Stereocontrolled Synthesis of the C^{21}–C^{38} Fragment of the Unnatural Enantiomer of the Antibiotic Nystatin A_1

Thilo Berkenbusch[a] and Reinhard Brückner*[b]

Abstract: The C^{21}–C^{38} fragment all-*trans*-**41** of the unnatural enantiomer **1** of nystatin A_1 was prepared starting from the *N*-propionyl oxazolidinone **9**. Aldol adduct *ent*-**8** (*ee* > 96%) derived in two steps was hydroborated with (thexyl)BH_2. Oxidative work-up and treatment with acid furnished δ-lactone **4**. It contains the complete stereotetrade of the target molecule. The α,β-unsaturated ester **28** was reached after another four steps. It should be a precursor for the polyene moieties of a variety of polyol,polyene macrolides. Illustrating that, the α,β-unsaturated aldehyde **29** obtained from **28** and DIBAL was extended by 10 C atoms in four steps yielding the C^{21}–C^{38} segment **41**. The latter set of transformations included the regio- and stereoselective Claisen rearrangement **32**→**35**.

Keywords: aldol reaction · Horner–Wadsworth–Emmons reaction · polyol,polyene macrolides · Claisen rearrangement · stereoselective synthesis

Introduction

Nystatin A_1 and amphotericin B are drugs of choice for the treatment of life-threatening fungal infections.[1] They are typical representatives of more than 200 polyol,polyene macrolides discovered so far.[2] Nystatin A_1 became the first member of this important class of antibiotics when it was isolated from *Streptomyces noursei* in 1950.[3] Amphotericin B, a secondary metabolite from *Streptomyces nodosus*, was discovered shortly later.[4] Its X-ray crystal structure having been reported in 1970,[5] it stayed the only polyol,polyene macrolide throughout two decades for which the complete 3D structure was known (its mirror image, see **5**, Scheme 1). The stereostructure of nystatin A_1 was assigned more recently by controlled degradation and partial syntheses (its mirror image, see **1**, Scheme 1).[6,7] Either of these antibiotics is a macrolactone and comprises the following substructures: a hydrophilic polyol moiety (C^1–C^{12}), a pyranoside ring (C^{13}–C^{19}), a lipophilic polyene moiety (C^{20}–C^{33}), and a small polypropionate section (C^{34}–C^{38}). The first and third substructure are different in nystatin A_1 versus amphotericin B—albeit only slightly—while substructures 2 and 4 are identical.

Several total[8,9] and partial[10] syntheses of amphotericin B or its aglycon ("amphoteronolide B") have been completed to date. Of the synthetic efforts directed towards nystatin A_1,[7b,c,11] the most advanced is Solladié's.[11d]: He and his co-workers obtained the polyol portion (C^1–C^{13}) with the natural configuration. We worked in this field, too, synthesizing a C^{14}–C^{20} building block[10g] and a C^{33}–C^{38} fragment,[10c] both with the natural configuration. In the meantime we modified our goals—and since then have strived for *analogues* of the mentioned antibiotics. These, hopefully, will help understanding whether and how much stereochemistry matters for the biological activity of such polyol,polyene antibiotics. Promising analogues ought to be, among others, the *unnatural* enantiomers **1** and **5** of nystatin A_1 and amphotericin B, respectively (Scheme 1). We traced them back retrosynthetically to an α,β-unsaturated ester **3**. This is a C^{31}–C^{38} building block both for **1** and **5**. It was elaborated to a type-**2** C^{21}–C^{38} building block (only) for **1**. Ester **3** was prepared from δ-lactone **4**, which exhibited already all stereocenters.

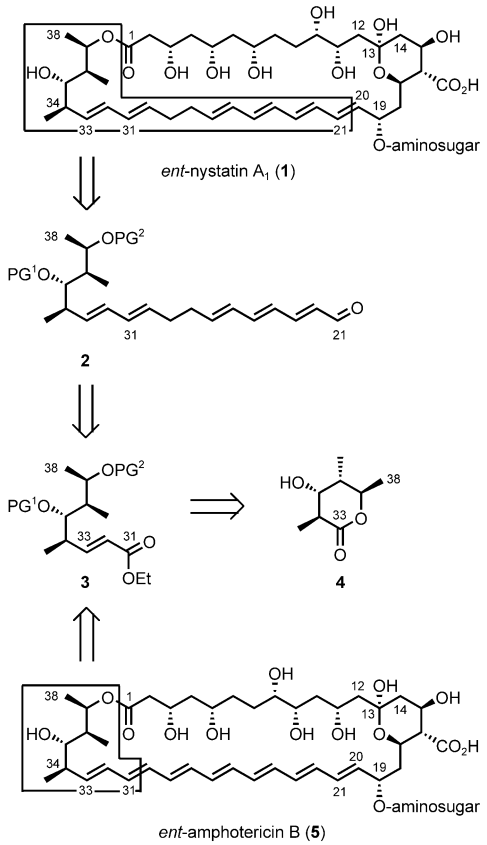
Results and Discussion

The boron-mediated addition[12] of Evans' norephedrine-based oxazolidinone **6**[13,14] to (*E*)-tiglinaldehyde[15] delivered the known[16] *syn*-aldol product **7** with the C^{34} and C^{35} configurations of *natural* nystatin A_1 and amphotericin B (Scheme 2; 88%; *ds* > 98%). The C^{34} and C^{35} configurations

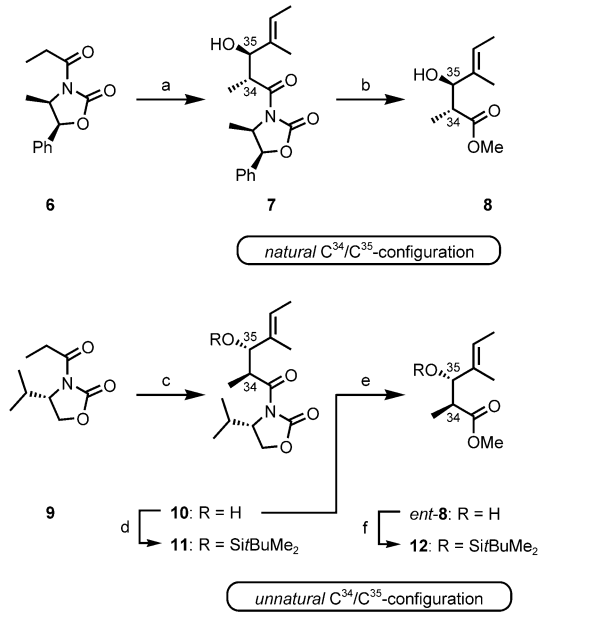
[a] Dr. T. Berkenbusch
Present address: Bayer AG
BCH-FCH-RD-LP2
Building G 8, 51368 Leverkusen (Germany)

[b] Prof. Dr. R. Brückner
Institut für Organische Chemie und Biochemie
der Albert-Ludwigs-Universität
Albertstrasse 21, 79104 Freiburg (Germany)
Fax: (+49) 761-203-6100
E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de

 DOI: 10.1002/chem.200305540



Scheme 1. Unnatural enantiomers **1** of nystatin A_1 and **5** of amphotericin B and retrosynthetic analysis of the boxed sections of these species.

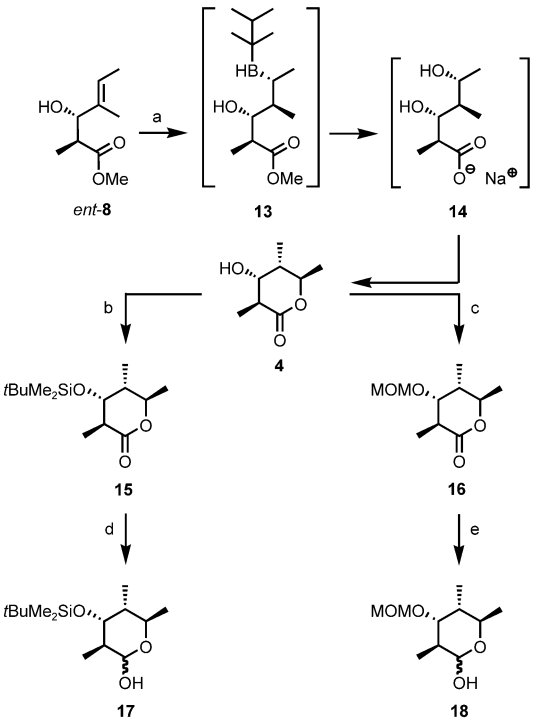


Scheme 2. a) NEt_3 (1.2 equiv), nBu_2BOTf (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, → −78 °C; (*E*)-2-methyl-2-butenal (1.15 equiv), → 0 °C within 1 h; 0 °C, 1 h; phosphate buffer (pH 7), MeOH, 35 % H_2O_2, 1 h; 88 % (*ds* > 98:2). b) NaOMe (1.6 equiv), MeOH, 0 °C, 8 min; 75 %. c) Same as a); 96 % (*ds* > 98:2). d) $tBuMe_2SiOTf$ (1.5 equiv), 2,6-lutidine (2.2 equiv), CH_2Cl_2, 0 °C, 1.5 h; 94 %. e) Same as b); 86 %. f) Same as d); 99 %.

of *unnatural* nystatin A_1 and amphotericin B were established analogously—in aldol adduct **10** previously not described—from the same aldehyde and the valinol-derived oxazolidinone **9** (96 %; *ds* >98:2).[17,18] The chiral auxiliaries were removed by methanolysis according to Seebach et al.[19]: Treatment of **7** and **10** with NaOMe and purification by flash chromatography on silica gel[20] provided methyl esters **8**[21] (75 %) and *ent*-**8** (86 %), respectively, both with >96 % *ee* (along with 90–95 % recovered chiral auxiliary). Compound **8**[21] had the undesired absolute configuration but was needed for assessing the enantiopurity of the enantiomer *ent*-**8** with the desired configuration. Hydroxyoxazolidinone **10** and the identically configured β-hydroxyester *ent*-**8** were protected[22] as *tert*-butyldimethylsilyl ethers **11** (94 % yield) and **12** (99 % yield), respectively.

Having completed a set of four differently substituted, albeit identically configured allyl alcohols (*ent*-**8**, **10**) or allyl silyl ethers (**11**, **12**), we proceeded testing whether hydroboration/oxidation would lead in just one more step to the δ-lactone **4** (Scheme 3). The latter exhibits the complete stereotetrade of our target molecules **2** and **3**. This plan called for *anti*-Markovnikov and *syn*-selective hydroborations with respect to the relative orientation of the OH groups in the dihydroxycarboxylate precursor **14** of lactone **4**. Literature precedent[23] made such stereocontrol likely. 9-BBN or BH_3•SMe_2 turned out to fail as hydroborating agents: Substrates *ent*-**8**, **10**, **11**, and **12** were essentially inert towards 9-BBN while they reacted with BH_3•SMe_2 readily, yet not only with their C=C but also with their C=O bonds. Besides that, the *tert*-butyldimethylsilyl ethers **11** and **12** lost their silyl groups depending on the detailed conditions of the oxidative work-up: 35 % H_2O_2/10 % NaOH led to partial deprotection, whereas sodium perborate[24] affected neither the silyl groups nor, surprisingly, the B–C bond. Screening other hydroborating agents, the combination of $(thexyl)BH_2$[25] with the unprotected ester *ent*-**8** proved to work nicely when 35 % H_2O_2 combined with "Sharpless-solution"[26] [NaOH (9 M) and NaCl] was employed as an oxidizing mixture (→ **13**; Scheme 3). This apparently provided carboxylate **14**. It was never isolated but treated with concentrated HCl so that it lactonized spontaneously. After purification by flash chromatography on silica gel[20] we isolated δ-lactone **4** in 60 % yield as a single diastereomer.[27] Its stereostructure was established by X-ray crystallography.

From this point onward we continued our synthesis on two routes differing by the protecting group which was about to be installed (Scheme 3). The first route proceeded via the $tBuMe_2Si$-containing lactol **17**, the second via the MOM-containing lactol **18**. These compounds were obtained from lactone **4** in two steps: 1) Protection of the free hydroxy group with *tert*-butyldimethylsilyl triflate[22] in the presence of 2,6-lutidine delivered lactone **15**.[28] The yield did not exceed 72 % because we could not prevent that **15** underwent about 25 % elimination of $tBuMe_2SiOH$ (→ ca. 25 % α,β-unsaturated lactone). The ensuing reduction **15** → **17**[29] with DIBAL in toluene at −78 °C was accomplished in 100 % yield. 2) Using chloromethyl methyl ether and Hünig's base[30] for protecting lactone **4** and DIBAL in toluene at low temperature for the subsequent reduction, the MOM-protected lactol **18** of the second route resulted in



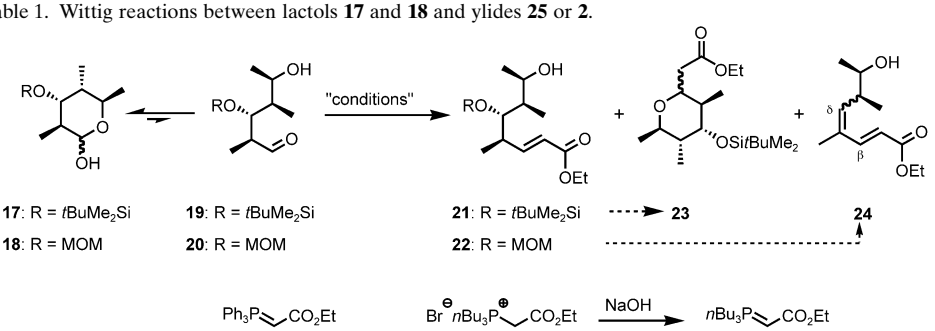
Scheme 3. a) (Thexyl)BH_2 (2.0 equiv), addition of *ent*-**8**, 0 °C, 30 min, → RT, 16 h; → 0 °C, NaOH (9 M, 8.4 equiv), 35 % H_2O_2 (9.2 equiv), NaCl (1.0 equiv), 2 h, → RT, 2 h; conc. HCl until pH ≤ 1; 60 % (*ds* > 98:2). b) *t*$BuMe_2SiOTf$ (2.6 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 12 h; 72 %. c) MOMCl (8.2 equiv), NE*ti*Pr_2 (8.7 equiv), *n*Bu_4NI (1.1 mol %), CH_2Cl_2, RT, 1.5 h; 99 %. d) DIBAL (2.2 equiv), toluene, −78 °C, 2.5 h; 99 %. e) Same as d); 99 %.

98 % yield over both steps.[31] ^{1}H- and ^{13}C NMR spectroscopy revealed the siloxy-containing lactol **17** to be a 60:40 mixture of anomers and the MOM-containing lactol **18** a 79:21 mixture. There was no indication of the presence of the respective open-chain hydroxyaldehyde isomers **19** and **20** (see Table 1).

Nonetheless, the latter species were the ones to be scavenged in the next step by a Wittig olefination effecting a C_2 elongation by furnishing the α,β-unsaturated ethyl esters **21** and **22**, respectively (Table 1). While *trans*-selectivities were satisfactory (> 92:8) from the beginning and regardless which ylide or solvent we employed, our yields stayed low for an extended period of time. Starting with standard conditions,[32] that is, combining substrate **17** and ylide **25** in CH_2Cl_2, THF, DMF or benzene at room temperature, no more than 17 % of the desired ester **21** were obtained (experiments not shown in Table 1). At reflux temperature in toluene, a 2 h run led to the desired product **21** in 11 % yield along with 68 % recovered lactol **17** (entry 1). In contrast to that, a 24 h run went to complete conversion but hardly improved the yield of **21** (17 %; entry 2). This was because the reaction proceeded beyond that stage through tetrahydropyran formation by an intramolecular Michael addition. It furnished 42 % **23** as a 74:26 mixture of diastereomers, which were separated by flash chromatography on silica gel[20] but remained configurationally unassigned.

This kind of over-reaction is known from Wittig reactions of sugar lactols.[33] In a few cases,[34] the addition of a small amount of carboxylic acid and use of tributylphosphorane **27**—freshly prepared from tributylphosphonium bromide **26**[35]—instead of triphenylphosphorane **25** turned out to increase the yield of acyclic product (and the *trans*-selectivity as well). Therefore, we added benzoic acid (20 mol %) to our olefination mixtures and employed phosphorane **27** (entry 4) as an alternative to phosphorane **25** (entry 3).[36] This led to the acyclic product (**21**) as desired and to no tetrahydropyran **23** at all. The yield of **21** remained nevertheless low: 26 and 31 %, respectively. Therefore, we gave up elaborating the TBDMS-containing lactol **17**, exchanging it for its MOM-protected analogue **18**.[37] Continuing to rely upon the beneficial effects both of added benzoic acid and of employing the tributylphosphorane (**27**) we found that the formation of the desired unsaturated ester **22** was sluggish at < 85 °C in toluene and once again exhibited moderate yields (23–37 %; entries 5 and 6). Increasing the temperature accelerated the reaction. Unfortunately, this also promoted loss of the MOMO group through β-elimination:

Table 1. Wittig reactions between lactols **17** and **18** and ylides **25** or **2**.



Entry	Reaction conditions (solvent: toluene)	Yield [%] **17**[a]	**18**[a]	**21**	**22**	**23**	**24**
1	**17**, **25** (3.0 equiv), 110 °C, 2 h	63		11		n. a.	
2	**17**, **25** (2.0 equiv), 110 °C, 1 d	–		17		42[b]	
3	**17**, **25** (3.0 equiv), benzoic acid (20 mol %), 110 °C, 3 h	n.a.		26		–	
4	**17**, **27** (3.0 equiv), benzoic acid (20 mol %), 95 °C, 3 h	n.a.		31		–	
5	**18**, **27** (6.0 equiv), benzoic acid (40 mol %), 85 °C, 4 h		54		23		–
6	**18**, **27** (2.5 equiv), benzoic acid (20 mol %), 85 °C, 9.5 h		5		37		< 2[c]
7	**18**, **27** (4.0 equiv), benzoic acid (30 mol %), 90 °C, 5 h		< 2[c]		55		6
8	**18**, **27** (6.0 equiv), benzoic acid (40 mol %), 92 °C, 2.5 h		47		37		< 2[c]
9	**18**, **27** (3.7 equiv), benzoic acid (20 mol %), 95 °C, 2 h		12		46		11
10	**18**, **27** (3.5 equiv), benzoic acid (40 mol %), 105 °C, 2 h		–		–		53

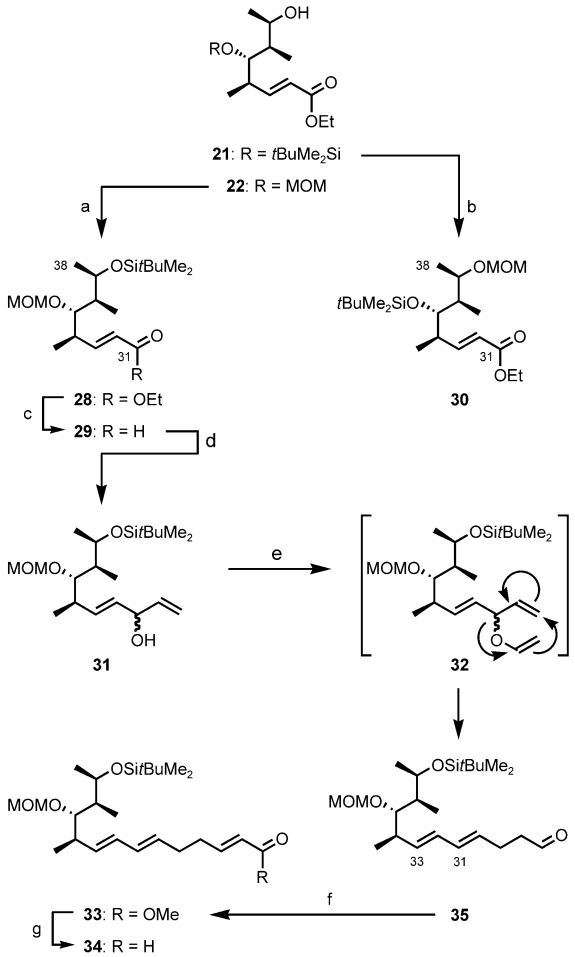
[a] That is, recovered starting material. [b] 74:26 mixture of diastereomers, which was separated by flash chromatography.[20] [c] Very small amounts of the compound in question were detected by TLC but neither isolated nor subjected to an exact yield determination.

