Synthesis of the C1–C17 Macrolactone of Tedanolide

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Abstract: The vinylogous Mukaiyama aldol reaction is a useful method to build up complex polyketide structures. It is successfully employed in the synthesis of the C1–C17 macrolactone of tedanolide, a highly cytotoxic marine natural product. These studies present a practical approach toward the total synthesis of tedanolide; it is pursued using the appropriate C13–C23 segment that is introduced by a pivotal aldol reaction to join both hemispheres.

Key words: aldol reactions, macrocycles, Mitsunobu, tedanolide, total synthesis

Introduction

Polyketides play a major role among natural products since they host a great variety of biologically active compounds. Prominent examples are the epothilones,[1] discodermolide[2] and the leptomycin family.[3] These compounds are not only important lead structures for the development of promising antitumor drugs or antibiotics, but they also serve as tools in the identification of new biological targets and for unravelling biological processes at the cellular level. As a consequence, a new field – chemical genomics – has emerged from these findings.[4] For these types of studies, it is tempting to use the isolated natural products, which are believed in most cases to be synthesized from microorganisms in order to interact with biological targets; however, their supply is not always guaranteed. In the case of marine natural products, for example, fermentation is generally excluded. In addition, chemical transformations are needed to identify structure–activity relationships. This sets the stage for organic synthesis, which has to provide not only derivatives, but also de novo chemical syntheses, in order to evaluate the full potential of active structures and to fine-tune their biological properties.

Synthesis of Polyketide Subunits

Despite several significant differences among them, many laboratory syntheses parallel the biosynthetic pathway in one aspect: most structures are generated by aldol or aldol-related transformations in which only two (acetate) or three (propionate) carbon atoms are added at a time to the growing polyketide chain. The biosynthesis requires large polyketide–enzyme complexes and in the laboratory synthesis, tedious functional group transformations and protecting group shuffling is required. To make synthesis more efficient, different research groups have developed strategies that allow for the incorporation of larger segments in the course of the synthesis. Established examples are the Evans–Metternich[5] and Paterson[6] aldol reactions in which dipropionate fragments are employed in a stereoselective aldol reaction. Another powerful method is the dithiane strategy that allows for bidirectional fragment coupling, in particular with chiral epoxides.[7] Marshall et al.[8] used chiral allenes in order to construct polyketides that generated the corresponding alkynes. In addition to the widespread allylation and crotylation protocols,[9] Panek and co-workers have established their chiral allylsilanes as powerful reagents for the introduction of five-carbon building blocks.[10] Among the alternative procedures are such non-traditional approaches as dipolar cycloadditions[11,12] and Lewis acid-induced epoxide rearrangements.[13]

The Vinylogous Mukaiyama Aldol Reaction

One strategy uses the vinylogous aldol reaction for the introduction of combined acetate–propionate building blocks (Figure 1).[14]

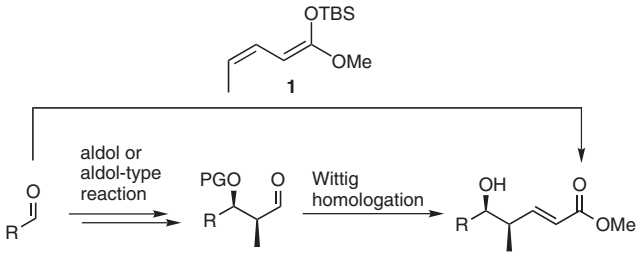

Figure 1 Synthesis of propionate–acetate subunits.

Beyond their contributions to Lewis acid activation studies, Campagne[15,16] (Scheme 1) and Denmark[17] (Scheme 2) established additions of γ-substituted dienolates through enolate activation.[18]

Among other groups,[19] we have focused on the Lewis acid-mediated vinylogous Mukaiyama aldol reaction during our syntheses of different natural products.

In our synthesis of the polyketide ratjadone, it became obvious that the vinylogous Mukaiyama aldol reaction (VMAR) used for the formation of the C14–C24 fragment

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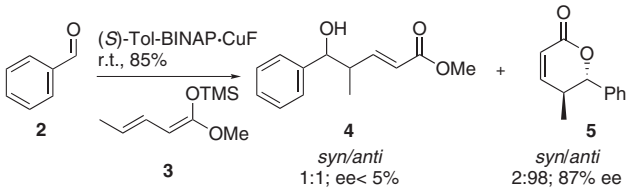
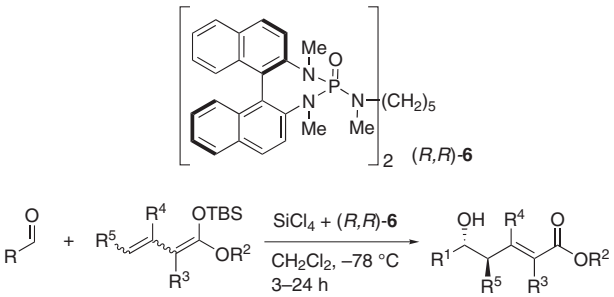
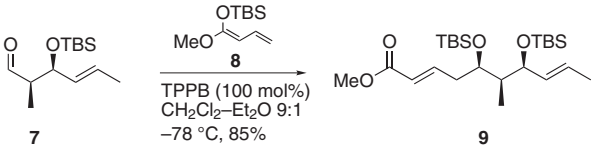


Scheme 1 Vinylogous aldol reaction through enolate activation.



Scheme 2 Denmark's vinylogous aldol reaction.

significantly shortened the synthesis and helped to avoid extensive protecting group manipulations.[20] In addition, it turned out that tris(pentafluorophenyl)borane (TPPB) is the superior Lewis acid in these cases. The vinylogous ketene acetal used in this synthesis introduces two acetate units while protecting the so-generated hydroxyl group in situ (Scheme 3).



Scheme 3 VMAR in the total synthesis of ratjadone.

