) and *Dess–Martin* periodinane (0.052 g, 0.122 mmol) at 0° under N_2, and the mixture was stirred at r.t. for 1 h. Then, the reaction was quenched with 1 : 1 mixture of sat. aq. soln. of $Na_2S_2O_3$ and $NaHCO_3$ (3 ml), the mixture was extracted with CH_2Cl_2 (2 × 15 ml), and the combined org. layers were washed with H_2O (15 ml), brine (10 ml), dried (Na_2SO_4), and concentrated, and the crude residue was purified by flash CC (SiO_2; AcOEt/hexane 10 : 90) to afford **2** (42 mg, 84%). Colorless syrup. Without further characterization, the aldehyde was used as such for next step.

To the evacuated MS in a round bottomed flask and aldehyde (0.042 g, 0.086 mmol) in THF (1.5 ml) were added **3** (0.065 g, 0.258 mmol) and $LiOH \cdot H_2O$ (0.061 g, 0.258 mmol) under N_2, and the mixture was heated at reflux for 12 h. The mixture was filtered through SiO_2 and washed with Et_2O (20 ml). The org. layer was dried (Na_2SO_4) and concentrated, and the residue was purified by CC (SiO_2; AcOEt/hexane 7 : 93) to give the *Wittig* product (0.022 g, 44%). Colorless syrup. $[\alpha]_D^{25} = +79.7$ ($c = 0.3$, $CHCl_3$). IR (neat): 3010, 2980, 1730, 1610, 1190. ^{1}H-NMR (500 MHz): 7.43–7.17 (*m*, 10 H); 7.06 (*dd*, *J* = 6.4, 9.7, 1 H); 6.73 (*dd*, *J* = 10.1, 14.9, 1 H); 6.50 (*d*, *J* = 15.7, 1 H); 6.29 (*dd*, *J* = 10.5, 14.9, 1 H); 6.04 (*d*, *J* = 9.7, 1 H); 5.78 (*dd*, *J* = 6.8, 14.9, 1 H); 4.61–4.38 (*m*, 3 H); 4.00 (*dd*, *J* = 2.8, 10.5, 1 H); 3.69–3.60 (*m*, 1 H); 2.37–2.24 (*m*, 1 H); 2.06–1.91 (*m*, 1 H); 1.89–1.38 (*m*, 8 H); 0.98–0.84 (*m*, 15 H); 0.06 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR (75 MHz): 164.1; 150.9; 137.8; 131.9; 129.6; 128.5; 128.3; 128.0; 127.7; 126.2; 122.9; 120.9; 84.3; 76.0; 71.7; 50.0; 43.8; 39.7; 37.2; 33.6; 29.6; 27.8; 25.9; 21.0; 14.8; 11.0; −3.7; −4.7. HR-ESI-MS: 611.3527 ($[M + Na]^+$, $C_{37}H_{52}NaO_4Si^+$; calc. 611.3533).

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