Above 105 °C we isolated preponderantly the dienoic ester **24** (53 %) rather than **22** (entry 10). The C^{α}=C^{β} bond of **24** was exclusively *trans*-configured ($J_{\alpha,\beta}$ = 15.6 Hz), while the C^{γ}=C^{δ} bond belonged to an isomeric mixture (89:11). The best we managed doing in the tightrope act of achieving good conversions of lactol **18** *and* avoiding the formation of **24** was maintaining the temperature between 90 and 95 °C and working up the reaction mixture as soon as TLC indicated the formation of dienoate **24**. In that manner the desired Wittig product **23** was obtained as a pure *trans*-isomer in up to 55 % isolated yield or in up to 70 % yield based on recovered lactol **18** (entries 7 and 9, respectively).

α,β-Unsaturated esters **21** (TBDMS-protected) and **22** (MOM-protected) were protected as regioisomeric TBDMS- and MOM-containing esters **28** (84 % yield) and **30** (85 % yield) following standard procedures[22,30] (Scheme 4). Both **28** and **30** are equivalents of the C^{31}–C^{38} fragment **3** of our retrosynthetic analysis of *ent*-nystatin A_1 (**1**) and *ent*-amphotericin B (**5**; Scheme 1). Thus, their preparation meant reaching an important subgoal. Due to the better accessibility of **28** (59 % overall yield from lactone **4**) compared to **30** (19 % overall yield) we continued our synthesis with the former compound.

For further elaboration of the carbon framework, we adjusted the oxidation state of ester **28** by DIBAL reduction in CH_2Cl_2 at −78 °C and by oxidizing the resulting crude allylic alcohol with MnO_2[38] in CH_2Cl_2. This provided 89 % of the α,β-unsaturated aldehyde **29** (*trans*:*cis* > 98:2). This compound furnished the divinyl carbinol **31** (93 % yield; *ds* ≈ 50:50) by the addition of vinylmagnesium bromide.[39] A one-pot vinyl ether exchange/Claisen rearrangement protocol[40] was applied next. It meant refluxing a solution of compound **31** and a stoichiometric amount of $Hg(OAc)_2$ in *tert*-butyl vinyl ether (70 equiv). This gave rise to the short-lived vinyl ether **32** (1:1 diastereomeric mixture) and caused the latter to undergo a Claisen rearrangement. Of the two allylic C=C bonds, the rearrangement involved primarily the one sterically least hindered. Regiocontrol was 82:18 at least, as evidenced by the following findings:[41] First, purification by flash chromatography on silica gel[20] gave an unanalyzed mixture of the regioisomeric Claisen products (95 % yield). Therefrom, we obtained 78 % of the pure rearrangement product **35** by another passage through flash silica gel; the *trans*,*trans*-configuration of segment C^{30}=C^{31}–C^{32}=C^{34} of **35** follows from the magnitude of its olefinic couplings: $J_{30,31}$ = $J_{32,33}$ = 14.5 Hz. The yield of any regioisomer(s) of **35** was thereby limited to 95 % − 78 % = 17 %. Aldehyde **35** was then C_2-homologated in 79 % yield (→ α,β-unsaturated aldehyde **34**) by a Wittig reaction[32] with PH_3P=CH−CO_2Me (**35** → **33**; *trans*:*cis* > 98:2), by a reduction, and an oxidation.

The final steps of our synthesis of the C^{21}–C^{38} fragment of *ent*-nystatin A_1 (**1**) were realized with Horner-Wadsworth-Emmons (HWE) reactions (Scheme 5).[42] Initially, we combined our most advanced intermediate, namely the C^{25}–C^{38} aldehyde **34**, with the lithio derivative obtained from phosphonate **36** (*trans*:*cis* > 90:10) and LDA. Surprisingly, this afforded a 24:76 mixture (52 % yield, separable) in which the expected trienoic ester **40** was the minor constituent and



Scheme 4. a) *t*$BuMe_2SiOTf$ (2.0 equiv), 2,6-lutidine (3.6 equiv), CH_2Cl_2, 0 °C, 15 h; 84 %. b) MOMCl (8.3 equiv), NEt*i*Pr_2 (10 equiv), *n*Bu_4NI (14 mol %), CH_2Cl_2, RT, 18 h; 85 %. c) (i) DIBAL (3.1 equiv), CH_2Cl_2, 78 °C, 1.5 h; (ii) MnO_2 (22 equiv), CH_2Cl_2, RT, 4 h; 89 %. d) H_2C=CH-MgBr (2.3 equiv), THF, −78 °C, 70 min; 93 % (*ds* ≈ 50:50). e) $Hg(OAc)_2$ (1.1 equiv), *tert*-butyl vinyl ether (70 equiv), reflux, 9 h; 78 %. f) Ph_3P=CH-CO_2Me (3.1 equiv), toluene, RT, 16 h; 89 % (*trans*:*cis* > 98:2). g) i) DIBAL (2.6 equiv), CH_2Cl_2, −78 °C, 2.5 h; ii) MnO_2 (20 equiv), CH_2Cl_2, RT, 14 h; 89 %.

the cyclohexadiene-containing isomer **39** dominated.[43] This outcome suggests that lithio-**36** attacked the α,β-unsaturated aldehyde **34** preferentially in a conjugate addition and involved C-γ rather than C-α of the phosphonate. The surmised intermediate **38** displays an aldehyde enolate as well as an ester-substituted alkene phosphonate. Proton transfer from the latter upon the former would lead to a more stable intermediate, equipped with an aldehyde moiety and a metalophosphonate. These functionalities ought to lead to product **39** by an intramolecular HWE reaction.

The C-3 elongation of C^{25}–C^{38} aldehyde **34** by HWE reagent **36** having failed, we moved the site of our retrosynthetic disconnection "westward" (Scheme 5). This called for a C-5 elongation of C^{27}–C^{38} aldehyde **35** by phosphonate **37** (accessible from 4-bromocrotonate[44]). Treating this reagent (*trans*,*trans*:*cis*$^{H_2CC=C}$,*trans*$^{C=CCO_2Me}$ 90:10) first with LDA and then with aldehyde **35**, we obtained an inseparable 66:34 mixture of the all-*trans*-configured unsaturated ester **40** and

its *cis*^{26,27}-isomer (74% yield). Isomerization in an NMR tube with 8 mol% of iodine in $CDCl_3$ increased the all-*trans*-content to 93:7.[45] Without purification we proceeded to aldehyde all-*trans*-**41** in 78% overall yield by sequential oxidation and reduction. This compound stands for the C^{21}–C^{38} fragment **2** of *ent*-nystatin A_1 (**1**). Because of its carbonyl group, it is properly set up for appending a C^{x}–C^{20} synthon en route to the full structure of *ent*-nystatin A_1.

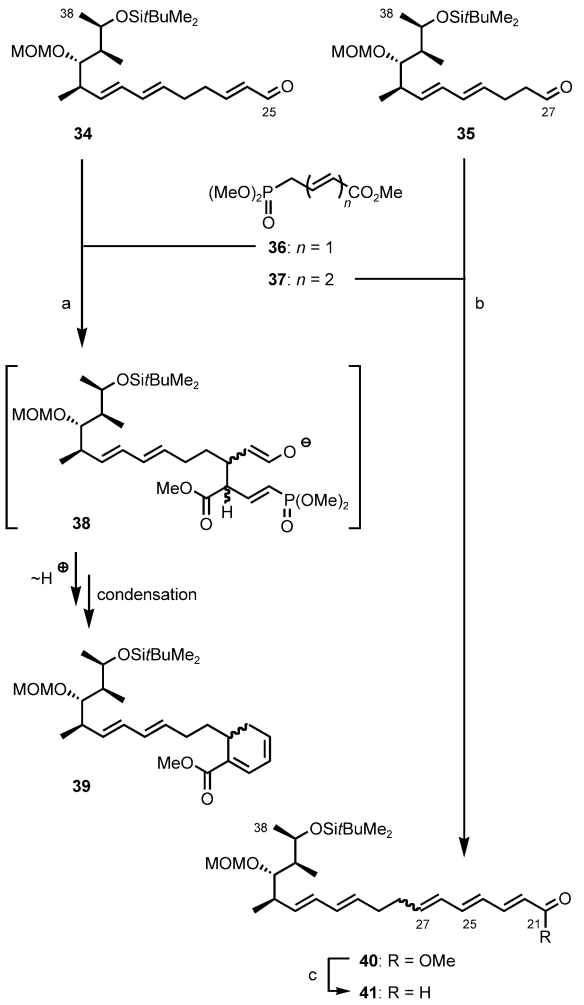
The connectivities and stereostructures of all-*trans*- and *cis*^{26,27}-**40** as well as all-*trans*-**41** were established by 500 MHz ^{1}H NMR spectroscopy (Table 2). The C^{22}=C^{23} and C^{24}=C^{25} bonds were clearly *trans*-configured because of the sizes of the $J_{22,23}$ (15.2–15.3 Hz) and $J_{24,25}$ (14.7–14.8 Hz). Likewise, in compounds all-*trans*-**40** and all-*trans*-**41** we found $J_{26,27}$ = 15.1 Hz. This contrasts with $J_{26,27}$ = 10.8 Hz in the isomer *cis*^{26,27}-**40**, to which we therefore attributed one *cis*-configured C=C bond.

Conclusion

A stereoselective and straightforward synthesis of compound all-*trans*-**41** has been developed. It was obtained from the *N*-propionyl oxazolidinone **9** in 9.8% yield over 12 steps. A key intermediate was the α,β-unsaturated ester **28**. It might be used for the construction of *other* polyol,polyene macrolides like, for example, *ent*-amphotericin B (**5**). Efforts to elaborate all-*trans*-**41** into unnatural nystatin A_1 (**1**) are currently underway in our laboratory.

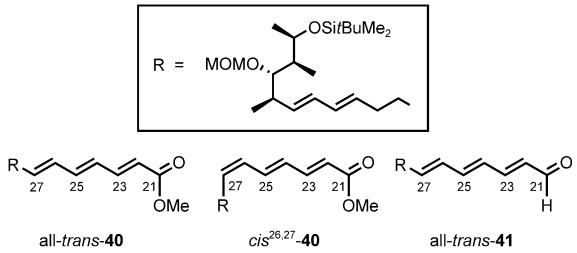
Experimental Section

General methods: Reactions with light-sensitive compounds were performed in brown glassware or in ordinary glassware wrapped in aluminum foil. Products were purified by flash chromatography[20] on Merck silica gel 60 (eluent given in parentheses). Yields refer to analytically pure samples. Isomer ratios were derived from suitable ^{1}H NMR integrals. ^{1}H [$CHCl_3$ (7.26 ppm) as internal standard in $CDCl_3$] and ^{13}C NMR [$CDCl_3$ (77.00 ppm) as internal standard in $CDCl_3$]: Bruker AM 400 or DRX 500; integrals in accord with assignments; coupling constants in Hz. The assignments of ^{1}H and ^{13}C NMR resonances refer to the IUPAC nomenclature; primed numbers belong to the side chain. Combustion analy-



Scheme 5. a) **36** (1.9 equiv), LDA (2.3 equiv), THF, −60 °C, 25 min; addition of **34**, → −30 °C, 2 h; 52% (21% **39**, 20% of a 93:7 mixture of **39** and **40**, and 11% **40**). b) **37** (1.9 equiv), LDA (1.8 equiv), THF, −60 °C, 30 min, → 0 °C during 15 min, → −60 °C; addition of **35**, →−60 °C, 1 h; 74% (*trans*^{26,27}:*cis*^{26,27} = 66:34). c) i) I_2 (8.0 mol%), $CDCl_3$, RT, 9 min (→ *trans*^{26,27}:*cis*^{26,27} = 93:7); ii) DIBAL (2.7 equiv), CH_2Cl_2, −78 → −60 °C, 1 h; iii) MnO_2 (39 equiv), CH_2Cl_2, RT, 1 h; 78%.

Table 2. 500 MHz ^{1}H NMR data in $CDCl_3$ of the conjugated triene segments of esters **40** and aldehyde **41**; chemical shifts in ppm, coupling constants in Hz.



all-*trans*-**40** *cis*^{26,27}-**40** all-*trans*-**41**

	C^{22}=C^{23}			C^{24}=C^{25}			C^{26}=C^{27}		
	$\delta_{22\text{-H}}$	$J_{22,23}$	$\delta_{23\text{-H}}$	$\delta_{24\text{-H}}$	$J_{24,25}$	$\delta_{25\text{-H}}$	$\delta_{26\text{-H}}$	$J_{26,27}$	$\delta_{27\text{-H}}$
all-*trans*-**40**[a]	5.85	15.3	7.30	6.22	14.8	6.52	6.15	15.1	5.92
cis^{26,27}-**40**[b]	5.88	15.3	7.35	6.30	14.7	6.93	6.10	10.8	5.67
all-*trans*-**41**	6.13	15.2	7.11	6.35	14.8	6.64	6.20	15.1	–[c]

[a] Sample of a 93:7 mixture of all-*trans*-**40** and *cis*^{26,27}-**40**. [b] Sample of a 66:34 mixture of all-*trans*-**40** and *cis*^{26,27}-**40**. [c] Superimposed.

ses: H. Bähr and E. Hickl, Institut für Organische Chemie und Biochemie, Universität Freiburg. MS: Dr. J. Wörth, Institut für Organische Chemie und Biochemie, Universität Freiburg. IR spectra: Perkin–Elmer PARAGON 1000. Optical rotations measured with a Perkin–Elmer polarimeter 341 at 589 nm and calculated according to the Drude equation $\{[\alpha]_{\tilde{\nu}}^{\vartheta} = (\alpha_{\mathrm{exptl}} \times 100)/(c \times d)\}$; rotational values are the average of five measurements of α in given solution of the respective sample. Melting points: Dr. Tottoli apparatus (Fa. Büchi), uncorrected.

(3*S*,4*R*,5*S*,6*R*)-Tetrahydro-4-hydroxy-3,5,6-trimethyl-2-pyranone (4): At −10 °C a solution of 2,3-dimethyl-2-butene (1.24 mL, 879 mg, 10.5 mmol, 2.0 equiv) in THF (6 mL) was added dropwise to a solution of $BH_3{\cdot}SMe_2$ (10 M, 1.05 mL, 10.5 mmol, 2.0 equiv) in THF (2 mL). The addition was completed after 25 min, and the mixture was warmed to 0 °C. After stirring for 2 h at this temperature, the reaction mixture was treated dropwise with a solution of methyl ester *ent*-**8** (921 mg, 5.35 mmol) in THF (7 mL) within 30 min. The mixture was allowed to reach room temperature and stirred for 16 h. The reaction was terminated at 0 °C by careful addition of an aqueous solution [5 mL of a solution prepared from NaOH (30 g), NaCl (5 g) and H_2O (90 mL): ca. 45 and 5.1 mmol, respectively, ca. 8.4 and 1.0 equiv, respectively] and H_2O_2 (30 % in water, 5.0 mL, 1.7 g, 49 mmol, 9.2 equiv). Stirring was continued for 2 h at 0 °C and then for another 2 h at room temperature The organic phase was separated and the aqueous phase extracted with *t*BuOMe (4 × 70 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL). The combined aqueous phases were treated with aqueous conc. HCl (until the pH value was <1) and with Na_2SO_3 (to destroy the excess of H_2O_2; peroxide test!). After a second extraction with *t*BuOMe (5 × 150 mL) the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 1:1) to afford δ-lactone **4** (504 mg, 60 %) as a pure diastereomer and a colorless solid. M.p. 116–117 °C; $[\alpha]_D^{25} = +23.1$ ($c = 0.87$ in $CDCl_3$); ^{1}H NMR [500 MHz; contains contaminant-peak (s) at $\delta = 1.25$]: $\delta = 1.06$ (d, $J_{5\text{-}Me,5} = 6.9$, 5-Me)*, 1.32 (d, $J_{3\text{-}Me,3} = 7.5$, 3-Me)*, 1.37 (d, $J_{6\text{-}Me,6} = 6.3$, 6-Me)*, 1.84 (dqd, $J_{5,6} = 10.1$, $J_{5,5\text{-}Me} = 6.8$, $J_{5,4} = 3.4$, 5-H), 2.06 (brs, OH), 2.68 (qd, $J_{3,3\text{-}Me} = 7.4$, $J_{3,4} = 4.0$, 3-H), 3.73 (dd, $J_{4,3} = J_{4,5} = 3.6$, 4-H), 4.47 (dq, $J_{6,5} = 9.9$, $J_{6,6\text{-}Me} = 6.4$, 6-H); * assigned by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz; peak of contaminant at $\delta = 29.68$): $\delta = 12.55$ (5-CH_3)*, 15.82 (3-CH_3)*, 19.54 (6-CH_3)*, 37.22 (C-5)**, 43.44 (C-3)**, 73.32 (C-4)***, 76.64 (C-6)***, 174.11 (C-2); *,**,*** distinguishable by a C,H-correlation spectrum; IR ($CDCl_3$): $\tilde{\nu} = 3460$, 2980, 2940, 2855, 1730, 1600, 1460, 1385, 1360, 1240, 1205, 1100, 1045, 975, 930, 920, 910 cm^{-1}; elemental analysis calcd (%) for $C_8H_{14}O_3$ (158.2): C 60.74, H 8.92; found: C 60.51, H 9.06.