We envisioned that this methodology would be even more powerful if it could be extended to substituted ketene acetals.[21] It became clear that not only does the 3,4-double bond geometry play an important role in the selectivities, but that two different catalytic processes lead to the product, albeit with different selectivities (Scheme 4). Both the

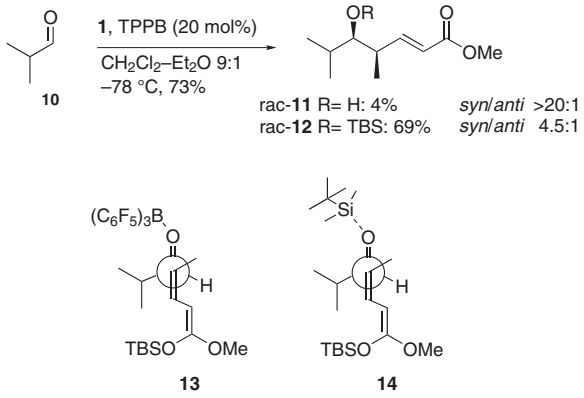
Biographical Sketches

Jorma Hassfeld, born in 1975, studied chemistry at the University of Hannover. In the course of his studies, he spent one year in the group of Professor Paul A. Wender at Stanford University, USA for undergraduate research work in 1998–99. Following his diploma degree in 2001, he started his doctoral studies at the Free University of Berlin under the supervision of Professor Markus Kalesse with whom he relocated to the University of Hannover in 2003.

Ulrike Eggert was born in 1959. After vocational training as chemical-technical assistant, she joined the group of H. Martin R. Hoffmann at the University of Hannover in 1983. Since 2003, she works in the group of Markus Kalesse.

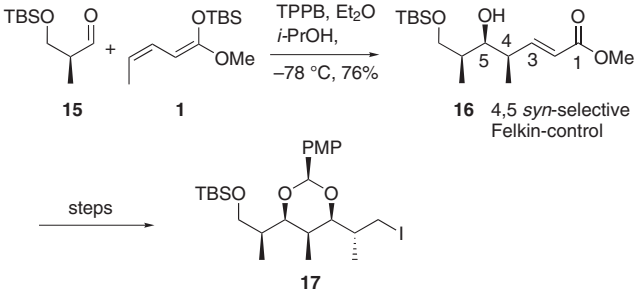
Markus Kalesse, born in 1961, was awarded the Dr. rer. nat. in the group of Dieter Schinzer at the University of Hannover in 1991. Between 1991 and 1992, he undertook two postdoctoral investigations at the University of Wisconsin (Madison) with Steven D. Burke and Laura L. Kiessling. After returning to the University of Hannover, he completed his habilitation with Ekkehard Winterfeldt as his mentor in 1997. He was visiting professor at the University of Wisconsin (Madison) between 1998 and 1999 and held a temporary chair in Organic Chemistry at the University of Kiel in 1999. He was offered the chair in Organic Chemistry at the University of Oslo before he accepted a call from the Free University of Berlin (2002). Since July 2003 he holds the chair (C4) of Organic Chemistry at the University of Hannover.

Lewis acid and the R_3Si^+ species catalyze the aldol reaction. The catalysis through TPPB (transition state **13**) provides the alcohol **11** with greater than 20:1 *syn* selectivity. Catalysis through the antiperiplanar R_3Si^+ species **14** similarly generates the TBS-protected aldol product **12**, but the observed *syn* selectivity drops to 4.5:1.[21]



Scheme 4 Initial attempts with γ-substituted ketene acetal **1**.

A more thorough investigation of the Lewis acid catalysis revealed that it is not the tris(pentafluorophenyl)borane itself, but rather a hydrated species, present in most commercially available sources, that is the active Lewis acid.[22] The uncoordinated anhydrous Lewis acid in fact leads to decomposition of the substrate. Having realized this subtle difference, we precipitated the monohydrate from a pentane solution of TPPB[23] and used it in the vinylogous Mukaiyama aldol reaction; we saw significant improvement in the yields. This is also the case for TPPB·OEt_2 which is easily employed by dissolving TPPB in Et_2O, cooling to –78 °C and subsequent addition of the aldehyde. In order to demonstrate the applicability of our vinylogous Mukaiyama aldol reaction, we synthesized the C1–C7 segment of oleandolide.[24] In our approach, the addition of the ketene acetal to aldehyde **15** is followed by reduction and Sharpless epoxidation to generate the allylic alcohol (Scheme 5). Subsequent cuprate addition yields the desired stereopentad for the synthesis of oleandolide. Final oxidative acetalization and Appel reaction furnished the C1–C7 segment **17**, comparable to the one that had been used in Panek's approach.[25]

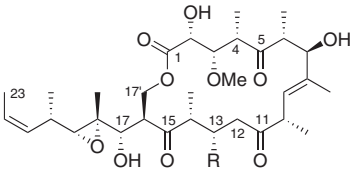


Scheme 5 Synthesis of the C1–C7 segment of oleandolide.

The obvious advantages of the VMAR protocol over conventional methods also inspired us in our efforts towards the synthesis of tedanolide.[26]

Application in the Total Synthesis of Tedanolide

Tedanolide (**18**) and 13-deoxytedanolide (**19**), two closely related polyketides with promising antitumor activity, were isolated from marine organisms by Schmitz[27] and Fusetani,[28] respectively (Figure 2). Their biological activity, in combination with their challenging structure, has drawn much attention over the past decade, and a variety of fragment syntheses as well as important fundamental studies have been published on these natural products.[29] Recently, Smith et al. published the first total synthesis of 13-deoxytedanolide (**19**),[30] while a total synthesis of macrolide **18** has not yet been accomplished.