(4*R*,5*S*)-3-[(2*R*,3*R*,4*E*)-3-Hydroxy-2,4-dimethyl-4-hexenoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one (7): Dibutylboron triflate (4.4 mL of a 1.0 M solution in CH_2Cl_2, 4.4 mmol, 1.1 equiv) was added dropwise at 0 °C within 12 min to a solution of oxazolidinone **6** (930 mg, 3.99 mmol) and triethylamine (0.67 mL, 49 mg, 4.8 mmol, 1.2 equiv) in CH_2Cl_2 (12 mL). After stirring for 1 h, the mixture was cooled to −78 °C, and a solution of (*E*)-2-methylbutenal (425 μL, 307 mg, 4.39 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) was added dropwise during 25 min. The reaction mixture was allowed to reach 0 °C over 1 h, stirred for 1 h at this temperature and treated with phosphate buffer (pH 7, 4 mL) and MeOH (12 mL). Then a mixture of aqueous H_2O_2 (35 %, 4 mL) and MeOH (8 mL) was added dropwise taking care that the reaction temperature was kept below 4 °C. After stirring for 1 h at 0 °C, water (40 mL) was added, and the mixture was extracted with *t*BuOMe (5 × 60 mL). The combined organic phases were washed with semisaturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL) and dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 3:1) to afford a diastereomeric mixture (33 mg, 2.6 %) and the title compound **7** (1.117 g, 88 %, ref.[16] 70 %) as a pure diastereomer and a colorless solid. M.p. 87 °C, ref.[16] 86–87 °C; $[\alpha]_D^{25} = +33.4$ ($c = 1.22$ in $CDCl_3$), ref.[16] 35.5 ($c = 1.70$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.90$ (d, $J_{4\text{-}Me,4} = 6.6$, 4-Me)*, 1.17 (d, $J_{2'\text{-}Me,2'} = 7.0$, 2′-Me), 1.64 (m, 4′-Me), 1.66 (dm, $J_{6',5'} = 6.8$, 6′-H_3), 2.74 (d, $J_{OH,3'} = 2.8$, OH), 3.99 (qd, $J_{2',2'\text{-}Me} = 7.0$, $J_{2',3'} = 3.8$, 2′-H), 4.37 (brs, 3′-H), 4.77 (qd, $J_{4,4\text{-}Me} = J_{4,5} = 6.8$, 4-H), 5.63 (qdq, $J_{5',6'} = 6.7$, $^4J_{5',3'} \approx {}^4J_{5',4'\text{-}Me} \approx 1.3$, 5′-H), 5.67 (d, $J_{5,4} = 7.3$, 5-H), 7.30–7.33 and 7.36–7.45 (2 × m, 5 Ar-H); * distinguished from 2′-Me through the presence of a cross-peak with the 4-H resonance ($\delta = 4.77$) in an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz): $\delta = 10.43$ (2′-CH_3)*, 13.03 and 13.07 (4′-CH_3, C-6)*, 14.31 (4-CH_3)*, 40.66 (C-2′), 54.92 (C-4), 75.53 (C-3′)**, 78.94 (C-5)**, 120.50 (C-5′)***, 125.59 and 128.73 (each 2-fold intensity, 2 *ortho* and 2 *meta* C), 128.81, 133.12 and 134.29 (*ipso* C, *para* C, C-4′), 152.59 (C-1′), 176.85 (C-2); *,** distinguishable by a C,H-correlation spectrum; *** assigned by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 3605$, 3530, 2985, 2925, 2865, 1780, 1690, 1455, 1365, 1345, 1235, 1195, 1150, 1120, 1090, 1070, 1030, 990, 960 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{23}NO_4$ (317.4): C 68.12, H 7.30, N 4.41; found: C 67.99, H 7.34, N 4.24.

(2*S*,3*S*,4*E*)-3-Hydroxy-2,4-dimethyl-4-hexenoic acid methyl ester (*ent*-8): Na (554 mg, 24.1 mmol, 1.4 equiv) was dissolved in MeOH (85 mL), and the mixture was cooled to 0 °C. A solution of the oxazolidinone **10** (4.633 g, 17.20 mmol) in MeOH (15 mL) was then added in one portion. The mixture was stirred for 10 min and then poured into phosphate buffer (pH 7, 110 mL). The solution was extracted with CH_2Cl_2 (4 × 200 mL), and the combined organic extracts were dried with $MgSO_4$ and evaporated in vacuo. The residue was submitted to flash chromatography (cyclohexane/EtOAc 4:1) to afford methyl ester *ent*-**8** (2.536 g, 86 %) as a colorless liquid. The chiral auxiliary could be recovered by flushing the column with EtOAc. $[\alpha]_D^{25} = -13.8$ ($c = 0.84$ in $CDCl_3$); ^{1}H NMR (500 MHz): $\delta = 1.14$ (d, $J_{2\text{-}Me,2} = 7.1$, 2-Me), 1.59 (m, presumably interpretable as dq, $^4J_{4\text{-}Me,5} \approx {}^5J_{4\text{-}Me,6} \approx 1.0$, 4-Me), 1.62 (dm, $J_{6,5} = 6.8$, 6-H_3), 2.30 (brs, OH), 2.69 (qd, $J_{2,2\text{-}Me} = 7.1$, $J_{2,3} = 5.5$, 2-H), 3.68 (s, OMe), 4.26 (brd, $J_{3,2} = 5.4$, 3-H), 5.55 (qdq, $J_{5,6} = 6.7$, $^4J_{5,3} \approx {}^4J_{5,4\text{-}Me} \approx 1.3$, 5-H); ^{13}C NMR (125.7 MHz): $\delta = 11.28$ (2-CH_3)*, 12.24 (4-CH_3)*, 12.98 (C-6)*, 42.97 (C-2), 51.70 (OCH_3), 76.97 (C-3), 121.15 (C-5), 134.66 (C-4), 176.06 (C-1); * distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 2935$, 2895, 2860, 1780, 1650, 1500, 1470, 1400, 1255, 1215, 1160, 1090, 1060, 970, 915, 840, 780 cm^{-1}; elemental analysis calcd (%) for $C_9H_{16}O_3$ (172.1): C 62.77, H 9.36; found: C 62.48, H 9.66.

(2*R*,3*R*,4*E*)-3-Hydroxy-2,4-dimethyl-4-hexenoic acid methyl ester (8): Na (59 mg, 2.6 mmol, 1.6 equiv) was dissolved in MeOH (15 mL), and the mixture was cooled to 0 °C. A solution of the oxazolidinone **7** (513 mg, 1.62 mmol) in MeOH (4.5 mL) was then added in one portion. The mixture was stirred for 8 min and then poured into phosphate buffer (pH 7, 20 mL). The solution was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic extracts were dried with $MgSO_4$ and evaporated in vacuo. The residue was submitted to flash chromatography (cyclohexane/EtOAc 4:1) to afford methyl ester **8** (208 mg, 75 %) as a colorless liquid. The chiral auxiliary could be recovered by flushing the column with EtOAc. $[\alpha]_D^{25} = +13.3$ ($c = 0.47$ in $CDCl_3$); ^{1}H NMR,^{13}C NMR and IR data were identical with those of *ent*-**8**.

(4*S*)-3-[(2*S*,3*S*,4*E*)-3-Hydroxy-2,4-dimethyl-4-hexenoyl]-4-isopropyl-1,3-oxazolidin-2-one (10): Dibutylboron triflate (50 mL of a 1.0 M solution in CH_2Cl_2, 50 mmol, 1.1 equiv) was added dropwise at −3 °C within 35 min to a solution of oxazolidinone **9** (8.149 g, 45.45 mmol) and triethylamine (7.6 mL, 5.5 g, 55 mmol, 1.2 equiv) in CH_2Cl_2 (130 mL). After stirring for 1 h, the mixture was cooled to −78 °C, and a solution of (*E*)-2-methylbutenal (4.8 mL, 4.2 g, 50 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL) was added dropwise during 85 min. The reaction mixture was allowed to reach 0 °C over 1 h, stirred for 1 h at this temperature and treated with phosphate buffer (pH 7, 45 mL) and MeOH (150 mL). Then a mixture of aqueous H_2O_2 (35 %, 50 mL) and MeOH (60 mL) was added dropwise taking care that the reaction temperature was kept below 4 °C. After stirring for 1 h at 0 °C, water (300 mL) was added, and the mixture was extracted with *t*BuOMe (4 × 400 mL). The combined organic phases were washed with semisaturated aqueous $NaHCO_3$ (400 mL) and brine (250 mL) and dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue (15 g) which was submitted to flash chromatography (cyclohexane/EtOAc 4:1) to afford the title compound **10** (11.756 g, 96 %) as a pure diastereomer and a colorless oil. $[\alpha]_D^{25} = +59.7$ ($c = 1.45$ in $CDCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.89$ (d, $J_{1'\text{-}Me(1),1'} = 6.9$, 1′-$Me^1$), 0.92 (d, $J_{1'\text{-}Me(2),1'} = 7.1$, 1′-$Me^2$), 1.18 (d, $J_{2''\text{-}Me,2''} = 7.1$, 2″-Me)*, 1.60 (m, 4″-Me), 1.64 (dm, $J_{6'',5''} = 6.8$, 6″-H_3), 2.38 (qqd, $J_{1',1'\text{-}Me(1)} = J_{1',1'\text{-}Me(2)} = 7.0$, $J_{1',4} = 4.0$, 1′-H), 2.88 (brs, OH), 3.98 (qd, $J_{2'',2''\text{-}Me} = 7.0$, $J_{2'',3''} = 3.7$, 2″-H), AB signal ($\delta_A = 4.22$, $\delta_B = 4.28$, $J_{AB} = 8.9$, in addition split by $J_{A,4} = 3.0$, $J_{B,4} = 8.7$, 5-H_2), 4.32–4.35 (m, 3″-H), 4.46 (ddd, $J_{4,5\text{-}H(B)} = 8.3$, $J_{4,1'} = 4.0$, $J_{4,5\text{-}H(A)} = 3.0$, 4-H), 5.62 (qdq, $J_{5'',6''} = 6.8$, $^4J_{5'',3''} \approx {}^4J_{5'',4''\text{-}Me} \approx 1.4$, 5″-H); * distinguished from 1′-Me^1/1′-Me^2 through the presence of a cross-peak with the 2″-H resonance ($\delta = 3.98$) in an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz): $\delta =$

10.97 (2″-CH_3)*, 13.02 and 13.15 (4″-CH_3, C-6″)*, 14.68 (1′-CH_3^1)*, 17.89 (1′-CH_3^2)*, 28.37 (C-1′), 40.39 (C-2″), 58.37 (C-4)**, 63.34 (C-5)**, 75.10 (C-3″)**, 120.52 (C-5″)***, 134.07 (C-4″), 153.49 and 177.46 (C-1″, C-2); *,** distinguishable by a C,H-correlation spectrum; *** assigned by a C,H-correlation spectrum; IR (film): $\tilde{\nu}$ = 3605, 3530, 2970, 2935, 2880, 1780, 1690, 1460, 1380, 1300, 1205, 1120, 990, 930, 885, 760 cm^{-1}; *m/z*: 269.1627 ±5 mDa [M^+] confirmed by HRMS (EI, 70 eV); elemental analysis calcd (%) for $C_{14}H_{23}NO_4$ (269.3): C 62.43, H 8.61, N 5.20; found: C 62.07, H 8.64, N 5.15.

(4*S*)-3-[(2*S*,3*S*,4*E*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-4-hexenoyl]-4-isopropyl-1,3-oxazolidin-2-one (11): At 0 °C *tert*-butyldimethylsilyl triflate (0.84 mL, 0.97 g, 3.7 mmol, 1.5 equiv) was added to a solution of alcohol **10** (653 mg, 2.43 mmol) and 2,6-lutidine (0.62 mL, 0.57 g, 5.3 mmol, 2.2 equiv) in CH_2Cl_2 (30 mL). After stirring at this temperature for 1.5 h, the mixture was hydrolyzed with phosphate buffer (pH 7, 80 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 8:1) to afford the title compound **11** (876 mg, 94 %) as a colorless oil. $[\alpha]_D^{25} = +48.7$ (c = 0.62 in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = -0.05$ and 0.02 (2 × s, $SiMe_2$), 0.87 (d, $J_{1'\text{-Me}(1),1'}$ = 6.9, 1′-Me^1), 0.88 (s, $SiCMe_3$), 0.90 (d, $J_{1'\text{-Me}(2),1'}$ = 7.1, 1′-Me^2), 1.20 (d, $J_{2''\text{-Me},2''}$ = 7.0, 2″-Me), 1.54–1.58 (m, 4″-Me, 6″-H_3), 2.36 (qqd, $J_{1',1'\text{-Me}(1)} = J_{1',1'\text{-Me}(2)}$ = 7.0, $J_{1',4}$ = 3.9, 1′-H), 4.08 (dq, $J_{2'',3''}$ = 7.8, $J_{2'',2''\text{-Me}}$ = 6.8, 2″-H), 4.14–4.20 (m, 5-H_2), 4.21 (br d, $J_{3'',2''}$ = 7.8, 3″-H), 4.31 (ddd, $J_{4,5\text{-H}(1)}$ = 7.4, $J_{4,5\text{-H}(2)} = J_{4,1'}$ = 3.6, 4-H), 5.39 (q m, $J_{5'',6''} \approx 6$, 5″-H); ^{13}C NMR (125.7 MHz): $\delta = -5.28$ and −4.77 [$Si(CH_3)_2$], 11.26 and 13.00 (4″-CH_3, C-6″)*, 13.93 (2″-CH_3)*, 14.72 (1′-CH_3^1)*, 17.98 (1′-CH_3^2)*, 18.17 [Si*C*$(CH_3)_3$], 25.79 [3-fold intensity, Si$C(CH_3)_3$], 28.49 (C-1′), 42.42 (C-2″), 58.79 (C-4)**, 63.20 (C-5)**, 79.07 (C-3″)**, 121.54 (C-5″)***, 136.37 (C-4″)***, 153.65 and 175.23 (C-1″, C-2); *,**,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}$ = 3385, 2960, 2935, 2875, 2855, 1775, 1700, 1465, 1385, 1305, 1250, 1220, 1205, 1120, 1100, 1070, 1030, 990, 875, 835, 775, 700 cm^{-1}; *m/z*: 326.1876 ±5 mDa [$M^+ - t$Bu] confirmed by HRMS (EI, 70 eV); elemental analysis calcd (%) for $C_{20}H_{37}NO_4Si$ (383.6): C 62.62, H 9.72, N 3.65; found: C 62.93, H 10.16, N 3.43.

(2*S*,3*S*,4*E*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-4-hexenoic acid methyl ester (12): At 0 °C *tert*-butyldimethylsilyl triflate (340 μL, 391 mg, 1.48 mmol, 1.6 equiv) was added to a solution of hydroxy ester *ent*-**8** (160 mg, 0.930 mmol) and 2,6-lutidine (0.25 mL, 0.23 g, 2.1 mmol, 2.3 equiv) in CH_2Cl_2 (17 mL). After stirring at this temperature for 50 min, the mixture was allowed to reach romm temp. and after further 20 min stirring hydrolyzed with phosphate buffer (pH 7, 20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 20:1) to afford the title compound **12** (264 mg, 99 %) as a colorless oil. $[\alpha]_D^{25} = -2.9$ (c = 1.25 in $CHCl_3$); ^{1}H NMR (500 MHz; contains small impurity signals which might be caused by *t*$BuMe_2SiOH$): $\delta = -0.04$ and 0.02 (2 × s, $SiMe_2$), 0.87 (s, $SiCMe_3$), 1.14 (d, $J_{2\text{-Me},2}$ = 6.9, 2-Me), 1.54–1.58 (m, 4-Me, 6-H_3), 2.63 (qd, $J_{2,2\text{-Me}} = J_{2,3}$ = 7.0, 2-H), 3.59 (s, OMe), 4.10 (br d, $J_{3,2}$ = 7.7, 3-H), 5.55 (q m, $J_{5,6} \approx$ 6.6, 5-H); ^{13}C NMR (125.7 MHz; contains small impurity signals which might be caused by *t*$BuMe_2SiOH$): $\delta = -5.27$ and −4.68 [$Si(CH_3)_2$], 11.11 and 12.93 (2-fold intensity, 2 resonances of 3-fold total intensity for 3 C atoms: 2-CH_3, 4-CH_3, C-6), 18.16 [(Si*C*$(CH_3)_3$], 25.77 [3-fold intensity, Si$C(CH_3)_3$], 45.31 (C-2), 51.28 (OCH_3), 79.97 (C-3), 121.38 (C-5), 136.25 (C-4), 175.20 (C-1); IR (film): $\tilde{\nu}$ = 2955, 2930, 2885, 2860, 1740, 1460, 1435, 1390, 1360, 1345, 1255, 1195, 1165, 1125, 1090, 1060, 1030, 1005, 880, 835, 775 cm^{-1}; *m/z*: 229.1260 ±5 mDa [$M^+ - t$Bu] confirmed by HRMS (EI, 70 eV); elemental analysis calcd (%) for $C_{15}H_{30}O_3Si$ (286.5): C 62.89, H 10.55; found: C 62.39, H 9.62.

(3*S*,4*R*,5*R*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-tetrahydro-3,5,6-trimethyl-2-pyranone (15): At 0 °C *tert*-butyldimethylsilyl triflate (0.30 mL, 0.35 mg, 1.3 mmol, 2.6 equiv) was added to a solution of β-hydroxy-δ-lactone **4** (78.0 mg, 0.493 mmol) and 2,6-lutidine (86 μL, 79 mg, 0.73 mmol, 1.5 equiv) in CH_2Cl_2 (8 mL). After stirring at this temperature for 12 h, the reaction mixture was hydrolyzed with phosphate buffer (pH 7, 40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo at 0 °C to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 15:1 → fraction 44, 12:1 → fraction 65, 10:1 → fraction 80) to afford the title compound **15** (96.8 mg, 72 %) as colorless needles. M.p. 82 °C; $[\alpha]_D^{20} = +0.7$ (c = 0.41 in $CDCl_3$), ref.[10n] −0.8° (enantiomer, c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.06$ and 0.08 (2 × s, $SiMe_2$), 0.89 (s, $SiCMe_3$), 0.99 (d, $J_{5\text{-Me},5}$ = 6.8, 5-Me)*, 1.27 (d, $J_{3\text{-Me},3}$ = 7.5, 3-Me)*, 1.35 (d, $J_{6\text{-Me},6}$ = 6.5, 6-Me)*, 1.81 (dqd, $J_{5,6}$ = 9.9, $J_{5,5\text{-Me}}$ = 6.8, $J_{5,4}$ = 2.3, 5-H), 2.64 (qd, $J_{3,3\text{-Me}}$ = 7.6, $J_{3,4}$ = 2.7, 3-H), 3.64 (dd, $J_{4,3} = J_{4,5}$ = 2.5, 4-H), 4.47 (dq, $J_{6,5}$ = 9.9, $J_{6,6\text{-Me}}$ = 6.4, 6-H); * signal assigned by comparison with the analogous resonances and coupling constants of **4**; ^{13}C NMR (125.7 MHz; peak of contaminant at δ = 15.77): $\delta = -4.83$ and −4.50 [$Si(CH_3)_2$], 13.92 (5-CH_3)*, 16.54 (3-CH_3)*, 17.97 [Si*C*$(CH_3)_3$], 19.85 (6-CH_3)*, 25.71 [3-fold intensity, Si$C(CH_3)_3$], 36.09 (C-5)*, 44.13 (C-3)*, 74.47 (C-4)*, 77.32 (C-6)*, 174.20 (C-2); * signals assigned by comparison with the analogous resonances of **4**; IR ($CDCl_3$): $\tilde{\nu}$ = 2955, 2935, 2885, 2860, 1720, 1465, 1385, 1360, 1255, 1240, 1130, 1100, 1060, 1035, 860, 840 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{28}O_3Si$ (272.5): C 61.72, H 10.36; found: C 61.76, H 10.45.

(3*S*,4*R*,5*S*,6*R*)-Tetrahydro-4-(methoxymethoxy)-3,5,6-trimethyl-2-pyranone (16): At 0 °C (chloromethyl) methyl ether (2.4 mL, 2.5 g, 32 mmol, 5.8 equiv) was added dropwise to a solution of β-hydroxy-δ-lactone **4** (868 mg, 5.49 mmol) and diisopropylethylamine (5.7 mL, 4.3 g, 33 mmol, 6.1 equiv) in CH_2Cl_2 (20 mL). The reaction mixture was treated with tetrabutylammonium iodide (22.6 mg, 0.0612 mmol, 1.1 mol %) and allowed to reach RT. After stirring at this temperature for 17.5 h, (chloromethyl) methyl ether (1.0 mL, 1.1 g, 13 mmol, 2.4 equiv) and diisopropylethylamine (2.4 mL, 1.8 g, 14 mmol, 2.6 equiv) were added (once again) and the reaction was terminated after stirring for another 5 h by addition of aqueous saturated $NaHCO_3$ (10 mL). Stirring was continued for 1 h to destroy the excess of (chloromethyl) methyl ether. Then the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 5:2) to afford the title compound **16** (1.102 g, 99 %) as a colorless liquid. $[\alpha]_D^{25} = +7.2$ (c = 1.16 in $CDCl_3$); ^{1}H NMR [500 MHz; small peak of contaminant (s) at δ = 1.25]: $\delta = 1.06$ (d, $J_{5\text{-Me},5}$ = 6.9, 5-Me)*, 1.31 (d, $J_{3\text{-Me},3}$ = 7.6, 3-Me)*, 1.36 (d, $J_{6\text{-Me},6}$ = 6.5, 6-Me)*, 1.90 (dqd, $J_{5,6}$ = 9.7, $J_{5,5\text{-Me}}$ = 6.9, $J_{5,4}$ = 2.8, 5-H), 2.85 (qd, $J_{3,3\text{-Me}}$ = 7.6, $J_{3,4}$ = 3.0, 3-H), 3.39 (OMe), 3.58 (dd, $J_{4,3} = J_{4,5}$ = 2.9, 4-H), 4.46 (dq, $J_{6,5}$ = 9.9, $J_{6,6\text{-Me}}$ = 6.4, 6-H), AB signal (δ_A = 4.64, δ_B = 4.72, J_{AB} = 7.1, -OCH_2OMe); * signal assigned by comparison with the analogous resonances and coupling constants of **4**; ^{13}C NMR (125.7 MHz): δ = 13.36 (5-CH_3)*, 16.56 (3-CH_3)*, 19.96 (6-CH_3)*, 35.38 (C-5)**, 40.78 (C-3)**, 55.88 (OCH_3), 76.74 (C-6)***, 79.09 (C-4)***, 95.93 (OCH_2OCH_3), 173.88 (C-2); *,**,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}$ = 2980, 2940, 2890, 2825, 1735, 1460, 1385, 1355, 1300, 1235, 1150, 1095, 1040, 980, 965, 930 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{18}O_4$ (202.2): C 59.39, H 8.97; found: C 59.15, H 8.69.

(3*S*,4*R*,5*R*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-3,4,5,6-tetrahydro-3,5,6-trimethyl-2(1*H*)-pyranol as an 85:15 mixture of unassigned α- and β-anomer (17): At −78 °C DIBAL (2.1 M in toluene, 1.7 mL, 3.6 mmol, 2.2 equiv) was added dropwise to a solution of δ-lactone **15** (441.9 mg, 1.622 mmol) in toluene (12 mL). After stirring for 2.5 h, the reaction mixture was poured into aqueous saturated sodium potassium tartrate (30 mL) and stirred at RT for 1 h. The aqueous phase was extracted with *t*BuOMe (3 × 20 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford lactol **17** (441.1 mg, 99 %) as a colorless oil, which could be used for the next reaction without further purification. ^{1}H NMR (500 MHz; peak of contaminant at δ = 0.92): *major isomer*: $\delta = 0.10$ and 0.14 (2 × s, $SiMe_2$), 0.87 (d, $J_{5\text{-Me},5}$ = 6.9, 5-Me)*, 0.94 (s, $SiCMe_3$), 1.02 (d, $J_{3\text{-Me},3}$ = 7.3, 3-Me)*, 1.21 (d, $J_{6\text{-Me},6}$ = 6.3, 6-Me)*, 1.67 (dqd, $J_{5,6}$ = 10.1, $J_{5,5\text{-Me}}$ = 7.0, $J_{5,4}$ = 2.6, 5-H)**, 2.03 (qdd, $J_{3,3\text{-Me}}$ = 7.3, $J_{3,4}$ = 2.8, $J_{3,2}$ = 1.0, 3-H)**, 3.71 (dd, $J_{4,5}$ = 4.2,*** $J_{4,3}$ = 2.4,*** 4-H),**** 3.96 (dq, $J_{6,5}$ = 10.5, $J_{6,6\text{-Me}}$ = 6.2, 6-H),**** 4.85 (br d, $J_{2,OH}$ = 10.7, 2-H)*****, 5.47 (d, $J_{OH,2}$ = 10.7, OH)*****; *,**,**** distinguishable by an H,H-correlation spectrum; *** interchangeable; ***** distinguishable by a H/D-exchange experiment with D_2O; *minor isomer*: $\delta = 0.04$ and 0.07 (2 × s, $SiMe_2$), 0.80 (d, $J_{5\text{-Me},5}$ = 6.9, 5-Me)*, 0.90 (s, $SiCMe_3$), 0.95 (d, $J_{3\text{-Me},3}$ = 7.1, 3-Me)*, 1.18 (d, $J_{6\text{-Me},6}$ = 6.3, 6-Me)*, 1.55 (m, 5-H)**, 1.88–1.94 (m, 3-H)**, 2.65 (br s, OH), 3.63 (dd, $J_{4,5} = J_{4,3}$ = 2.8, 4-H),*** 3.67 (dq, $J_{6,5}$ = 10.2, $J_{6,6\text{-Me}}$ = 6.3, 6-H),*** 5.19 (m, 2-H); *,**,*** distinguishable by an H,H-correlation spectrum; ^{13}C NMR

(125.7 MHz): *major isomer*: $\delta = -4.91$ and -4.56 [$Si(CH_3)_2$], 14.66 (5-CH_3)*, 15.02 (3-CH_3)*, 17.98 [Si*C*$(CH_3)_3$], 19.28 (6-CH_3)*, 25.83 [3-fold intensity, SiC(CH_3)$_3$], 36.12 (C-5)**, 39.87 (C-3)**, 64.49 (C-6)***, 76.50 (C-4)***, 96.81 (C-2); *,**,*** distinguishable by a C,H-correlation spectrum; *minor isomer*: $\delta = -4.94$ and -4.51 [$Si(CH_3)_2$], 8.88 (5-CH_3)*, 13.83 (3-CH_3)*, 19.39 (6-CH_3)*, 36.47 (C-5)**, 41.46 (C-3)**, 72.13 (C-6)***, 76.57 (C-4)***, 93.60 (C-2); *,**,*** interchangeable; IR (film): $\tilde{\nu} = 3690$, 3605, 3465, 2955, 2935, 2870, 1775, 1715, 1605, 1460, 1385, 1260, 1110, 1030, 930, 845, 760, 710, 650 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{30}O_3Si$ (274.5): C 61.26, H 11.02; found: C 61.45, H 11.12.

(3*S*,4*R*,5*S*,6*R*)-Tetrahydro-4-(methoxymethoxy)-3,5,6-trimethyl-2-pyranol as a 79:21 mixture of unassigned α- and β-anomer (18): At −78 °C DIBAL (1.5 M in toluene, 0.90 mL, 1.4 mmol, 2.2 equiv) was added dropwise to a solution of δ-lactone **16** (126.8 mg, 0.6277 mmol) in toluene (5 mL). After stirring for 2.5 h, the reaction mixture was poured into aqueous saturated Rochelle's salt (20 mL) and stirred at RT for 1 h. The aqueous phase was extracted with *t*BuOMe (3 × 20 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford lactol **18** (127.2 mg, 99 %) as a colorless oil, which could be used for the next reaction without further purification. ^{1}H NMR (500 MHz): *major isomer*: $\delta = 0.93$ (d, $J_{5\text{-Me},5} = 6.8$, 5-Me)*, 1.05 (d, $J_{3\text{-Me},3} = 7.4$, 3-Me)*, 1.22 (d, $J_{6\text{-Me},6} = 6.3$, 6-Me)*, 1.73 (dqd, $J_{5,6} = 10.2$, $J_{5,5\text{-Me}} = 6.9$, $J_{5,4} = 3.1$, 5-H)**, 2.17 (qdd, $J_{3,3\text{-Me}} = 7.3$, $J_{3,4} = 2.8$, $J_{3,2} = 1.1$, 3-H)**, 3.43 (OMe), 3.61 (dd, $J_{4,5} = 4.1$, $J_{4,3} = 2.7$, 4-H), 3.93 (dq, $J_{6,5} = 10.5$, $J_{6,6\text{-Me}} = 6.2$, 6-H), AB signal ($\delta_A = 4.63$, $\delta_B = 4.78$, $J_{AB} = 6.9$, OCH_2OMe), 4.87 (d, $J_{2,OH} = 10.5$, 2-H), 5.10 (d, $J_{OH,2} = 10.5$, OH)***; *,** distinguishable by an H,H-correlation spectrum; *** distinguishable by a H/D-exchange experiment with D_2O; *minor isomer*: $\delta = 0.89$ (d, $J_{5\text{-Me},5} = 6.9$, 5-Me)*, 0.98 (d, $J_{3\text{-Me},3} = 7.1$, 3-Me)*, 1.20 (d, $J_{6\text{-Me},6} \approx 7$, 6-Me)*, 1.64 (dqd, $J_{5,6} = 10.1$, $J_{5,5\text{-Me}} = 6.9$, $J_{5,4} = 3.2$, 5-H)**, 2.13 (qdd, $J_{3,3\text{-Me}} = 7.1$, $J_{3,2} = J_{3,4} = 2.8$, 3-H)**, 2.75 (br s, OH)***, 3.39 (OMe), 3.54 (dd, $J_{4,3} = J_{4,5} = 2.8$, 4-H), 3.65 (dq, $J_{6,5} = 10.2$, $J_{6,6\text{-Me}} = 6.3$, 6-H), AB signal ($\delta_A = 4.60$, $\delta_B = 4.74$, $J_{AB} = 6.9$, OCH_2OMe), 5.15 (m, 2-H)****; *,** distinguishable by an H,H-correlation spectrum; *** exchangable with D_2O; **** resonates in a H/D-exchange experiment with D_2O at $\delta = 5.14$ (d, $J_{2,3} = 2.4$, 2-H); ^{13}C NMR (125.7 MHz): *major isomer*: $\delta = 14.12$ (5-CH_3)*, 15.10 (3-CH_3)*, 19.32 (6-CH_3)*, 35.29 (C-5)**, 37.29 (C-3)**, 56.28 (OCH_3), 65.05 (C-6)***, 81.29 (C-4)***, 96.51 and 96.63 (C-2, OCH_2OCH$_3$); *,**,*** distinguishable by a C,H-correlation spectrum; *minor isomer*: $\delta = 8.92$ (3-CH_3)*, 13.34 (5-CH_3)*, 19.48 (6-CH_3)*, 35.65 (C-5)**, 37.92 (C-3)**, 55.75 (OCH_3), 72.63 (C-6)***, 81.70 (C-4)***, 93.84 (C-2)****, 95.96 (OCH_2OCH$_3$)****; **,**,***,**** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 3425$, 2970, 2935, 2905, 1715, 1650, 1455, 1380, 1330, 1280, 1215, 1155, 1100, 1040, 990, 955, 920, 895 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{20}O_4$ (204.3): C 58.80, H 9.87; found: C 58.76, H 9.62.

(2*E*,4*R*,5*S*,6*R*,7*R*)-5-(*tert*-Butyldimethylsiloxy)-7-hydroxy-4,6-dimethyl-2-octenoic acid ethyl ester (21): A solution of tributyl(ethoxycarbonylmethyl)phosphonium bromide (**26**, 389 mg, 1.05 mmol, 2.3 equiv) in CH_2Cl_2 (15 mL) was washed with aqueous NaOH (1 M, 2 × 10 mL), dried with $MgSO_4$ and diluted with toluene (4 mL). The CH_2Cl_2 was successively evaporated in vacuo. This solution was then transferred via cannula to a solution of lactol **17** (126 mg, 0.459 mmol) and benzoic acid (11 mg, 0.090 mmol, 20 mol %) in toluene (8 mL), which was stirred at 95 °C. After stirring at this temperature for 3 h, the reaction mixture was cooled to RT and purified by flash chromatography (3.0 cm, cyclohexane/EtOAc 5:1) to afford the α,β-unsaturated ethyl ester **21** (48.9 mg, 31 %) as a colorless liquid. $[\alpha]_D^{25} = +9.9$ ($c = 0.44$ in $CDCl_3$); ^{1}H NMR (500 MHz; slightly contaminated by a diastereomer): $\delta = 0.08$ and 0.11 (2 × s, $SiMe_2$), 0.85 (d, $J_{6\text{-Me},6} = 7.1$, 6-Me)*, 0.92 (s, SiCMe_3), 1.08 (d, $J_{4\text{-Me},4} = 6.8$, 4-Me)*, 1.14 (d, $J_{8,7} = 6.1$, 8-H_3)*, 1.29 (t, $J_{2',1'} = 7.2$, 2′-H_3), 1.67 (dqd, $J_{6,7} = 8.2$, $J_{6,6\text{-Me}} = 7.0$, $J_{6,5} = 5.7$, 6-H), 2.57 (qddd, $J_{4,4\text{-Me}} = J_{4,3} = J_{4,5} = 6.6$, $^4J_{4,2} = 1.3$, 4-H), 2.79 (br s, OH), 3.63 (dd, $J_{5,6} = 5.7$, $J_{5,4} = 4.7$, 5-H), 3.73 (dq, $J_{7,6} = 8.2$, $J_{7,8} = 6.2$, 7-H), 4.16–4.23 (m, 1′-H_2), 5.82 (dd, $J_{trans} = 15.8$, $^4J_{2,4} = 1.3$, 2-H), 6.97 (dd, $J_{trans} = 15.8$, $J_{3,4} = 7.9$, 3-H); * distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz): $\delta = -4.20$ and -3.97 [$Si(CH_3)_2$], 14.26, 14.42 and 14.70 (4-CH_3, 6-CH_3, C-2′), 18.23 [Si*C*$(CH_3)_3$], 20.67 (C-8)*, 26.03 [3-fold intensity, SiC(CH_3)$_3$], 41.89 (C-4)**, 44.62 (C-6)**, 60.23 (C-1′)***, 69.53 (C-7)***, 79.70 (C-5)***, 121.11 (C-2), 152.21 (C-3), 166.58 (C-1); *,**,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 3455$, 2960, 2930, 2900, 2860, 1725, 1650, 1465, 1370, 1330, 1255, 1185, 1150, 1080, 1040, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{36}O_4Si$ (344.6): C 62.74, H 10.53; found: C 63.02, H 10.66.

(2*E*,4*R*,5*S*,6*R*,7*R*)-7-Hydroxy-5-(methoxymethoxy)-4,6-dimethyl-2-octenoic acid ethyl ester (22): A solution of tributyl(ethoxycarbonylmethyl)-phosphonium bromide (**26**, 5.99 g, 16.2 mmol, 6.0 equiv) in CH_2Cl_2 (50 mL) was washed with aqueous NaOH (1 M, 2 × 30 mL), dried with $MgSO_4$ and diluted with toluene (10 mL). The CH_2Cl_2 was successively evaporated in vacuo. This solution was then transferred via cannula to a solution of lactol **18** (552 mg, 2.70 mmol) and benzoic acid (132 mg, 1.08 mmol, 40 mol %) in toluene (20 mL), which was stirred at 92 °C. After stirring at this temperature for 2.5 h, the reaction mixture was cooled to RT and purified by flash chromatography (5.0 cm, cyclohexane/EtOAc 4:1 → fraction 35, 3:1 → fraction 60, 2:1 → fraction 120) to afford unconsumed lactol **18** (259.3 mg, 47 %) and α,β-unsaturated ethyl ester **22** (274.1 mg, 37 %; 70 % based on recovered starting material) as a colorless liquid. $[\alpha]_D^{25} = +28.9$ ($c = 0.94$ in $CDCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.88$ (d, $J_{6\text{-Me},6} = 7.1$, 6-Me)*, 1.11 (d, $J_{4\text{-Me},4} = 6.8$, 4-Me)*, 1.17 (d, $J_{8,7} = 6.3$, 8-H_3)*, 1.29 (t, $J_{2',1'} = 7.1$, 2′-H_3), 1.77 (qdd, $J_{6,6\text{-Me}} = J_{6,5} = J_{6,7} = 7.1$, 6-H), 2.64 (qddd, $J_{4,4\text{-Me}} = J_{4,3} = 7.0$, $J_{4,5} = 4.1$, $^4J_{4,2} = 1.5$, 4-H), 2.78 (br s, OH), 3.40 (s, OMe), 3.50 (dd, $J_{5,6} = 7.2$, $J_{5,4} = 4.2$, 5-H), 3.84 (br dq, $J_{7,6} = J_{7,8} = 6.5$, 7-H), 4.19 (q, $J_{1',2'} = 7.1$, 1′-H_2), AB signal ($\delta_A = 4.62$, $\delta_B = 4.64$, $J_{AB} = 6.8$, OCH_2OMe), 5.85 (dd, $J_{trans} = 15.8$, $^4J_{2,4} = 1.4$, 2-H), 7.01 (dd, $J_{trans} = 15.8$, $J_{3,4} = 7.4$, 3-H); * distinguishable by an H,H-correlation spectrum; ^{13}C NMR [125.7 MHz; peaks of contaminant(s) at $\delta = 29.26$ and 53.80]: $\delta = 13.53$ (4-CH_3)*, 13.86 (6-CH_3)*, 14.24 (C-2′)*, 20.30 (C-8)*, 39.70 (C-4)**, 43.18 (C-6)**, 56.34 (OCH_3)***, 60.29 (C-1′)***, 69.63 (C-7)****, 85.61 (C-5)****, 97.92 (OCH_2OCH$_3$), 120.97 (C-2), 151.94 (C-3), 166.58 (C-1); *,**,***,**** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 3450$, 2975, 2935, 1715, 1650, 1455, 1370, 1300, 1265, 1185, 1150, 1095, 1035, 960, 920 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_5$ (274.4): C 61.29, H 9.55; found: C 61.01, H 9.79.