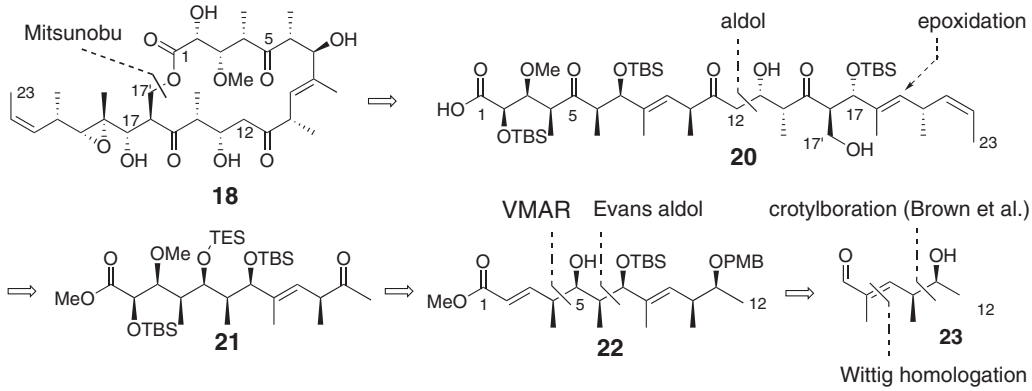
18 R = OH tedanolide
19 R = H 13-deoxytedanolide

Figure 2 Tedanolide and 13-deoxytedanolide.

Retrosynthetic Analysis

Our retrosynthetic analysis proposed an aldol coupling between C12 and C13 (Scheme 6). The connection between C4 and C5 should be accomplished through a VMAR with subsequent dihydroxylation of the double bond. Since we planned to make extensive use of TBS and TES protecting groups in our synthesis, the question arose whether a TBS-protected hydroxyl group at C2 would be too sterically hindered for further transformations. Another question was whether the C11 keto group could be tolerated in the cyclization step, or if a protecting group inducing the Thorpe–Ingold effect, as used in the Smith synthesis of 13-deoxytedanolide (**19**), would be necessary for successful macrolactonization.

In the synthetic direction, the C12–C13 coupling could be performed by an aldol reaction. An elegant analysis of aldol reactions of such methyl ketones has been reported by Roush et al. who demonstrated that the α-methyl group of the methyl ketone in combination with the α- and β-stereocenters of the aldehyde affect the stereochemical outcome of the reaction towards the Felkin product.[29e,t] Another obvious problem in the total synthesis of **18** and **19** was the fact that the three ketone carbonyl groups in the natural product are sensitive to retro-aldol processes. We therefore decided to carry them through the synthesis as protected alcohols, which could be selectively liberated and oxidized at a later stage. Selective epoxidation of the

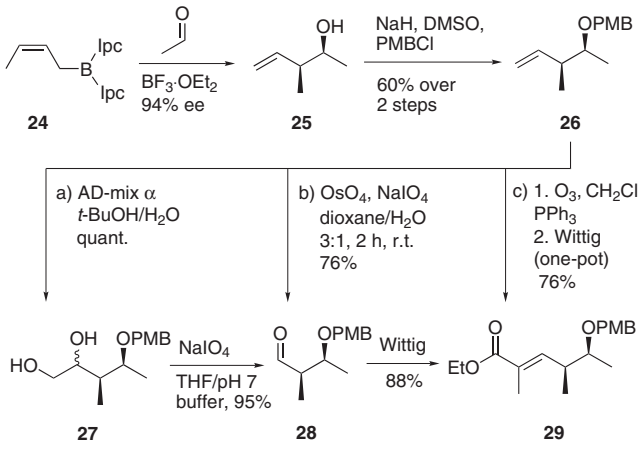


Scheme 6 Retrosynthetic analysis of tedanolide (**18**).

C18/C19 allylic double bond would then be expected to afford the final product. With these prerequisites in mind, we generated the C1–C12 segment as the all-*syn* polyketide in which the C5-ketone was the TES-protected alcohol.

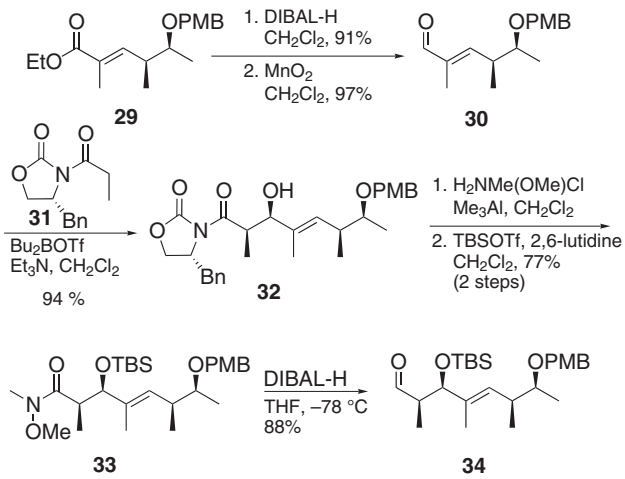
Synthesis of the Eastern Hemisphere

At the outset of our synthesis, we planned to establish a route that could provide large quantities of tedanolide and its precursors. Aldehyde **34** can be rapidly accessed through crotylboration according to the Brown protocol.[31] Reaction of acetaldehyde with Brown's crotylborane **24** provided alcohol **25**. Subsequent PMB-protection gave the protected olefin in 60% yield over two steps (Scheme 7).[32] This protocol was followed by ozonolysis and in situ Wittig reaction to the α,β-unsaturated ester **29** in only one step and 76% yield. It was also possible to perform an in situ dihydroxylation/diol cleavage sequence to furnish aldehyde **28**. Alternatively, olefin **26** could be dihydroxylated to diol **27** and then cleaved to the corresponding aldehyde **28** in an additional step which facilitates purification of multi-gram quantities.[33] In the second and third approaches, the desired ester **29** was also obtained from **28** after a Wittig reaction.



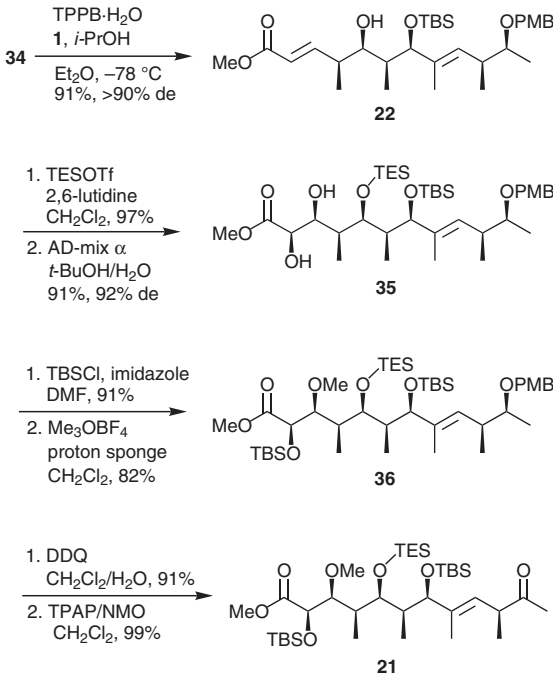
Scheme 7 Elaboration of ester **29**.