[(3*R*,4*R*,5*R*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-tetrahydro-3,5,6-trimethyl-pyran-2-yl]acetic acid ethyl ester (23) as a 74:26 mixture of two unassigned C-2′ diastereomers, which could be separated by flash chromatography: A refluxing solution of lactol **17** (151 mg, 0.551 mmol) and (ethoxycarbonylmethylen)triphenylphosphorane (**25**, 1.35 g, 3.88 mmol, 7.0 equiv) in toluene (15 mL) was stirred for 24 h. After cooling to RT, the solvent was evaporated in vacuo to a volume of ca. 2 mL, and the residue was submitted to flash chromatography (cyclohexane/EtOAc 5:1) to afford a contaminated diastereomeric mixture of **23** (121 mg) and the α,β-unsaturated ethyl ester **21** (32.1 mg, 17 %) as a colorless liquid. The mixture was resubmitted to flash chromatography (cyclohexane/EtOAc 12:1) to afford the pure major diastereomer of **23** (58.1 mg, 31 %) and the pure minor diastereomer of **23** (20.2 mg, 11 %) as a colorless liquid (each).

Major diastereomer: $[\alpha]_D^{25} = +15.1$ ($c = 0.74$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.04$ (s, $SiMe_2$), 0.79 (d, $J_{5'\text{-Me},5'} = 6.9$, 5′-Me)*, 0.917 (s, SiC$Me_3$), superimposed by 0.923 (d, $J_{3'\text{-Me},3'} = 6.9$, 3′-Me)*, 1.11 (d, $J_{6'\text{-Me},6'} = 6.3$, 6′-$CH_3$)*, 1.25 (t, $J_{2'',1''} = 7.2$, 2″-H_3), 1.51 (dqd, $J_{5',6'} = 9.8$, $J_{5',5\text{-Me}} = 7.0$, $J_{5',4'} = 2.6$, 5′-H)**, 1.65 (qdd, $J_{3',3'\text{-Me}} = 7.1$, $J_{3',2'} = J_{3',4'} = 2.7$, 3′-H)**, AB signal ($\delta_A = 2.30$, $\delta_B = 2.54$, $J_{AB} = 14.6$, in addition split by $J_{A,2'} = 6.6$, $J_{B,2'} = 7.8$, 2-H_2), 3.55 (dd, $J_{4',3'} = J_{4',5'} = 2.9$, 4′-H)***, partly superimposed by 3.57 (dq, $J_{6',5'} = 10.1$, $J_{6',6'\text{-Me}} = 6.2$, 6′-H)***, extreme AB signal ($\delta_A = 4.10$, $\delta_B = 4.16$, $J_{AB} = 10.8$, in addition split by $J_{A,2''} = J_{B,2''} = 7.1$, 1″-$H_2$), 4.36 (ddd, $J_{2',2\text{-H(B)}} = 7.8$, $J_{2',2\text{-H(A)}} = 6.7$, $J_{2',3'} = 2.3$, 2′-H)***; *,** distinguishable by an H,H-correlation spectrum; *** 2′-H (ddd), 4′-H (dd) and 6′-H (dq) were distinguished by the differing multiplicity and by the concerning coupling constants; ^{13}C NMR (125.7 MHz; peak of contaminant at $\delta = 68.26$): $\delta = -4.88$ and -4.48 [$Si(CH_3)_2$], 10.80 (3′-CH_3)*, 14.21 (C-2″)*, 14.40 (5′-CH_3)*, 18.12 [3-fold intensity, Si*C*$(CH_3)_3$], 19.53 (6′-CH_3)*, 25.86 [SiC(CH_3)$_3$]**, 36.81 (C-5′)**, 38.43 (C-2)**, 39.37 (C-3′)**, 60.29 (C-1″)***, 70.47 (C-2′)***, 73.86 (C-6′)***, 75.84 (C-4′)***, 171.47 (C-1); *,**,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 2960$, 2930, 2900, 2860, 1740, 1460, 1380, 1330, 1285, 1270, 1255, 1180, 1115, 1075, 1035, 1005, 865, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{36}O_4Si$ (344.6): C 62.74, H 10.53; found: C 63.07, H 11.05.

Minor diastereomer: $[\alpha]_D^{25} = +15.9$ ($c = 0.42$ in $CDCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.05$ (s, $SiMe_2$), 0.91 (s, SiCMe_3), 0.92 (d, $J_{5'\text{-Me},5'} = 6.9$, 5′-Me)*, 1.00 (d, $J_{3'\text{-Me},3'} = 7.1$, 3′-Me)*, 1.18 (d, $J_{6'\text{-Me},6'} = 6.6$, 6′-Me)*, 1.25 (t, $J_{2'',1''} = 7.1$, 2″-H_3), 1.65 (dqd, $J_{5',6'} = J_{5',5\text{-Me}} = 6.8$, $J_{5',4'} = 3.7$, 5′-H)**, 1.70 (qdd, $J_{3',3'\text{-Me}} = 6.9$, $J_{3',2'} = J_{3',4'} = 5.5$, 3′-H)**, AB signal ($\delta_A = 2.67$, $\delta_B = 2.84$,

$J_{AB}=15.0$, in addition split by $J_{A,2'}=4.8$, $J_{B,2'}=8.9$, 2-H_2), 3.61 (dd, $J_{4',3'}=5.8$, $J_{4',5'}=3.7$, 4′-H)***, 3.80 (dq, $J_{6',5'}=J_{6',6'\text{-Me}}=6.5$, 6′-H)***, 3.92 (ddd, $J_{2',2\text{-H(B)}}=8.9$, $J_{2',2\text{-H(A)}}=J_{2',3'}=4.7$, 2′-H)***, 4.14 (q, $J_{1'',2''}=7.1$, 1″-H_2); *,** distinguishable by an H,H-correlation spectrum; *** 2′-H (ddd), 4′-H (dd) and 6′-H (dq) were distinguished by the differing multiplicity and by the concerning coupling constants; ^{13}C NMR (125.7 MHz): $\delta=-4.71$ and -4.45 [Si(CH_3)$_2$], 13.76 (5′-CH_3)*, 14.24 (C-2″)*, 16.15 (3′-CH_3)*, 18.13 [Si*C*(CH_3)$_3$], 18.55 (6′-CH_3)*, 25.94 [3-fold intensity, SiC(*C*H_3)$_3$], 38.03 (C-5′)**, 38.30 (C-3′)**, 39.01 (C-2)**, 60.25 (C-1″)***, 69.77 (C-6′)***, 73.21 (C-2′)***, 73.96 (C-4′)***, 172.10 (C-1); *,**,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=2960$, 2930, 2905, 2860, 1740, 1465, 1380, 1310, 1255, 1180, 1150, 1120, 1090, 1065, 1025, 865, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{36}O_4Si$ (344.6): C 62.74, H 10.53; found: C 60.77, H 9.58.

(2*E*,6*S*,7*R*)-7-Hydroxy-4,6-dimethyl-2,4-octadienoic acid ethyl ester as a inseparable 89:11 mixture of two unassigned C^4–C^5-bond isomers (24): A solution of tributyl(ethoxycarbonylmethyl)phosphonium bromide (**26**, 468 mg, 1.27 mmol, 2.6 equiv) in CH_2Cl_2 (15 mL) was washed with aqueous NaOH (1 M, 2 × 15 mL), dried with $MgSO_4$ and diluted with toluene (3 mL). The CH_2Cl_2 was successively evaporated in vacuo. This solution was then transferred via cannula to a refluxing solution of lactol **18** (99.1 mg, 0.485 mmol) and benzoic acid (10.9 mg, 0.0893 mmol, 18 mol%) in toluene (5 mL). After stirring for 2 h, the reaction mixture was cooled to RT and purified by flash chromatography (2.5 cm, cyclohexane/EtOAc 5:1) to afford the title compound **24** (54.6 mg, 53%) as a light yellow liquid. ^{1}H NMR (500 MHz; slightly contaminated): *major isomer*: $\delta=1.02$ (d, $J_{6\text{-Me},6}=6.8$, 6-Me), 1.18 (d, $J_{8,7}=6.3$, 8-H_3), 1.30 (t, $J_{2',1'}=7.2$, 2′-H_3), 1.60–1.88 (m, OH), superimposed by 1.82 (d, $^4J_{4\text{-Me},5}=1.2$, 4-Me), 2.57 (dqd, $J_{6,5}=10.0$, $J_{6,6\text{-Me}}=6.5$, $J_{6,7}=6.4$, 6-H), 3.67 (dq, $J_{7,6}=J_{7,8}=6.2$, 7-H), 4.21 (q, $J_{1',2'}=7.1$, 1′-H_2), 5.79 (br d, $J_{5,6}=10.0$, 5-H), 5.83 (dd, $J_{trans}=15.7$, $^5J_{2,5}=0.5$, 2-H), 7.34 (dd, $J_{trans}=15.7$, $^4J_{3,5}=0.6$, 3-H); *minor isomer**: $\delta=1.31$ (t, $J_{2',1'}=7.2$, 2′-H_3), 1.90 (d, $^4J_{4\text{-Me},5}=1.2$, 4-Me), 2.76 (br dqd, $J_{6,5}=10.3$, $J_{6,6\text{-Me}}=J_{6,7}=6.6$, 6-H), 3.64 (dq, $J_{7,6}=J_{7,8}=6.2$, 7-H), 4.23 (q, $J_{1',2'}=7.1$, 1′-H_2), 5.64 (br d, $J_{5,6}=10.0$, 5-H), 5.93 (dd, $J_{trans}=15.6$, $^5J_{2,5}=0.7$, 2-H), 7.71 (d, $J_{trans}=15.5$, 3-H); * other signals are superimposed; ^{13}C NMR (125.7 MHz): *major isomer*: $\delta=12.57$, 14.28, 16.45 and 20.53 (4-CH_3, 6-CH_3, C-8, C-2′), 40.87 (C-6), 60.20 (C-1′)*, 71.49 (C-7)*, 116.44, 140.97, 143.30, 149.23 (C-2, C-3, C-4, C-5), 167.39 (C-1); * interchangeable; *minor isomer**: $\delta=13.60$, 17.21, 20.28 and 20.55 (4-CH_3, 6-CH_3, C-8, C-2′), 39.89 (C-6), 60.33 (C-1′)**, 71.54 (C-7)**, 167.45 (C-1); * other signals superimposed; ** interchangeable; IR (film): $\tilde{\nu}=3450$, 2975, 2930, 2875, 1715, 1625, 1450, 1395, 1370, 1310, 1275, 1175, 1095, 1095, 1030, 985, 940, 905, 850 cm^{-1}; *m*/*z*: 212.1409 ±5 mDa [M^+] confirmed by HRMS (EI, 70 eV); elemental analysis calcd (%) for $C_{12}H_{20}O_3$ (212.3): C 67.89, H 9.50; found: C 67.28, H 9.98.

Tributyl(ethoxycarbonylmethyl)phosphonium bromide (26): At 0 °C, a solution of bromoacetic acid ethyl ester (13.4 mL, 20.2 g, 121 mmol, 1.0 equiv) in toluene (20 mL) was added dropwise to a solution of tributylphosphine (30 mL, 24 g, 0.12 mol) in toluene (120 mL). The reaction mixture was allowed to reach RT, and after 22 h the resulting precipitate was filtered and dried in vacuo (6×10^{-4} mbar) at 50 °C for 20 h to afford the title compound **26** (37.9 g, 86%) as a colorless solid. M.p. 96 °C; ^{1}H NMR (400 MHz): $\delta=0.98$ (t, $J_{4',3'}=7.0$, 3 × 4′-H_3), 1.31 (t, $J_{2,1}=7.2$, 2-H_3), 1.48–1.64 (m, 3 × 2′-H_2, 3 × 3′-H_2), 2.61 (m, 3 × 1′-H_2), 4.18 (d, $^2J_{1'',P}=13.1$, 1″-H_2), partly superimposed by 4.22 (q, $J_{1,2}=7.1$, 1-H_2). ^{13}C NMR (100.6 MHz): $\delta=13.38$ (3-fold intensity, s, 3 × C-4′), 13.95 (s, C-2), 19.56 (3-fold intensity, d, $^1J_{C\text{-}1',P}=47$, 3 × C-1′), 23.80 (3-fold intensity, br s, 3 × C-2′), 23.90 (d, $^3J_{C\text{-}3',P}=10$, 3 × C-3′), 27.55 (d, $^1J_{C\text{-}1'',P}=54$, C-1″), 62.80 (s, C-1), 165.68 (s, C=O); IR ($CDCl_3$): $\tilde{\nu}=2965$, 2935, 2875, 2205, 1725, 1465, 1400, 1380, 1310, 1190, 1135, 1095, 1020, 930, 925, 890, 885 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{34}BrO_2P$ (369.3): C 52.03, H 9.28; found: C 52.15, H 9.41.

(2*E*,4*R*,5*S*,6*S*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-(methoxymethoxy)-4,6-dimethyl-2-octenoic acid ethyl ester (28): At 0 °C *tert*-butyldimethylsilyl triflate (77 μL, 89 mg, 0.34 mmol, 2.0 equiv) was added to a solution of alcohol **22** (46.3 mg, 0.169 mmol) and 2,6-lutidine (70 μL, 64 mg, 0.60 mmol, 3.6 equiv) in CH_2Cl_2 (6 mL). After stirring at this temperature for 15 h, the reaction mixture was hydrolyzed with aqueous saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 13:1) to afford the title compound **28** (55.2 mg, 84%) as a colorless oil. $[\alpha]_D^{25}=+14.0$ ($c=1.03$ in $CDCl_3$); ^{1}H NMR (500 MHz): $\delta=0.046$ and 0.050 (2 × s, $SiMe_2$), 0.86 (d, $J_{6\text{-Me},6}=7.1$, 6-Me)*, 0.88 (s, SiCMe_3), 1.06 (d, $J_{8,7}=6.2$, 8-H_3)*, 1.08 (d, $J_{4\text{-Me},4}=6.8$, 4-Me)*, 1.29 (t, $J_{2',1'}=7.2$, 2′-H_3), 1.85 (qdd, $J_{6,6\text{-Me}}=J_{6,5}=7.2$, $J_{6,7}=4.5$, 6-H), 2.61 (qddd, $J_{4,4\text{-Me}}=J_{4,3}=6.9$, $J_{4,5}=3.7$, $^4J_{4,2}=1.4$, 4-H), 3.37 (s, OMe), 3.41 (dd, $J_{5,6}=7.7$, $J_{5,4}=3.8$, 5-H), 4.05 (qd, $J_{7,8}=6.2$, $J_{7,6}=4.6$, 7-H), 4.19 (q, $J_{1',2'}=7.1$, 1′-H_2), AB signal ($\delta_A=4.55$, $\delta_B=4.56$, $J_{AB}=6.9$, OCH_2OMe), 5.83 (dd, $J_{trans}=15.8$, $^4J_{2,4}=1.4$, 2-H), 7.03 (dd, $J_{trans}=15.8$, $J_{3,4}=7.4$, 3-H); * distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz): $\delta=-4.75$ and -4.32 [Si(CH_3)$_2$], 10.38 (6-CH_3)*, 13.13 (4-CH_3)*, 14.27 (C-2′)*, 18.04 [Si*C*(CH_3)$_3$], 18.52 (C-8)*, 25.87 [3-fold intensity, SiC(*C*H_3)$_3$], 38.77 (C-4)**, 43.15 (C-6)**, 56.09 (OCH_3)***, 60.20 (C-1′)***, 68.14 (C-7)***, 83.19 (C-5)***, 97.65 (O*C*H_2OCH$_3$), 120.55 (C-2), 152.64 (C-3), 166.63 (C-1); *,**,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=2955$, 2930, 2890, 2835, 1720, 1650, 1470, 1465, 1385, 1370, 1330, 1300, 1255, 1180, 1160, 1140, 1100, 1035, 995, 965, 940, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{40}O_5Si$ (388.6): C 61.81, H 10.37; found: C 61.86, H 10.35.

(2*E*,4*R*,5*S*,6*S*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-(methoxymethoxy)-4,6-dimethyl-2-octenal (29): At −78 °C DIBAL (1.5 M in toluene, 1.8 mL, 2.7 mmol, 3.1 equiv) was added dropwise to a solution of ethyl ester **28** (340 mg, 0.875 mmol) in CH_2Cl_2 (20 mL). After stirring for 80 min, the reaction mixture was poured into aqueous saturated Rochelle's salt (50 mL) and stirred at RT for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue which was dissolved in CH_2Cl_2 (23 mL) and treated with MnO_2 (1.69 g, 19.6 mmol, 22 equiv). After 4 h stirring at RT, the reaction mixture was filtered through a pad of Celite, and the filter cake was washed with CH_2Cl_2 (3 × 5 mL). The filtrate and washings were evaporated in vacuo to afford a residue which was submitted to flash chromatography (cyclohexane/EtOAc 8:1) to afford aldehyde **29** (269 mg, 89%) as a colorless oil. $[\alpha]_D^{25}=+7.0$ ($c=1.17$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.05$ and 0.06 (2 × s, $SiMe_2$), 0.857 (d, $J_{6\text{-Me},6}=6.9$, 6-Me)*, superimposes in part 0.864 (s, SiCMe_3), 1.05 (d, $J_{8,7}=6.3$, 8-H_3)*, 1.11 (d, $J_{4\text{-Me},4}=6.8$, 4-Me)*, 1.85 (dqd, $J_{6,5}=8.0$, $J_{6,6\text{-Me}}=7.1$, $J_{6,7}=4.3$, 6-H), 2.74 (qddd, $J_{4,4\text{-Me}}=J_{4,3}=6.8$, $J_{4,5}=3.3$, $^4J_{4,2}=1.5$, 4-H), 3.33 (s, OMe), 3.45 (dd, $J_{5,6}=8.1$, $J_{5,4}=3.4$, 5-H), 4.02 (qd, $J_{7,8}=6.3$, $J_{7,6}=4.4$, 7-H), extreme AB signal ($\delta_A=4.54$, $\delta_B=4.55$, $J_{AB}=6.9$, OCH_2OMe), 6.11 (ddd, $J_{trans}=15.7$, $J_{2,1}=7.8$, $^4J_{2,4}=1.5$, 2-H), 6.95 (dd, $J_{trans}=15.8$, $J_{3,4}=6.8$, 3-H), 9.52 (d, $J_{1,2}=7.7$, 1-H); * distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz): $\delta=-4.71$ and -4.29 [Si(CH_3)$_2$], 10.70 (6-CH_3)*, 12.79 (4-CH_3)*, 18.04 [Si*C*(CH_3)$_3$], 18.65 (C-8)*, 25.86 [3-fold intensity, SiC(*C*H_3)$_3$], 39.19 (C-4)*, 43.21 (C-6)*, 56.08 (OCH_3)*, 68.31 (C-7)*, 83.24 (C-5)*, 97.68 (O*C*H_2OCH$_3$), 131.81 (C-2), 162.52 (C-3), 195.06 (C-1); * assignment by comparison with the analogous resonance of ethyl ester **28**—criterion of assignment: $\Delta(\delta)\leq 0.5$ ppm; IR (film): $\tilde{\nu}=2955$, 2930, 2890, 2835, 1695, 1635, 1465, 1385, 1255, 1150, 1100, 1035, 965, 835, 775 cm^{-1}; *m*/*z*: 313.2199 ±5 mDa [M^+−OMe] confirmed by HRMS (EI, 70 eV); elemental analysis calcd (%) for $C_{18}H_{36}O_4Si$ (344.6): C 62.74, H 10.53; found: C 62.93, H 10.78.