A sequence of DIBAL-H reduction and MnO_2 oxidation generated the corresponding aldehyde **30** which was converted to the Evans aldol product **32**. Transamination and TBS protection was followed by DIBAL-H reduction to furnish aldehyde **34** (Scheme 8) and to set the stage for the vinylogous Mukaiyama aldol reaction (Scheme 9).



Scheme 8 Formation of aldehyde **34**.

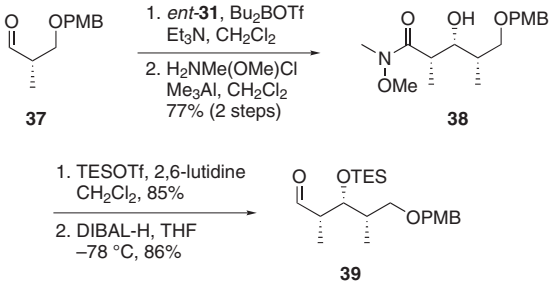
For this transformation, aldehyde **34** was stirred in diethyl ether with TPPB monohydrate, and ketene acetal **1** (in diethyl ether containing 1.1 equivalents of 2-propanol) was added over two hours. This modified version of our general VMAR protocol provided 91% of the desired *syn*-aldol product **22** (dr >20:1). Next, the alcohol was TES-protected and a Sharpless asymmetric dihydroxylation gave 87% of diol **35** together with 4% of the minor diastereoisomer.[29f] The hydroxyl group at C2 was selectively protected as the TBS ether and methylation at the C3 hydroxyl group was accomplished with Me_3OBF_4 and proton sponge.[34] For successive generation of methyl ketone **21**, PMB ether **36** was treated with DDQ to remove the PMB protecting group, and was subsequently oxidized with TPAP/NMO.[35]



Scheme 9 VMAR and subsequent transformations.

Synthesis of a Model C13–C17 Aldehyde

The preceeding transformations established the carbon skeleton of the C1–C12 backbone of tedanolide. In order to investigate the macrocyclization of the sterically hindered *seco*-acid, the aldol coupling of the C1–C12 segment with an abbreviated western part of tedanolide (C13–C17′) had to be investigated. The synthesis of model aldehyde **39** starts from the known Roche aldehyde **37**[36] which was subjected to Evans aldol conditions and then further elaborated along the lines established by Shibasaki et al.[37] (Scheme 10).



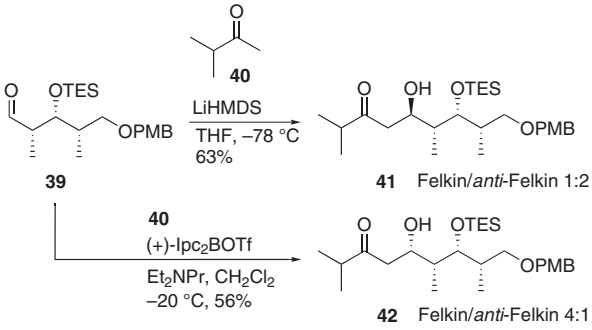
Scheme 10 Synthesis of model aldehyde **39**.

Aldol Reaction Studies

The thus-generated aldehyde **39** was used in aldol couplings with methyl ketone **21** under various conditions. By investigating different bases for this coupling, we found that the use of LiHMDS predominantly provided the aldol product **43** in 51% yield as a 1:1 mixture of Felkin and *anti*-Felkin isomers. This result was rather surprising since it is known through work from the Evans[38] and Roush[29e] laboratories that the stereochemistry at C3 would favor the *anti*-Felkin product.

Model reactions carried out with aldehyde **39** and methyl isopropyl ketone (**40**) also supported their findings, giving a 2:1 mixture of aldol products in favor of the *anti*-Felkin isomer (Scheme 11). By using the (+)-diisopinocampheylboron enolate of the ketone, the selectivity could be changed to a 4:1 mixture of Felkin/*anti*-Felkin isomers by reagent control. Unfortunately, this method was not transferable to the reaction of **21**, since the increased steric hindrance of the enolate prohibited reaction with **39** even after prolonged reaction time.

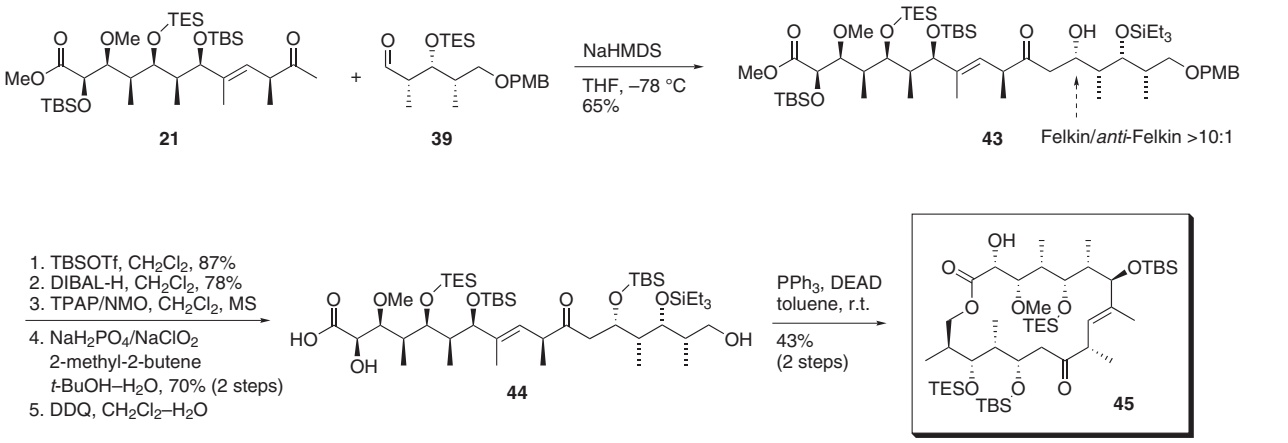
After extensive optimization, the use of NaHMDS or KHMDS as the base was determined to be superior over a variety of other methods. With the sodium enolate, the desired Felkin product **43** was obtained in 61% yield along with 4% of the *anti*-Felkin isomer (Scheme 12). Additionally, 7% of a second Felkin product was isolated, presumably bearing an *epi*-C10 methyl group which is believed to result from non-optimal workup conditions of the aldol reaction. The unexpected stereochemistry at the newly generated stereocenter was confirmed by analogy[39] and through the Mosher ester method.[40] We believe that the inherent stereochemistry of the methyl ketone overrides the *anti*-Felkin preference of the all-*syn* aldehyde.