(2*E*,4*R*,5*S*,6*R*,7*R*)-5-(*tert*-Butyldimethylsiloxy)-7-(methoxymethoxy)-4,6-dimethyl-2-octenoic acid ethyl ester (30): At 0 °C (chloromethyl) methyl ether (0.66 M in CH_2Cl_2, 0.70 mL, 0.46 mmol, 5.3 equiv) was added dropwise to a solution of alcohol **21** (30.2 mg, 0.0876 mmol) and diisopropylethylamine (90 μL, 68 mg, 0.53 mmol, 6.0 equiv) in CH_2Cl_2 (4 mL). After 40 min stirring the reaction mixture was allowed to reach RT and stirred for 6 h at this temperature. (Chloromethyl) methyl ether (0.66 M in CH_2Cl_2, 0.40 mL, 0.26 mmol, 3.0 equiv), diisopropylethylamine (60 μL, 45 mg, 0.35 mmol, 4.0 equiv) and tetrabutylammonium iodide (4.4 mg, 0.012 mmol, 14 mol%) were added, and the reaction was terminated after stirring for another 12 h by addition of water (8 mL). Stirring was continued for 1 h to destroy the excess of (chloromethyl) methyl ether. Then the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated in vacuo to afford an oily residue which was submitted to flash chromatography (cyclohexane/EtOAc 10:1) to afford the title compound **30** (29.0 mg, 85%) as a colorless oil. $[\alpha]_D^{25}=+10.6$ ($c=0.60$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.03$ and 0.05 (2 × s, $SiMe_2$), 0.87 (d, $J_{6\text{-Me},6}=7.1$, 6-Me)*, 0.91 (s, SiCMe_3), 1.06 (d, $J_{4\text{-Me},4}=6.8$, 4-Me)*, 1.09 (d, $J_{8,7}=6.2$, 8-H_3)*, 1.29 (t, $J_{2',1'}=7.2$, 2′-H_3), 1.90 (dqd, $J_{6,5}=J_{6,6\text{-Me}}=6.9$,

$J_{6,7}=5.3$, 6-H), 2.55 (poorly resolved qddd, $J_{4,4\text{-Me}}=J_{4,3}=7.0$, $J_{4,5}=4.0$, $^4J_{4,2}=1.3$, 4-H), 3.35 (s, OMe), 3.64 (dd, $J_{5,6}=6.5$, $J_{5,4}=4.0$, 5-H), 3.85 (qd, $J_{7,8}=J_{7,6}=6.0$, 7-H), 4.19 [m; perhaps interpretable as extreme AB signal ($\delta_A=4.18$, $\delta_B=4.20$, $J_{AB}=3.2$, in addition split by $J_{A,2'}=J_{B,2'}=7.1$, 1′-H_2)], AB signal ($\delta_A=4.60$, $\delta_B=4.64$, $J_{AB}=6.8$, OCH_2OMe), 5.80 (dd, $J_{trans}=15.7$, $^4J_{2,4}=1.4$, 2-H), 7.00 (dd, $J_{trans}=15.8$, $J_{3,4}=7.6$, 3-H); * distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz)*: $\delta=-4.00$ and -3.95 [Si(CH_3)$_2$], 10.75 (6-CH_3)*, 13.69 (4-CH_3)*, 14.26 or 14.28 (C-2′)**, 16.13 (C-8)*, 18.49 [SiC(CH_3)$_3$], 26.06 [3-fold intensity, SiC(CH_3)$_3$], 39.80 (C-4)***, 42.91 (C-6)***, 55.31 (OCH_3)****, 60.14 (C-1′)****, 73.38 (C-7)****, 76.24 (C-5)****, 95.00 (OCH_2OCH$_3$), 120.49 (C-2), 153.26 (C-3), 166.66 (C-1); * distinguishable by a C,H-correlation spectrum; ** two resonances of the same intensity, i.e., one is based on a—albeit unknown—contaminant; ***,**** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=2960$, 2930, 2885, 2860, 1720, 1655, 1465, 1370, 1265, 1185, 1110, 1045, 840, 780 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{40}O_5Si$ (388.6): C 61.81, H 10.37; found: C 62.06, H 10.46.

(4*E*,6*R*,7*S*,8*S*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-7-(methoxymethoxy)-6,8-dimethyl-1,4-decadien-3-ol (31) as a 50:50 mixture of two C-3 diastereomers: At −78 °C vinylmagnesium bromide (1.6 M in Et_2O, 0.50 mL, 0.8 mmol, 2.3 equiv) was added dropwise to a solution of aldehyde **29** (119.0 mg, 0.3454 mmol) in THF (10 mL). After stirring for 70 min, the reaction was terminated by addition of MeOH (0.5 mL) in one portion and after that aqueous semisaturated $NaHCO_3$ (12 mL). The aqueous phase was extracted with *t*BuOMe (3 × 12 mL), and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue which was submitted to flash chromatography (cyclohexane/EtOAc 6:1) to afford divinyl carbinol **31** (120.1 mg, 93 %) as a colorless oil. ^{1}H NMR (500 MHz; a 50:50 mixture of two diastereomers—in case of differing resonances for analogous protons the signals are indicated with "dia.-A" and "dia.-B"): $\delta=0.04$ and 0.05 (2 × s, $SiMe_2$), 0.84 (d, $J_{8\text{-Me},8}=7.1$, 8-Me)*, 0.89 (s, $SiMe_3$), 1.02 [d, $J_{6,6\text{-Me}}=6.9$, 6-Me (dia.-A)]*, superimposed by 1.03 [d, $J_{6\text{-Me},6}=6.8$, 6-Me (dia.-B)]*, 1.04 (d, $J_{10,9}=6.2$, 10-H_3)*, 1.70 (br s, OH), 1.84 (dqd, $J_{8,7}=8.3$, $J_{8,8\text{-Me}}=7.1$, $J_{8,9}=4.3$, 8-H), 2.45 (m, 6-H), 3.29 (br dd, $J_{7,8}=8.4$, $J_{7,6}=3.4$, 7-H), 3.370 [s, OMe (dia. A)], poorly separated from 3.371 [s, OMe (dia. B)], 4.07 [qd, $J_{9,10}=6.2$, $J_{9,8}=4.5$, 9-H (dia.-A)], superimposes in part 4.09 [qd, $J_{9,10}=6.3$, $J_{9,8}=4.1$, 9-H (dia.-B)], AB signal [$\delta_A=4.54$, $\delta_B=4.58$, $J_{AB}=6.9$, OCH_2OMe (dia.-A)], superimposed by AB signal [$\delta_A=4.54$, $\delta_B=4.59$, $J_{AB}=6.8$, OCH_2OMe (dia.-B)], superimposed by 4.60 (br dd, $J_{3,2}=J_{3,4}=7.2$, 3-H), 5.13 (d m, $J_{cis}=10.3$, 1-H^E), 5.26 (ddd, $J_{trans}=17.2$, $J_{gem}=^4J_{1\text{-}H(Z),3}=1.4$, 1-H^Z), 5.53 (ddd, $J_{trans}=15.6$, $J_{4,3}=6.5$, $^4J_{4,6}=1.2$, 4-H), 5.77 {m, perhaps interpretable as two dd's: 5.76 [dd, $J_{trans}=17.1$, $J_{5,6}=8.1$, $^4J_{5,3}=1.2$, 5-H (dia. A)] and 5.78 [dd, $J_{trans}=15.4$, $J_{5,6}=7.3$, $^4J_{5,3}=1.2$, 5-H (dia. B)]}, 5.90 (m, probably interpretable as ddd with a small extra-peak indicating transition to higher-order spectrum, $J_{trans}=17.2$, $J_{cis}=10.4$, $J_{2,3}=5.9$, 2-H); * distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz, most signals with two resonances due to the existence of two diastereomers): $\delta=-4.67$ (1.5-fold intensity), -4.36 and -4.32 [Si(CH_3)$_2$], 10.13 and 10.17 (8-CH_3)*, 13.31 and 13.50 (6-CH_3)*, 18.06, 18.07, 18.19 and 18.22 [C-10, SiC(CH_3)$_3$]*, 25.88 [3-fold intensity, SiC(CH_3)$_3$], 38.12 and 38.29 (C-6)*, 42.90 and 42.96 (C-8)*, 56.02 (OCH_3)*, 68.09 and 68.16 (C-9)*, 73.84 (C-3)*, 84.59 and 84.67 (C-7)*, 97.94 (OCH_2OCH$_3$), 114.84 (C-1)**, 130.19 and 130.27 (C-4)**, 136.58 and 136.77 (C-5)**, 139.61 and 139.65 (C-2)**; * assignment by comparison with the analogous resonance of ethyl ester **28**—criterion of assignment: $\Delta(\delta)\leq 1.2$ ppm; ** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=3415$, 2955, 2930, 2885, 2855, 1470, 1465, 1385, 1360, 1255, 1140, 1105, 1035, 990, 970, 920, 835, 800, 775 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{40}O_4Si$ (372.6): C 64.47, H 10.82; found: C 64.76, H 11.00.

(2*E*,6*E*,8*E*,10*R*,11*S*,12*S*,13*R*)-13-(*tert*-Butyldimethylsiloxy)-11-(methoxymethoxy)-10,12-dimethyl-2,6,8-tetradecatrienoic acid methyl ester (33): A solution of aldehyde **35** (91.0 mg, 0.228 mmol) and (methoxycarbonylmethylen)triphenylphosphorane (234 mg, 0.701 mmol, 3.1 equiv) in toluene (3 mL) was stirred at RT for 16 h. The reaction mixture was submitted to flash chromatography (cyclohexane/EtOAc 18:1) to afford α,β-unsaturated methyl ester **33** (92.7 mg, 89 %) as a pure diastereomer and a colorless oil. $[\alpha]_D^{25}=+11.9$ ($c=0.52$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta=0.036$ and 0.044 (2 × s, $SiMe_2$), 0.85 (d, $J_{12\text{-Me},12}=7.1$, 12-Me)*, 0.88 (s, $SiCMe_3$), 1.02 (d, $J_{10,10\text{-Me}}=6.8$, 10-Me)*, 1.05 (d, $J_{14,13}=6.2$, 14-H_3)*, 1.84 (dqd, $J_{12,11}=J_{12,12\text{-Me}}=7.2$, $J_{12,13}=4.5$, 12-H)*, 2.23 (br td, $J_{5,4}=J_{5,6}=7.0$, 5-H_2)**, 2.30 (td with small extra-peaks indicating transition to higher-order spectrum and/or unresolved $^4J_{4,2}$, $J_{4,5}=J_{4,3}=7.0$, 4-H_2)**, 2.44 (br dqd, $J_{10,9}=J_{10,10\text{-Me}}=6.9$, $J_{10,11}=4.2$, 10-H)*, 3.29 (dd, $J_{11,12}=7.8$, $J_{11,10}=3.9$, 11-H)*, 3.37 (s, OCH$_2$OMe)*, 3.73 (s, CO_2Me), 4.09 (qd, $J_{13,14}=6.2$, $J_{13,12}=4.5$, 13-H)*, AB signal ($\delta_A=4.56$, $\delta_B=4.59$, $J_{AB}=6.6$, OCH_2OMe)*, 5.56 (dt with small extra-peaks indicating transition to higher-order spectrum, $J_{trans}=14.5$, $J_{6,5}=7.0$, 6-H)*, 5.62 (dd, $J_{trans}=14.5$, $J_{9,10}=7.6$, 9-H)*, 5.84 (dt with small extra-peaks indicating transition to higher-order spectrum, $J_{trans}=15.7$, $^4J_{2,4}=1.5$, 2-H), 6.01 (m, 7-H, 8-H)*, 6.96 (dt, $J_{trans}=15.7$, $J_{3,4}=6.7$, 3-H); * assignment by comparison with the analogous resonance of aldehyde **35**—criterion of assignment: $\Delta(\delta)\leq 0.02$ ppm; ** distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz)*: $\delta=$?4.69 and ?4.32 [Si(CH_3)$_2$], 10.21 (12-CH_3)*, 14.09 (10-CH_3)*, 18.06 [SiC(CH_3)$_3$], 18.33 (C-14)*, 25.89 [3-fold intensity, SiC(CH_3)$_3$], 30.99 (C-5)**, 32.02 (C-4)**, 38.85 (C-10)*, 42.98 (C-12)*, 51.40 (CO_2CH_3), 56.07 (OCH$_2$OCH_3)*, 68.10 (C-13)*, 84.42 (C-9)*, 97.87 (OCH_2OCH$_3$), 121.32 (C-2)***, 129.19 and 131.44 (C-7, C-8)***, 130.59 (C-6)***, 136.86 (C-9)***, 148.60 (C-3)***, 167.02 (C-1); * assignment by comparison with the analogous resonance of aldehyde **35**—criterion of assignment: $\Delta(\delta)\leq 0.5$ ppm; **,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=2955$, 2930, 2890, 2855, 1730, 1660, 1460, 1440, 1380, 1315, 1270, 1255, 1200, 1170, 1140, 1100, 1035, 990, 965, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{46}O_5Si$ (454.7): C 66.03, H 10.20; found: C 66.29, H 10.31.

(2*E*,6*E*,8*E*,10*R*,11*S*,12*S*,13*R*)-13-(*tert*-Butyldimethylsiloxy)-11-(methoxymethoxy)-10,12-dimethyl-2,4,6-tetradecatrienal (34): At −78 °C DIBAL (1.11 M in toluene, 0.40 mL, 0.44 mmol, 4.1 equiv) was added dropwise to a solution of methyl ester **33** (49.0 mg, 0.108 mmol) in CH_2Cl_2 (5 mL). After stirring for 2.5 h, the reaction mixture was poured into aqueous saturated Rochelle's salt (8 mL) and stirred at RT for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue which was dissolved in CH_2Cl_2 (8 mL) and treated with MnO_2 (190 g, 2.19 mmol, 20 equiv). After 14 h stirring at RT, the reaction mixture was filtered through a pad of Celite, and the filter cake was washed with CH_2Cl_2 (3 × 5 mL). The filtrate and washings were evaporated in vacuo to afford a residue which was submitted to flash chromatography (cyclohexane/EtOAc 10:1) to afford aldehyde **34** (40.6 mg, 89 %) as a colorless oil. $[\alpha]_D^{25}=+12.5$ ($c=0.42$ in $CHCl_3$). ^{1}H NMR (500 MHz): $\delta=0.036$ and 0.044 (2 × s, $SiMe_2$), 0.85 (d, $J_{12\text{-Me},12}=7.1$, 12-Me)*, 0.88 (s, $SiCMe_3$), 1.03 (d, $J_{10,10\text{-Me}}=6.8$, 10-Me)*, 1.05 (d, $J_{14,13}=6.2$, 14-H_3)*, 1.84 (dqd, $J_{12,11}=J_{12,12\text{-Me}}=7.2$, $J_{12,13}=4.5$, 12-H)*, 2.30 (br td, $J_{5,4}=J_{5,6}=7.2$, 5-H_2)**, 2.44 (td with small extra-peaks indicating transition to higher-order spectrum and/or unresolved $^4J_{4,2}$, $J_{4,5}\approx J_{4,3}\approx 7.0$, 4-$H_2$)**, superimposed by ca. 2.45 (m, 10-H)*, 3.30 (dd, $J_{11,12}=7.8$, $J_{11,10}=4.0$, 11-H)*, 3.37 (s, OMe), 4.09 (qd, $J_{13,14}=6.2$, $J_{13,12}=4.5$, 13-H)*, AB signal ($\delta_A=4.56$, $\delta_B=4.59$, $J_{AB}=6.8$, OCH_2OMe), 5.56 (dt, $J_{trans}=14.3$, $J_{6,5}=7.0$, 6-H)*, 5.64 (dd, $J_{trans}=14.5$, $J_{9,10}=7.5$, 9-H)*, 6.03 (m, 7-H, 8-H)*, 6.14 (ddt, $J_{trans}=15.7$, $J_{2,1}=7.9$, $^4J_{2,4}=1.5$, 2-H), 6.84 (dt, $J_{trans}=15.7$, $J_{3,4}=6.7$, 3-H), 9.51 (d, $J_{1,2}=7.8$, 1-H); * assignment by comparison with the analogous resonance of methyl ester **33**—criterion of assignment: $\Delta(\delta)\leq 0.02$ ppm; ** distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz; contains 4 mol % of an unassigned diastereomer)*: $\delta=-4.69$ and -4.31 [Si(CH_3)$_2$], 10.23 (12-CH_3)*, 14.08 (10-CH_3)*, 18.05 [SiC(CH_3)$_3$], 18.33 (C-14)*, 25.89 [3-fold intensity, SiC(CH_3)$_3$], 30.79 (C-5)*, 32.41 (C-4)*, 38.86 (C-10)*, 42.98 (C-12)*, 56.07 (OCH$_2$OCH_3)*, 68.10 (C-13)*, 84.39 (C-11)*, 97.84 (OCH_2OCH$_3$), 129.01 and 131.81 (C-7, C-8)**, 130.12 (C-6)**, 133.31 (C-2)**, 137.24 (C-9)**, 157.62 (C-3)**, 193.93 (C-1); * assignment by comparison with the analogous resonance of methyl ester **33**—criterion of assignment: $\Delta(\delta)\leq 0.4$ ppm; ** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=2955$, 2930, 2855, 1695, 1640, 1600, 1470, 1460, 1450, 1385, 1255, 1120, 1035, 1005, 990, 970, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{44}O_4Si$ (424.7): C 67.87, H 10.44; found: C 68.15, H 10.66.