Scheme 11 Model reactions of aldehyde **39** with ketone **40**.

Elaboration of the *seco*-Acid

Having accomplished the aldol coupling, we protected the C13 hydroxyl group as a TBS ether and then turned our attention to the macrolactonization step. The first problems occurred when we tried to saponify the methyl ester. In our hands, none of the known basic, acidic or S_N2 procedures to cleave methyl esters worked, paralleling the problems described by Smith et al. in their synthesis of 13-deoxytedanolide (**19**).[30] In the Smith synthesis of deoxytedanolide, a less sterically hindered C2 SEM-protected hydroxyl ester could only be hydrolyzed in 74% yield based on recovered starting material. In our case, the more sterically hindered C2 TBS ether gave no acid product at all. Basic procedures also led to elimination products, or to racemization of the C10 stereocenter.



Scheme 12 Aldol coupling and macrolactonization.

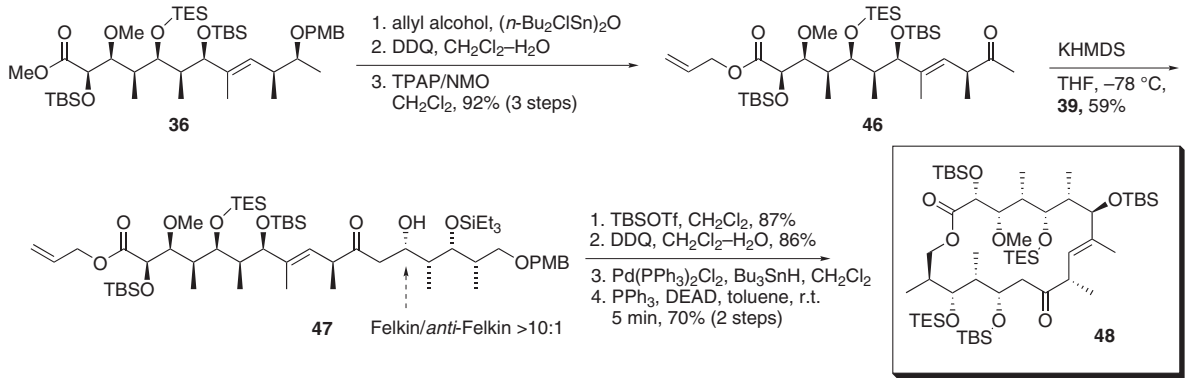
We decided to change tactics, from nucleophilic attack at the carboxyl group to Lewis acid activation, and reduced the ester to the primary alcohol with DIBAL-H. The resulting diol was reoxidized to the corresponding acid with TPAP/NMO and subsequent oxidation by sodium chlorite.[41] At this stage, the TBS protecting group was cleaved during workup, possibly due to the adjacent carboxylic acid which facilitates proton delivery. Deprotection with DDQ removed the PMB group and provided the precursor for macrolactonization, hydroxy acid **44**.

Macrolactonization

Since we had encountered difficulty in nucleophilic attack at the sterically hindered carboxylate, we envisioned that acylative macrolactonizations utilizing such a nucleophilic attack would not be very likely to succeed. Instead, the Mitsunobu reaction[42] with the C17′ primary alcohol of **44** was expected to provide the desired macrolactone **45**, since this would move the steric hindrance one bond away from the reacting center. Consequently, the Mitsunobu protocol, carried out under high dilution conditions, generated **45** in good yield. These results clearly indicated that macrolactonization occurred rapidly without the need to protect the ketone at C15. Unfortunately, the reaction yield of the double oxidation step on the way to **44** varied from 0% to quantitative, strongly depending on the quality of the TPAP used. In addition, PMB deprotection to the *seco*-acid was not possible without varying degrees of C2 TBS deprotection, while the yield after macrolactonization was much higher with the TBS group in place.

Route Optimization

To circumvent the encountered problems of methyl ester saponification and the alternative reduction/oxidation protocol, we decided to change the carboxyl protecting group (Scheme 13). With ester **36** in hand from our initial route, treatment with allyl alcohol and a tin oxide Lewis acid at high temperature cleanly provided the transesterification product.[43] PMB deprotection followed by TPAP oxidation afforded methyl ketone **46** in 92% yield over three steps, with just one chromatographic step. Deprotonation with KHMDS and addition of aldehyde **39** gave the desired Felkin aldol product **47** in excellent selectivity. The secondary hydroxyl group was protected with TBSOTf, while the primary PMB group was removed with DDQ. In contrast to the previous approach, the allyl moiety could now be cleanly and rapidly removed using palladium and tributyltin hydride.[44] The crude hydroxy acid, still containing the C2-OTBS group in proximity to the carboxy group, was then directly cyclized by Mitsunobu



Scheme 13 Alternative approach for macrocyclization.

macrolactonization. Macrolactone **48** was the only detectable product of this reaction, although proton NMR analysis revealed two closely related, inseparable isomers (4:1), presumably the result of epimerization at the C2 stereocenter of the *seco*-acid.