(4*E*,6*E*,8*R*,9*S*,10*S*,11*R*)-11-(*tert*-Butyldimethylsiloxy)-9-(methoxymethoxy)-8,10-dimethyl-4,6-dodecadienal (35): A refluxing solution of divinyl carbinol **31** (69.6 mg, 0.187 mmol) and $Hg(OAc)_2$ (64.1 mg, 0.201 mmol, 1.1 equiv) in *tert*-butyl vinyl ether (1.7 mL, 1.3 g, 13 mmol, 70 equiv) was stirred for 9 h. The reaction mixture was cooled to RT and then submitted to flash chromatography (cyclohexane/EtOAc 7:1) to

afford an unanalyzed mixture of (regio-)isomers (70.9 mg, 95%), from which the desired rearrangement product **35** (57.8 mg, 78% based on starting material **31**) was obtained as a pure diastereomer and colorless oil by a second flash chromatography (cyclohexane/EtOAc 12:1). $[\alpha]_D^{25} = +13.2$ ($c = 0.55$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 0.03$ and 0.04 (s, $SiMe_2$), 0.85 (d, $J_{10\text{-}Me,10} = 7.1$, 10-Me)*, 0.88 (s, $SiCMe_3$), 1.02 (d, $J_{8,8\text{-}Me} = 6.9$, 8-Me)*, 1.04 (d, $J_{12,11} = 6.3$, 12-H_3)*, 1.84 (dqd, $J_{10,9} = J_{10,10\text{-}Me} = 7.4$, $J_{10,11} = 4.6$, 10-H), 2.41 (brtd, $J_{3,2} = J_{3,4} = 6.9$, 3-H_2)**, superimposed by 2.45 (dqd, $J_{8,7} = J_{8,8\text{-}Me} = 6.9$, $J_{8,9} = 4.0$, 8-H), 2.53 (t with a small extra-peak indicating transition to higher-order spectrum and/or unresolved $J_{2,1}$, $J_{2,3} = 6.9$, 2-H_2)**, 3.29 (dd, $J_{9,10} = 7.7$, $J_{9,8} = 4.0$, 9-H), 3.37 (s, OMe), 4.08 (qd, $J_{11,12} = 6.2$, $J_{11,10} = 4.5$, 11-H), AB signal ($\delta_A = 4.56$, $\delta_B = 4.58$, $J_{AB} = 6.8$, OCH_2OMe), 5.57 (dt, $J_{trans} = 14.5$, $J_{4,3} = 7.0$, 4-H)***, 5.63 (dd, $J_{trans} = 14.5$, $J_{7,8} = 7.5$, 7-H)***, 5.96–6.07 (m, 5-H, 6-H)***, 9.78 (t, $J_{1,2} = 1.5$, 1-H); * signal assigned by comparison with the analogous resonances and coupling constants of ethyl ester **28**, aldehyde **29** and ethyl ester **30**; ** 2-H_2 (brtd) and 3-H_2 (t; unresolved $J_{2,1}$) were distinguished by the differing multiplicity and by the concerning coupling constants; *** distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz): $\delta = -4.69$ and -4.31 [$Si(CH_3)_2$], 10.23 (10-CH_3)*, 14.13 (8-CH_3)*, 18.06 [$SiC(CH_3)_3$], 18.35 (C-12)*, 25.12 (C-3)**, 25.89 [3-fold intensity, $SiC(CH_3)_3$], 38.87 (C-8)*, 42.98 (C-10)*, 43.32 (C-2)**, 56.08 (OCH_3)*, 68.10 (C-11)*, 84.40 (C-9)*, 97.85 (OCH_2OCH_3), 129.01 and 131.63 (C-5, C-6)***, 129.84 (C-4)***, 137.18 (C-7)***, 201.88 (C-1); * assignment by comparison with the analogous resonance of ethyl ester **28** and divinyl carbinol **31**—criterion of assignment: $\Delta(\delta) \leq 1.0$ ppm; **,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 2955$, 2930, 2890, 2855, 1730, 1600, 1470, 1465, 1445, 1410, 1385, 1360, 1255, 1140, 1100, 1035, 990, 965, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{42}O_4Si$ (398.7): C 66.28, H 10.62; found: C 66.09, H 10.89.

6-[(3*E*,5*E*,7*R*,8*S*,9*S*,10*R*)-10-(*tert*-Butyldimethylsiloxy)-8-(methoxymethoxy)-7,9-dimethyl-3,5-undecadienyl]-1,3-cyclohexadiene-1-carboxylic acid methyl ester as a 50:50 mixture of two C-6-epimers (39): At -60 °C a solution of a 90:10 mixture of phosphonates *trans*-**36** and *cis*-**36** (0.60 M in THF, 0.24 mL, 0.14 mmol, 1.9 equiv) was added dropwise to a solution of lithium *N*,*N*-diisopropyamide (0.29 M in THF, 0.60 mL, 0.17 mmol, 2.3 equiv). After stirring at this temperature for 25 min, the reaction mixture was treated dropwise with a solution of aldehyde **34** (30.9 mg, 0.0728 mmol) in THF (1.6 mL), allowed to reach -30 °C and after 2 h stirring, treated with aqueous semisaturated ammonium chloride (2 mL). The aqueous phase was extracted with *t*BuOMe (3 × 2 mL), and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue which was submitted to flash chromatography (cyclohexane/EtOAc 15:1) to afford the title compound **39** (7.7 mg, 21%), a 92.6:7.4 mixture (7.3 mg) of **39** (*pure* **39**: 6.8 mg, 18%) and all-*trans*-**40** (*pure* all-*trans*-**40**: 0.54 mg, 1.5%) and all-*trans*-**40** (4.1 mg, 11%). ^{1}H NMR (500 MHz): $\delta = 0.03$ and 0.04 (2 × s, $SiMe_2$), 0.84 (d, $J_{9'\text{-}Me,9'} = 6.9$, 9′-Me)*, 0.88 (s, $SiCMe_3$), 1.01 (d, $J_{7'\text{-}Me,7'} = 6.9$, 7′-Me)*, 1.04 (d, $J_{11',10'} = 6.3$, 11′-H_3)*, 1.41–1.52 (m, 1′-H_2), 1.83 (dqd, $J_{9',8'} = J_{9',9'\text{-}Me} = 7.1$, $J_{9',10'} = 4.5$, 9′-H)*, AB signal ($\delta_A = 1.99$, $\delta_B = 2.12$, $J_{AB} = 15.1$, in addition split by $J_{A,1'\text{-}H(1)}$***$= 8.7$, $J_{A,1'\text{-}H(2)} = J_{A,3'}$***$= 6.8$, $J_{B,1'\text{-}H(2)} = 9.4$****, $J_{B,1'\text{-}H(1)} = J_{B,3'}$****$= 5.6$, 2′-$H_2$)**, 2.34 (ddd, $J_{gem} = 18.4$, $J_{5\text{-}H(1),4} = 5.1$, $J_{5\text{-}H(1),6} = 1.9$, 5-$H^1$)**, ca. 2.36–2.46 (m, 5-H^2, 7′-H)**, 2.72 (dddd, $J_{6,1'\text{-}H(1)} = J_{6,5\text{-}H(2)} = 8.6$, $J_{6,1'\text{-}H(2)} = 5.6$, $J_{6,5\text{-}H(1)} = 1.7$, 6-H), 3.28 (dd, $J_{8',9'} = 7.9$, $J_{8',7'} = 3.9$, 8′-H)*, 3.37 (s, OCH_2OMe)*, 3.75 (s, CO_2Me), 4.09 (poorly resolved qd, $J_{10',11'} = 6.2$, $J_{10',9'} = 4.6$, 10′-H)*, AB signal ($\delta_A = 4.55$, $\delta_B = 4.59$, $J_{A,B} = 6.6$, OCH_2OMe)*, 5.53–5.61 (m, 3′-H, 6′-H)*, 5.96–6.06 (m, 3-H, 4-H, 4′-H, 5′-H), 6.99 (dd, $J_{2,3} = 4.1$, $^4J_{2,4} = 1.3$, 2-H); * signal assigned by comparison with the analogous resonances and coupling constants of methyl ester **33**, aldehyde **34**, and aldehyde **35**—criterion of assignment: $\Delta(\delta) \leq 0.02$ ppm; ** distinguishable by an H,H-correlation spectrum; *** interchangeable; **** interchangeable; APT-^{13}C NMR (125.7 MHz): $\delta =$ "+" -4.69 and "+" -4.33 [$Si(CH_3)_2$], "+" 10.17 (9′-CH_3)*, "+" 14.11 (7′-CH_3)*, "+" 18.05 [$SiC(CH_3)_3$], "+" 18.28 (C-11′)*, "+" 25.89 [3-fold intensity, $SiC(CH_3)_3$], "−" 27.32 and "−" 27.34 (C-5)**, "+" 29.79 (C-6)*, "−" 29.90 (C-2′)***, "−" 30.50 (C-1′)***, "+" 38.83 (C-7′)*, "+" 42.96 (C-9′)*, "+" 51.56 (CO_2CH_3), "+" 56.07 (OCH_2OCH_3)*, "+" 68.09 (C-10′)*, "+" 84.50 (C-8′)*, "−" 97.88 (OCH_2OCH_3), "+" 123.49, "+" 129.59, "+" 130.49, "+" 131.81, "+" 132.51, "+" 132.53 and "+" 135.93 (C-2, C-3, C-4, C-3′, C-4′, C-5′, C-6′), "−" 131.45 (C-1), "−" 167.82 (CO_2CH_3); * assignment by comparison with the analogous resonance of methyl ester **33**, aldehyde **34**, and aldehyde **35**—criterion of assignment: $\Delta(\delta) \leq 0.3$ ppm; ** two resonances for two C-6-epimers and assigned by a C,H-correlation spectrum; *** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu} = 2955$, 2930, 2855, 1710, 1575, 1470, 1465, 1435, 1380, 1360, 1255, 1140, 1095, 1035, 990, 965, 940, 920, 835, 805, 775, 735, 705 cm^{-1}; *m*/*z*: 506.3428 ±5 mDa ($C_{29}H_{50}O_5Si$ [M^+]) confirmed by HRMS (EI, 70 eV); no combustion analysis was performed.

(2*E*,4*E*,6*E*,10*E*,12*E*,14*R*,15*S*,16*S*,17*R*)-17-(*tert*-Butyldimethylsiloxy)-15-(methoxymethoxy)-14,16-dimethyl-2,4,6,10,12-octadecapentaenoic acid methyl ester (all-*trans*-40) as a 66.2:33.8 or 93.4:6.6 mixture with the 6-*cis*-isomer (*cis*^{26,27}-40): *HWE-reaction:* At -60 °C a solution of lithium *N*,*N*-diisopropyamide (0.29 M in THF, 0.75 mL, 0.22 mmol, 1.8 equiv) in THF (1.0 mL) was added dropwise to a solution of a 90:10 mixture of phosphonates *trans*,*trans*-**37** and *cis*$^{H_2CC=C}$,*trans*$^{C=CCO_2Me}$-**37** (54 mg, 0.23 mmol, 1.9 equiv). After stirring at this temperature for 30 min, the reaction mixture stirred at 0 °C for 15 min, then cooled to -60 °C and after 50 min treated dropwise with a solution of aldehyde **35** (47.3 mg, 0.119 mmol) in THF (2.3 mL). After stirring for 7 min, the reaction mixture was allowed to reach -40 °C and after further 1 h stirring, treated with aqueous semisaturated ammonium chloride (5 mL). The aqueous phase was extracted with *t*BuOMe (3 × 2 mL), and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue which was submitted to flash chromatography (cyclohexane/EtOAc 13:1 → fraction 9, 10:1 → fraction 30) to afford the title compound **40** (44.6 mg, 74%) as 66.2:33.8 mixture of the 6-*E*- and 6-*Z*-isomer.

Isomerization with iodine: At RT a solution of a 66.2:33.8 mixture (8.3 mg, 16 μmol) of all-*trans*-**40** and *cis*^{26,27}-**40** in $CDCl_3$ (0.5 mL) in a NMR tube was treated with iodine (0.031 M in $CDCl_3$, 42 μL, 1.3 μmol, 8.1 mol%). After 2 min, the isomerization was completed at a 93.4:6.6-equilibrium composition of all-*trans*-**40** and *cis*^{26,27}-**40** (^{1}H NMR, 500 MHz). The reaction mixture was used without purification for the preparation of aldehyde **41**.

all-*trans*-40: ^{1}H NMR (500 MHz; sample of a 93.4:6.6 mixture of all-*trans*-**40** and *cis*^{26,27}-**40**): $\delta = 0.036$ and 0.045 (2 × s, $SiMe_2$), 0.85 (d, $J_{16\text{-}Me,16} = 7.0$, 16-Me)*, 0.88 (s, $SiCMe_3$), 1.02 (d, $J_{14\text{-}Me,14} = 6.8$, 14-Me)*, 1.05 (d, $J_{18,17} = 6.2$, 18-H_3)*, 1.83 (dqd, $J_{16,15} = J_{16,16\text{-}Me} = 7.2$, $J_{16,17} = 4.5$, 16-H)*, 2.16–2.27 [m, presumably interpretable as: $\delta = 2.19$ (brtd, $J_{9,8} = J_{9,10} = 6.4$, 9-H_2)** and $\delta = 2.24$ (brtd, $J_{8,9} = J_{8,7} = 6.3$, 8-H_2)**], 2.44 (dqd, $J_{14,13} = J_{14,14\text{-}Me} = 7.0$, $J_{14,15} = 4.0$, 14-H)*, 3.29 (dd, $J_{15,16} = 7.8$, $J_{15,14} = 4.0$, 15-H)*, 3.367 (s, OCH_2OMe)*, 3.741 (s, CO_2Me), 4.09 (qd, $J_{17,18} = 6.2$, $J_{17,16} = 4.5$, 17-H)*, AB signal ($\delta_A = 4.56$, $\delta_B = 4.59$, $J_{AB} = 6.8$, OCH_2OMe)*, 5.57 (dt, $J_{trans} = 14.2$, $J_{10,9} = 6.7$, 10-H)*, 5.61 (dd, $J_{trans} = 14.0$, $J_{13,14} = 7.5$, 13-H)*, 5.85 (d, $J_{trans} = 15.4$, 2-H), 5.92 (dt, $J_{trans} = 15.1$, $J_{7,8} = 7.2$, 7-H)***, 5.97–6.05 (m, 11-H, 12-H)*, 6.15 (dd, $J_{trans} = 15.2$, $J_{6,5} = 10.7$, 6-H)***, 6.22 (dd, $J_{trans} = 14.8$, $J_{4,3} = 11.3$, 4-H)***, 6.52 (dd, $J_{trans} = 14.8$, $J_{5,6} = 10.7$, 5-H)***, 7.30 (dd, $J_{trans} = 15.3$, $J_{3,4} = 11.3$, 3-H); * signal assigned by comparison with the analogous resonances and coupling constants of methyl ester **33**—criterion of assignment: $\Delta(\delta) \leq 0.02$ ppm; **,*** distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz; sample of a 93.4:6.6 mixture of all-*trans*-**40** and *cis*^{26,27}-**40**): $\delta = -4.68$ and -4.32 [$Si(CH_3)_2$], 10.20 (16-CH_3)*, 14.11 (14-CH_3)*, 18.06 [$SiC(CH_3)_3$], 18.32 (C-18)*, 25.89 [3-fold intensity, $SiC(CH_3)_3$], 32.01 (C-9)**, 32.79 (C-8)**, 38.84 (C-14)*, 42.97 (C-16)*, 51.45 (CO_2CH_3), 56.07 (OCH_2OCH_3)*, 68.09 (C-17)*, 84.43 (C-15)*, 97.85 (OCH_2OCH_3), 119.72 (C-2)***, 128.04 (C-4)***, 129.32 and 131.13 (C-11, C-12)***, 130.23 (C-6)***, 131.32 (C-10)***, 136.55 (C-13)***, 139.50 (C-7)***, 141.08 (C-5)***, 144.96 (C-3)***, 167.59 (C-1); * assignment by comparison with the analogous resonance of methyl ester **33** and aldehyde **34**—criterion of assignment: $\Delta(\delta) \leq 0.4$ ppm; **,*** distinguishable by a C,H-correlation spectrum;

***cis*^{26,27}-40**: ^{1}H NMR (500 MHz; sample of a 66.2:33.8 mixture of all-*trans*-**40** and *cis*^{26,27}-**40**)*: $\delta = 2.34$ (brtd, $J_{8,9} = J_{8,7} = 7.6$, 8-H_2), 3.371 (s, OCH_2OMe), 3.747 (s, CO_2Me), AB signal ($\delta_A = 4.56$, $\delta_B = 4.59$, $J_{AB} = 6.7$, OCH_2OMe), 5.62 (dd, $J_{trans} = 14.3$, $J_{13,14} = 7.4$, 13-H)**, 5.67 (dt, $J_{cis} = 10.8$, $J_{7,8} = 7.7$, 7-H)**, 5.88 (d, $J_{trans} = 15.7$, 2-H)**, 6.10 (dd, $J_{cis} = J_{6,5} = 10.9$, 6-H)**, 6.30 (dd, $J_{trans} = 14.9$, $J_{4,3} = 11.4$, 4-H)**, 6.83 (dd, $J_{trans} = 14.7$, $J_{5,6} = 11.5$, 5-H)**, 7.35 (dd, $J_{trans} = 15.3$, $J_{3,4} = 11.3$, 3-H); * the signals of other (not listed) protons are superimposed or isochron with all-*trans*-**40**; ** distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz; sample of a 66.2:33.8 mixture of all-*trans*-**40** and *cis*^{26,27}-**40**)*: $\delta = 27.94$ (C-8), 32.40 (C-9), 51.48 (CO_2CH_3), 120.26 (C-2), 128.33 (C-6),

131.22 and 131.25 (C-10, C-11, C-12), 129.90 (C-4), 135.88 (C-5), 136.62 (C-7), 144.86 (C-3), 167.49 (C-1); * resonances of other (not listed) carbons are superimposed/isochron by/with all-*trans*-**40**; all signals are assigned by a C,H-correlation spectrum;

IR (film): $\tilde{\nu}$ = 3020, 2955, 2855, 1710, 1620, 1465, 1435, 1380, 1360, 1310, 1255, 1140, 1120, 1100, 1040, 1005, 990, 965, 940, 925, 835, 775 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{50}O_5Si$ (506.8): C 68.73, H 9.94; found: C 68.81, H 10.21.