Conclusion

In summary, we were able to prove that the vinylogous Mukaiyama aldol reaction is another useful method to build up complex polyketide structures. Additionally, it was shown that *seco*-acid **44** and its C2-OTBS derivative can be successfully transformed into the corresponding macrolactone, while the carbonyl group at C15 is tolerated in the cyclization step. These results should enable us to complete the total synthesis of tedanolide by using the appropriate eastern hemisphere. With such a convergent and efficient synthesis in hand, structure–activity studies will be the ultimate goal of our research.

All reactions were carried out in dried glassware under a positive pressure of Argon, using Schlenk techniques when air-sensitive compounds were employed. Commercially available materials were obtained from Aldrich, Fluka, Merck or Acros, and used without purification unless otherwise noted. TPPB was purchased from Acros and handled under N_2 in a glovebox. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone, dichloromethane, NEt_3 and $EtNiPr_2$ were distilled from CaH_2 prior to use. MeOH was distilled from $Mg(OMe)_2$. Acetone, DMF, DMSO and 2-propanol were distilled and stored over 4 Å molecular sieves. Flash chromatography was performed using Merck silica gel 230–400 mesh. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AMX 500, AVS 400, AM 250 or Jeol ECP 500 spectrometer, respectively. Data are reported in δ (ppm) with the residual undeuterated solvent peak ($CDCl_3$ at δ = 7.26 ppm, toluene-d8 at δ = 7.00 ppm) as an internal standard. High resolution mass spectroscopy (HRMS-EI) was performed using a Varian MAT 711 mass spectrometer, electrospray mass spectrometry (ESI) with a Waters Micromass LCT. Optical rotations were determined with a Perkin Elmer 241 polarimeter at 23 °C and a wavelength of 589.3 nm (sodium lamp) using a 1 mL quartz cell.

(2*S*,3*S*)-3-Methylpent-4-en-2-ol (25)[31]

To a stirred suspension (–78 °C) of KO(*t*-Bu) (14.0 g, 124 mmol, dried at 60 °C/0.3 mbar overnight) in THF (80 mL) was added *cis*-butene (20 mL, 0.22 mol) via double-tipped needle. *n*-BuLi (50.0 mL, 2.5 M in hexanes, 124 mmol) was added over 10 min. After complete addition, the mixture was warmed to –25 °C for 30 min and then recooled to –78 °C. A solution of (+)-methoxydiisopinocampheylborane (47.4 g, 150 mmol) in Et_2O (100 mL) was added slowly. After the resulting solution was stirred for 30 min, $BF_3{\cdot}OEt_2$ (20.0 mL, 0.158 mmol) was added dropwise, followed by dropwise addition of acetaldehyde (10.0 mL, 177 mmol) in Et_2O (10 mL). After 3 h, the reaction was quenched with 135 mL aqueous NaOH (2 M) and 37.5 mL aqueous H_2O_2 (30%), warmed to r.t. and then heated to reflux for 1 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$ and filtered. After evaporation of a major amount of solvent in vacuo (500 mbar, 40 °C water bath), the residual liquid was carefully fractionated to give 13.3 g (bp 50–72 °C/94 mbar, 82% yield corrected by NMR analysis) of alcohol **25**, containing residual THF and pinenol. The crude product was used directly in the next reaction. R_f = 0.35 (*n*-hexane–EtOAc, 2:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.85 (ddd, *J* = 17.6, 9.9, 7.7 Hz, 1 H), 5.04–5.14 (m, 2 H), 3.69 (qui-like, *J* = 6.0 Hz, 1 H), 2.24 (sext-like, *J* = 6.8 Hz, 1 H), 1.51 (br s, 1 H), 1.14 (d, *J* = 5.9 Hz, 3 H), 1.02 (d, *J* = 7.4 Hz, 3 H).

(1*S*,2*S*)-1,2-Dimethylbut-3-enyl 4-Methoxybenzoate (26)

Sodium hydride (2.25 g, 60% in mineral oil, 56.2 mmol) was washed with *n*-pentane (20 mL). DMSO (60 mL) was added and the suspension was stirred at r.t. for 1 h. Crude alcohol **25** (3.8 g, still containing THF and pinenol from the previous reaction) was added in THF (5 mL) over 2 min. The yellowish mixture was cooled to 0 °C and PMBCl (4.40 mL, 32.4 mmol) was added slowly. The mixture was warmed to r.t. and stirred overnight. Brine (80 mL) was added and the mixture was extracted with MTBE (4 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Silica gel chromatography afforded 4.17 g (18.9 mmol, 60% over 2 steps) of PMB-ether **26** as a colorless liquid. R_f = 0.54 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +1.4 (*c* 1.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (dm, *J* = 8.8 Hz, 2 H), 6.88 (dm, *J* = 8.8 Hz, 2 H), 5.83 (ddd, *J* = 17.4, 10.3, 7.4 Hz, 1 H), 5.01–5.08 (m, 2 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.42 (d, *J* = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.36 (qui-like, *J* = 12.4, 6.2 Hz, 1 H), 2.34–2.42 (m, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 140.8, 131.1, 129.1, 114.4, 113.7, 78.1, 70.3, 55.2, 43.0, 16.6, 15.9.

MS (EI): *m/z* (%) = 220 (4) $[M]^+$, 176 (1), 134 (2), 122 (9), 121 (100).

HRMS: *m/z* calcd for $C_{14}H_{20}O_2$: 220.14633; found: 220.14732.

Ethyl (*E*)-(4*S*,5*S*)-5-[(4-Methoxybenzyl)oxy]-2,4-dimethylhex-2-enoate (29)

A stream of O_3 in oxygen (50 L/h) was passed through a solution containing olefin **26** (200 mg, 0.90 mmol) and Sudan Red III (10 µL, sat. soln in EtOH) in CH_2Cl_2 (5 mL) at –78 °C. After 10 min, the color of the solution turned from red to gray. Excess O_3 was purged with argon, PPh_3 (348 mg, 1.33 mmol) was added and stirring was continued at –78 °C for 1 h. The mixture was warmed to r.t. and (1-ethoxycarbonylethylidene)triphenylphosphorane (2.2 g, 6.1 mmol) in CH_2Cl_2 (5 mL) was added. After 15 h, the solvents were evaporated in vacuo. The residue was filtered through a short pad of silica gel (*n*-hexane–EtOAc, 2:1) and the solvent was evaporated. Silica gel chromatography (*n*-hexane–EtOAc, 10:1) afforded 209 mg (0.68 mmol, 76%) of ester **29** as a colorless liquid. R_f = 0.41 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +7.8 (*c* 1.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dm, *J* = 8.8 Hz, 2 H), 6.86 (dm, *J* = 8.8 Hz, 2 H), 6.61 (dq, *J* = 10.3, 1.5 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.3 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.36 (qui-like, *J* = 6.4 Hz, 1 H), 2.63 (ddq, *J* = 10.3, 6.8, 6.8 Hz, 1 H), 1.84 (d, *J* = 1.5 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.13 (d, *J* = 6.2 Hz, 3 H), 1.05 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 159.1, 144.0, 130.9, 129.2, 127.6, 113.7, 77.9, 70.6, 60.4, 55.2, 39.5, 17.3, 16.0, 14.3, 12.6.

MS (EI): *m/z* (%) = 306 (1) $[M]^+$, 262 (1), 233 (1), 217 (1), 189 (1), 170 (20), 136 (4), 121 (100).

HRMS: *m/z* calcd for $C_{18}H_{26}O_4$: 306.18311; found: 306.18564.

(*E*)-(4*S*,5*S*)-5-[(4-Methoxybenzyl)oxy]-2,4-dimethylhex-2-en-1-ol

To a stirred solution (–78 °C) of ester **29** (2.51 g, 8.20 mmol) in CH_2Cl_2 (60 mL) was added DIBAL-H (24.6 mL, 1 M in *n*-hexane, 24.6 mmol). After 1 h of stirring, MTBE (60 mL) was added rapidly

and the mixture was warmed to r.t. Dropwise addition of H_2O (2.5 mL) led to the formation of a colorless gel. Upon addition of aqueous 2 N NaOH (5 mL) and additional H_2O (2.5 mL), a white solid precipitated. The resulting suspension was dried with $MgSO_4$, then filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 2:1) afforded 1.98 g (7.47 mmol, 91%) of the desired alcohol as a colorless liquid. R_f = 0.23 (*n*-hexane–EtOAc, 2:1); $[\alpha]_D^{23}$ = +11.2 (*c* 2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.26 (dq, *J* = 9.8, 1.3 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.37 (d, *J* = 11.4 Hz, 1 H), 3.98 (d, *J* = 1.0 Hz, 2 H), 3.80 (s, 3 H), 3.29 (dq, *J* = 6.9, 3.3 Hz, 1 H), 2.55 (ddq, *J* = 9.8, 6.8, 6.8 Hz, 1 H), 1.67 (d, *J* = 1.4 Hz, 3 H), 1.13 (d, *J* = 6.2 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 134.7, 131.1, 129.2, 128.6, 113.7, 78.7, 70.5, 68.9, 55.3, 38.1, 17.0 (2C), 14.0.

MS (EI): *m/z* (%) = 264 (2) $[M]^+$, 233 (1), 220 (2), 137 (6), 121 (100).

HRMS: *m/z* calcd for $C_{16}H_{24}O_3$: 264.17255; found: 264.17465.

(*E*)-(4*S*,5*S*)-5-[(4-Methoxybenzyl)oxy]-2,4-dimethylhex-2-enal (30)

Activated manganese dioxide (26.6 g) was suspended in CH_2Cl_2 (90 mL). (*E*)-(4*S*,5*S*)-5-[(4-Methoxybenzyl)oxy]-2,4-dimethylhex-2-en-1-ol (1.97 g, 7.44 mmol) was added in CH_2Cl_2 (10 mL) at r.t. and the mixture was stirred for 1 h. The mixture was filtered through a short pad of celite with CH_2Cl_2 (100 mL) and the solvent was evaporated in vacuo to afford pure aldehyde **30** (1.90 g, 7.25 mmol, 97%) as a colorless liquid. R_f = 0.40 (*n*-hexane–EtOAc, 2:1); $[\alpha]_D^{23}$ = +22.4 (*c* 1.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 6.36 (dq, *J* = 10.1, 1.4 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.37 (d, *J* = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.45 (quin-like, *J* = 6.3 Hz, 1 H), 2.84 (ddq, *J* = 10.1, 6.7, 6.6 Hz, 1 H), 1.75 (d, *J* = 1.4 Hz, 3 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.10 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.4, 159.2, 156.4, 138.9, 130.6, 129.2, 113.8, 77.2, 70.6, 55.2, 39.4, 16.9, 15.5, 9.5.

MS (EI): *m/z* (%) = 262 (1) $[M]^+$, 248 (1), 232 (1), 222 (1), 192 (2), 137 (8), 126 (15), 121 (100).

HRMS: *m/z* calcd for $C_{16}H_{22}O_3$: 262.15689; found: 262.15533.