(2*E*,4*E*,6*E*,10*E*,12*E*,14*R*,15*S*,16*S*,17R)-17-(*tert*-Butyldimethylsiloxy)-15-(methoxymethoxy)-14,16-dimethyl-2,4,6,10,12-octadecapentaenal (all-*trans*-41): At RT a 93.4:6.6 mixture (8.3 mg, 0.016 mmol) of the methyl esters all-*trans*-**40** and *cis*[26,27]-**40** plus iodine (0.031 M in $CDCl_3$, 42 μL, 1.3 μmol, 8.1 mol%) in $CDCl_3$ (0.5 mL) was treated with Na_2SO_3 (ca. 0.05 g) and water (20 μL). After the violet color of iodine had disappeared, the solution was filtered through a pipette with $MgSO_4$, and the filter cake was washed with CH_2Cl_2 (3 × 2 mL). The filtrate and washings were evaporated in vacuo to a remaining volume of 1.5 mL, cooled to −78 °C and treated with DIBAL (1.12 M in toluene, 50 μL, 0.056 mmol, 3.4 equiv). After stirring for 1 h, the reaction mixture was allowed to reach −55 °C and after stirring for another 30 min, quenched with aqueous semisaturated Rochelle's salt (0.3 mL) and MeOH (0.2 mL). The solution was filtered through a pipette with $MgSO_4$, and the filter cake was washed with CH_2Cl_2 (3 × 2 mL). The filtrate and washings were evaporated in vacuo to a remaining volume of 3 mL, treated with MnO_2 (56.1 mg, 0.645 mmol, 39 equiv) and stirred at RT for 1 h. After filtration, the solvent was evaporated in vacuo and at 0 °C to afford a residue which was submitted to flash chromatography (cyclohexane/EtOAc 8:1) to afford aldehyde **41** (6.0 mg, 78%) as a light yellow oil. $[\alpha]_D^{25} = +12.5$ (c = 0.42 in $CHCl_3$); $[\alpha]_D^{25} = +9.9$ (c = 0.24 in $CDCl_3$); ^{1}H NMR (500 MHz; slightly contaminated)*: δ = 0.036 and 0.045 (2 × s, $SiMe_2$), 0.85 (d, $J_{16\text{-}Me,16}$ = 7.1, 16-Me)*, 0.88 (s, $SiCMe_3$), 1.02 (d, $J_{14,14\text{-}Me}$ = 6.8, 14-Me)*, 1.05 (d, $J_{18,17}$ = 6.2, 18-H_3)*, 1.83 (dqd, $J_{16,15} = J_{16,16\text{-}Me}$ = 7.2, $J_{16,17}$ = 4.5, 16-H), 2.21 (br td, $J_{9,8} \approx J_{9,10} \approx$ 7.0, 9-H_2)**, 2.27 (br td, $J_{8,9} \approx J_{8,7} \approx$ 7.1, 8-H_2)**, 2.45 (dqd, $J_{14,13} = J_{14,14\text{-}Me}$ = 6.9, $J_{14,15}$ = 4.1, 14-H)*, 3.29 (dd, $J_{15,16}$ = 7.9, $J_{15,14}$ = 4.0, 15-H)*, 3.37 (s, OCH_2OMe), 4.09 (qd, $J_{17,18}$ = 6.2, $J_{17,16}$ = 4.5, 17-H)*, AB signal (δ_A = 4.56, δ_B = 4.59, J_{AB} = 6.6, OCH_2OMe), 5.57 (dt, J_{trans} = 14.3, $J_{10,9}$ = 7.1, 10-H)*, 5.62 (dd, J_{trans} = 14.5, $J_{13,14}$ = 7.8, 13-H)*, 5.98–6.06 (m, 7-H, 11-H*, 12-H*), 6.13 (dd, J_{trans} = 15.1, $J_{2,1}$ = 8.0, 2-H)***, 6.20 (br dd with unresolved $^4J_{6,8}$, J_{trans} = 15.1, $J_{6,5}$ = 10.8, 6-H)***, 6.35 (dd, J_{trans} = 14.8, $J_{4,3}$ = 11.2, 4-H)***, 6.64 (dd, J_{trans} = 14.8, $J_{5,6}$ = 10.7, 5-H)***, 7.11 (dd, J_{trans} = 15.2, $J_{3,4}$ = 11.1, 3-H)***, 9.55 (d, $J_{1,2}$ = 8.0, 1-H); * signal assigned by comparison with the analogous resonances and coupling constants of methyl esters **33** and all-*trans*-**40**—criterion of assignment: $\Delta(\delta) \leq$ 0.02 ppm; **,*** distinguishable by an H,H-correlation spectrum; ^{13}C NMR (125.7 MHz; peak of contaminant at δ = 29.69): δ = −4.68 and −4.32 [$Si(CH_3)_2$], 10.22 (16-CH_3)*, 14.10 (14-CH_3)*, 18.06 [$SiC(CH_3)_3$], 18.32 (C-18)*, 25.90 [3-fold intensity, $SiC(CH_3)_3$], 31.90 (C-9)**, 32.86 (C-8)**, 38.85 (C-14)*, 42.97 (C-16)*, 56.08 (OCH_2OCH_3)*, 68.09 (C-17)*, 84.44 (C-15)*, 97.85 (OCH_2OCH_3), 128.10 (C-4)***, 129.26 (one carbon of the signal group C-7, C-11, C-12)***, 130.19 (C-6)***, 130.83 (C-3)***, 131.12 (C-10)***, 131.25 (one carbon of the signal group C-7, C-11, C-12)***, 136.69 (C-13)***, 141.38 (one carbon of the signal group C-7, C-11, C-12)***, 142.96 (C-5)***, 152.24 (C-3)***, 193.53 (C-1); * assignment by comparison with the analogous resonance of methyl ester all-*trans*-**40**—criterion of assignment: $\Delta(\delta) \leq$ 0.1 ppm; **,*** distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}$ = 3065, 2980, 2940, 1720, 1600, 1450, 1375, 1315, 1275, 1180, 1115, 1070, 1025, 715 cm^{-1}; MS (CI, NH_3): m/z (%): 477 (12) [M^+], 445 (100) [M^+−HOMe]; elemental analysis calcd (%) for $C_{28}H_{48}O_4Si$ (476.8): C 70.54, H 10.15; found: C 72.14, H 11.39.

Acknowledgment

We thank Witco GmbH and Wacker AG for donating chemicals. We express our gratitude to Dr. Manfred Keller (Institut für Organische Chemie und Biochemie, Universität Freiburg) for measuring the NMR spectra and for assisting in their analysis as well as for performing the X-ray structure analysis of compound **4**.

[1] a) Autorenkollektiv in *Arzneimittelneben- und -wechselwirkungen* (Ed.: H. P. T. Ammon), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, **2001**, pp. 1456–1462; b) E. Mutschler, G. Geisslinger, H. K. Kroemer, M. Schäfer-Korting, *Mutschler Arzneimittelwirkungen—Lehrbuch der Pharmakologie und Toxikologie*, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, **2001**, pp. 836–839; c) F. Marty, E. Mylonakis, *Exp. Opin. Pharmacother.* **2002**, *3*, 91–102 and references therein.

[2] a) S. Omura, H. Tanaka in *Macrolide Antibiotics: Chemistry, Biology and Practice* (Ed.: S. Omura), Academic Press, New York, **1984**, pp. 351–404; b) J. M. Beau in *Recent Progress in the Chemical Synthesis of Antibiotics* (Eds.: G. Lukacs, M. Ohno), Springer, Berlin, **1990**, pp. 132–182; c) S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021–2040.

[3] Isolation: a) E. L. Hazen, R. Brown, *Science* **1950**, *112*, 423–430; b) E. L. Hazen, R. Brown, *Proc. Soc. Exp. Biol. Med.* **1951**, *76*, 93–98.

[4] Isolation: J. Vanderputte, J. L. Wachtel, E. T. Stiller, *Antibiot. Annu.* **1956**, 587–591.

[5] Structure: a) W. Mechlinski, C. P. Schaffner, P. Ganis, G. Avitabile, *Tetrahedron Lett.* **1970**, *11*, 3873–3876; b) P. Ganis, G. Avitabile, W. Mechlinski, C. P. Schaffner, *J. Am. Chem. Soc.* **1971**, *93*, 4560–4564.

[6] Elucidation of constitution: a) C. N. Chong, R. W. Rickards, *Tetrahedron Lett.* **1971**, *12*, 3873–3876; b) E. Borowski, J. Zielinski, L. Falkowski, T. Ziminski, J. Golik, P. Kolodziejczyk, E. Jereczek, M. Gdulewicz, Y. Shenin, T. Kotienko, *Tetrahedron Lett.* **1971**, *12*, 685–690.

[7] Elucidation of configuration: a) J.-M. Lancelin, F. Paquet, J.-M. Beau, *Tetrahedron Lett.* **1988**, *29*, *23*, 2827–2830 (relative configuration); b) K. C. Nicolaou, K. H. Ahn, *Tetrahedron Lett.* **1989**, *30*, 1217–1220 (absolute configuration by synthesis of the C^1–C^{10} fragment); c) J. Prandi, J.-M. Beau, *Tetrahedron Lett.* **1989**, *30*, 4517–4520 (absolute configuration by synthesis of a C^1–C^{10} fragment); d) J.-M. Lancelin, J.-M. Beau, *Tetrahedron Lett.* **1989**, *30*, 4521–4524.

[8] Total synthesis: a) K. C. Nicolaou, T. K. Chakraborty, Y. Ogawa, R. A. Daines, N. S. Simpkins, G. T. Furst, *J. Am. Chem. Soc.* **1988**, *110*, 4660–4672; b) K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685; c) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, Y. Ogawa, *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696; d) K. C. Nicolaou, R. A. Daines, Y. Ogawa, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705.

[9] Formal total syntheses: a) S. Masamune, P. Ma, H. Okumoto, J. W. Ellingboe, *J. Org. Chem.* **1984**, *49*, 2834–2837; b) D. Boschelli, T. Takemasa, Y. Nishitani, S. Masamune, *Tetrahedron Lett.* **1985**, *26*, 5239–5242; c) R. M. Kennedy, A. Abiko, T. Takemasa, H. Okumoto, S. Masamune, *Tetrahedron Lett.* **1985**, *26*, 5239–5242, and references therein; d) G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara, T. Oh, *J. Am. Chem. Soc.* **1986**, *108*, 4943–4952; e) G. J. McGarvey, J. A. Mathys, K. J. Wilson, *J. Org. Chem.* **1996**, *61*, 5704–5705, and references therein.

[10] Leading references: a) G. Solladié, N. Wilb, C. Bauder, *Eur. J. Org. Chem.* **1999**, 3021–3026; b) J. Krüger, E. M. Carreira, *Tetrahedron Lett.* **1998**, *39*, 7013–7016; c) C. Gibson, T. Buck, M. Walker, R. Brückner, *Synlett* **1998**, 201–205; d) A. Fürstner, J. Baumgartner, *Tetrahedron* **1993**, *49*, 8541–8560; e) S. David, A. Malleron, *New J. Chem.* **1993**, *17*, 505–511; f) S. Takano, Y. Shimazaki, Y. Sekiguchi, K. Ogasawara, *Chem. Lett.* **1988**, 2041–2044; g) R. Brückner, *Tetrahedron Lett.* **1988**, *29*, 5747–5750; h) D. Liang, A. DeCamp Schuda, B. Fraser-Reid, *Carbohydr. Res.* **1987**, 229–240, and references therein; i) M. Kinoshita, H. Takami, M. Taniguchi, T. Tamai, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2151–2161; j) M. Kinoshita, M. Morioka, M. Taniguchi, J. Shimizu, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4005–4014; k) S. Hanessian, S. P. Sahoo, M. Botta, *Tetrahedron Lett.* **1987**, *28*, 1143–1146; l) S. Hanessian, S. P. Sahoo, M. Botta, *Tetrahedron Lett.* **1987**, *28*, 1147–1150; m) G. Solladié, G. Demally, C. Greck, *Tetrahedron Lett.* **1985**, *26*, 435–438; n) D. W. Brooks, R. P. Kellogg, *Tetrahedron Lett.* **1982**, *23*, 4991–4994.

[11] a) C. Bonini, G. Righi, L. Rossi, *Tetrahedron* **1992**, *48*, 9801–9808; b) C. Bonini, A. Giugliano, R. Racioppi, G. Righi, *Tetrahedron Lett.*

1996, *37*, 2487–2490; c) C. Schneider, M. Rehfeuter, *Tetrahedron Lett.* **1998**, *39*, 9–12; d) G. Solladié, N. Wilb, C. Bauder, *J. Org. Chem.* **1999**, *64*, 5447–5452.
[12] Procedure: G. Dahmann, R. W. Hoffmann, *Liebigs Ann. Chem.* **1994**, 837–845.
[13] Compound **6** was prepared according to G. R. Pettit, D. D. Burkett, J. Barkóczy, G. L. Breneman, W. E. Pettit, *Synthesis* **1996**, 719–725.
[14] Leading references for asymmetrical Evans aldol reaction: a) D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett.* **1987**, *28*, 39–42; b) D. A. Evans, E. B. Sjogren, J. Bartoli, R. L. Dow, *Tetrahedron Lett.* **1986**, *27*, 4957–4960; c) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761; d) D. A. Evans, M. M. Morrissey, R. L. Dorow, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[15] (*E*)-2-Methylbutenal is commercially available from ALDRICH.
[16] Compound **7** was previously described by: a) K. J. Hale, G. S. Bhatia, S. Andrew Peak, S. Manaviazar, *Tetrahedron Lett.* **1993**, *34*, 5343–5346; b) J. D. White, A. T. Johnson, *J. Org. Chem.* **1994**, *59*, 3347–3358.
[17] Compound **9** was prepared according to: D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs, R. Zahler, *J. Am. Chem. Soc.* **1990**, *112*, 5291–5313.
[18] All new compounds gave satisfactory ^{1}H NMR and IR spectra. Except compounds **12**, **23**, **39**, and **41** they also gave correct combustion analyses.
[19] R. F. W. Jackson, M. A. Sutter, D. Seebach, *Liebigs Ann. Chem.* **1985**, 2313–2327.
[20] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.
[21] Earlier preparations of compound **8**: a) M. Ono, N. Yoshida, Y. Kokubu, E. Sato, H. Akita, *Chem. Pharm. Bull.* **1997**, *45*, 1428–1434 (racemic synthesis); b) H. Akita, H. Matskura, T. Oishi, *Tetrahedron Lett.* **1986**, *27*, 5241–5244 (synthesis with moderate enantioselectivity: 38% < *ee* < 64%); ref. [16a] (enantioselective synthesis via **7**).
[22] Procedure: E. J. Corey, H. Cho, C. Rücker, D. H. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455–3458.
[23] a) D. A. Evans, J. Bartoli, T. Godel, *Tetrahedron Lett.* **1982**, *23*, 4577–4580; b) W. C. Still, J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489; c) K. N. Houk, N. G. Rondan, Y.-D. Wu, J. T. Metz, M. N. Paddon-Row, *Tetrahedron* **1984**, *40*, 2257–2274.
[24] Method: G. W. Kalbaka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, *54*, 5930–5933.
[25] This reagent was freshly prepared from 2,3-dimethyl-2-butene and $BH_3{\cdot}SMe_2$ in THF (E.-I. Negishi, H. C. Brown, *J. Am. Chem. Soc.* **1972**, *94*, 3567–3572).
[26] This solution is normally used for the work-up of asymmetrical Sharpless epoxidations (Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780).
[27] Earlier preparation of compound **4**: Ref. [10i].
[28] Earlier preparation of compound **15**: Ref. [10n].
[29] Compound **17** could be used as a crude product.
[30] Procedure: G. Stork, T. Takahashi, *J. Am. Chem. Soc.* **1977**, *99*, 1275–1276.
[31] Compounds **16** and **18** were previously described: Ref. [10i].
[32] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.
[33] a) F. J. L. Aparicio, F. J. L. Herrera, *Carbohydr. Res.* **1980**, *80*, C4–C7; b) C. Lievre, C. Frechou, G. Demailly, *Tetrahedron Lett.* **1993**, *34*, 5895–5898; c) C. Lievre, C. Frechou, G. Demailly, *Tetrahedron Lett.* **1995**, *36*, 6467–6470.
[34] a) J. G. Buchanan, A. E. Edgar, M. J. Power, P. D. Teaker, *Carbohydr. Res.* **1974**, *38*, C22–C24; b) E. J. Corey, G. Goto, *Tetrahedron Lett.* **1980**, *21*, 3463–3466; c) C. Harcken, S. F. Martin, *Org. Lett.* **2001**, *3*, 3591–3593.
[35] Procedure: I. H. Aspinall, P. M. Cowley, G. Mitchell, C. M. Raynor, R. J. Stoodley, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2591–2600.
[36] We followed the procedure of ref. [34c].
[37] A unsuccessful Wittig reaction employing compound **18** is described in ref. [10i].
[38] Procedure: E. Adler, H.-D. Becker, *Acta Chem. Scand.* **1961**, *15*, 849–852.
[39] Isomer ratios were derived from suitable ^{13}C NMR integrals.
[40] Methods: a) P. A. Wender, T. M. Dore, *Tetrahedron Lett.* **1998**, *39*, 8589–8592 [$Hg(OAc)_2$ (cat.), *tert*-butyl vinyl ether, sealed vessel, 17 bar, 200 °C]; b) H. Zhang, M. Seepersaud, S. Seepersaud, D. R. Mootoo, *J. Org. Chem.* **1998**, *63*, 2049–2052 [$Hg(OAc)_2$ (1.0 equiv), *n*-butyl vinyl ether, reflux].
[41] First Claisen rearrangement of a vinyl ether derived from a symmetrical divinyl carbinol: S. F. Reed, Jr., *J. Org. Chem.* **1965**, *30*, 1663–1665. First Claisen rearrangement of a vinyl ether derived from an unsymmetrical divinyl carbinol: P. Cresson, L. Lacour, *C. R. Acad. Sci. Ser. C* **1966**, *262*, 1157–1160.
[42] In order to obtain compound **41** we also tested Hoffmann's aldehyde homologation strategy "$n+6$" with aldehyde **34** and their (dioxenyl)propenyl borolane (R. W. Hoffmann, F. Schäfer, E. Haeberlin, T. Rhode, K. Körber, *Synthesis* **2000**, 2060–2068), however, without success (T. Berkenbusch, Dissertation, Universität Freiburg, **2002**, pp. 134–138).
[43] For a related cyclocondensation from our laboratory giving a cyclohexadiene in an attempted Horner–Wadsworth–Emmons olefination see J. Hübner, Dissertation, Universität Freiburg, **2001**, pp. 125–145.
[44] Compound **37** was prepared from 4-bromocrotonate in 25% overall yield [DIBAL; MnO_2; $Ph_3P{=}CHCO_2Me$; $P(OMe)_3$] as a 90:10 *trans*,*trans*:*cis*$^{H_2CC=C}$,*trans*$^{C=CCO_2Me}$ mixture following the procedure of ref. [10i].
[45] Method: I. Ernest, A. J. Main, R. Menassé, *Tetrahedron Lett.* **1982**, *23*, 167–170.

Received: September 11, 2003 [F5540]