(*R*)-4-Benzyl-3-{(*E*)-(2*R*,3*R*,6*S*,7*S*)-3-hydroxy-7-[(4-methoxybenzyl)oxy]-2,4,6-(trimethyl)oct-4-enoyl}oxazolidin-2-one (32)

To a stirred solution (–78 °C) of (*R*)-(–)-4-benzyl-3-propionyl-2-oxazolidinone (**31**) (1.73 g, 7.44 mmol) in CH_2Cl_2 (13 mL) was added di(*n*-butyl)boryl(trifluoromethane)sulfonate (8.9 mL, 1 M in CH_2Cl_2, 8.9 mmol) and Et_3N (1.35 mL, 9.68 mmol). The mixture was warmed to 0 °C, stirred for 1 h and then cooled to –78 °C again. A solution of aldehyde **30** (1.89 g, 7.21 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min. After 20 min, the reaction was warmed to 0 °C and stirred for 1 h. The reaction was quenched by dropwise addition of pH7 phosphate buffer (7.5 mL), MeOH (22.5 mL) and a mixture of MeOH and 30% aqueous H_2O_2 (2:1, 22.5 mL) and stirred for 1 h. H_2O (20 mL) was added, the organic layer was separated and the aqueous layer was extracted with MTBE (4 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 2:1) afforded aldol **32** (3.36 g, 6.78 mmol, 94%) as a colorless liquid. R_f = 0.40 (*n*-hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ = –27.7 (*c* 0.9, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.35 (m, 2 H), 7.22–7.29 (m, 3 H), 7.17–7.21 (m, 2 H), 6.85 (dm, *J* = 8.7 Hz, 2 H), 5.37 (d, *J* = 10.0 Hz, 1 H), 4.64 (dq-like, *J* = 6.5, 3.2 Hz, 1 H), 4.50 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.3 Hz, 1 H), 4.34 (d, *J* = 4.1 Hz, 1 H), 4.09–4.14 (m, 2 H), 4.00 (dq, *J* = 6.9, 4.5 Hz, 1 H), 3.78 (s, 3 H), 3.29 (dq-like, *J* = 13.3, 6.2 Hz, 1 H), 3.24 (dd, *J* = 13.5, 3.2 Hz, 1 H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1 H), 2.67 (br s, 1 H), 2.56 (ddq, *J* = 10.2, 6.8, 6.8 Hz, 1 H), 1.63 (d, *J* = 1.2 Hz, 3 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.10 (d, *J* = 6.2 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6, 159.0, 152.9, 135.1, 133.5, 131.0, 129.5, 129.4, 129.1, 128.9, 127.3, 113.7, 78.9, 75.7, 70.5, 66.0, 55.2 (2C), 40.5, 38.2, 37.7, 17.4, 17.0, 13.4, 11.0.

MS (EI): *m/z* (%) = 495 (0.1) $[M]^+$, 477 (0.1), 451 (0.1), 433 (0.1), 386 (0.1), 359 (0.1), 342 (0.1), 330 (0.4), 313 (0.3), 233 (15), 121 (100).

HRMS: *m/z* calcd for $C_{29}H_{37}N_1O_6$: 495.26209; found: 495.26465.

(*E*)-(2*R*,3*R*,6*S*,7*S*)-3-Hydroxy-7-[(4-methoxybenzyl)oxy]-*N*-methoxy-*N*,2,4,6-tetramethyloct-4-enamide

To a stirred suspension (0 °C) of *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 g, 10.8 mmol) in CH_2Cl_2 (17 mL) was added Me_3Al (5.4 mL, 2 M in heptane, 10.8 mmol) over 5 min. The mixture was warmed to r.t. After 1 h, the clear solution was cooled to –20 °C and amide **32** (2.55 g, 5.14 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction was allowed to warm to r.t. over 5 h and was stirred overnight. The mixture was transferred via syringe to a second flask containing a vigorously stirred aq soln of tartaric acid (1 M, 30 mL) at 0 °C. After 1.5 h, H_2O (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product can be directly used in the next reaction, preferrably after crystallization of the Evans auxiliary from *n*-hexane–EtOAc (1:1). The amide can be obtained by silica gel chromatography (*n*-hexane–EtOAc, 2:1) to afford a colorless liquid (1.74 g, 4.57 mmol, 89%). R_f = 0.12 (*n*-hexane–EtOAc, 2:1); $[\alpha]_D^{23}$ = +3.7 (*c* 1.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dm, *J* = 8.7 Hz, 2 H), 6.85 (dm, *J* = 8.7 Hz, 2 H), 5.39 (d, *J* = 9.9 Hz, 1 H), 4.52 (d, *J* = 11.3 Hz, 1 H), 4.35 (d, *J* = 11.3 Hz, 1 H), 4.22–4.25 (m, 1 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.66–3.69 (m, 1 H), 3.25 (dq, *J* = 8.0, 6.2 Hz, 1 H), 3.17 (s, 3 H), 3.07 (br s, 1 H), 2.51 (ddq, *J* = 10.0, 8.0, 6.7 Hz, 1 H), 1.60 (d, *J* = 1.4 Hz, 3 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 159.0, 132.7, 131.1, 129.5, 129.2, 113.6, 79.0, 75.5, 70.6, 61.5, 55.2, 38.8, 36.9, 31.8, 17.5 (2C), 13.7, 10.6.

MS (EI): *m/z* (%) = 379 (0.1) $[M]^+$, 361 (1), 348 (1) $[M - CH_3O]^+$, 330 (5), 301 (1), 286 (2), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{21}H_{34}N_1O_5$ $[M + H]^+$: 380.2437; found: 380.2447.

(*E*)-(2*R*,3*R*,6*S*,7*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]-*N*-methoxy-*N*,2,4,6-tetramethyloct-4-enamide (33)

To a stirred solution (0 °C) of crude (*E*)-(2*R*,3*R*,6*S*,7*S*)-3-hydroxy-7-[(4-methoxybenzyl)oxy]-*N*-methoxy-*N*,2,4,6-tetramethyloct-4-enamide (2.75 g) in CH_2Cl_2 (35 mL) was slowly added 2,6-lutidine (1.47 mL, 12.6 mmol) and TBSOTf (2.16 mL, 9.40 mmol). The mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with MeOH (0.6 mL), diluted with CH_2Cl_2 (30 mL) and successively washed with sat. aq $NaHCO_3$ (20 mL), aq $NaHSO_4$ (1 M, 2 × 50mL) and brine (20 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude product can be directly used in the next reaction. Pure amide **33** can be obtained by silica gel chromatography (*n*-hexane–EtOAc, 2:1) to afford **33** (1.95 g, 3.96 mmol, 77% over 2 steps) as a colorless liquid. R_f = 0.53 (*n*-hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ = +12.2 (*c* 0.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.09 (d, *J* = 10.2 Hz, 1 H), 4.50 (d, *J* = 11.1 Hz, 1 H), 4.33 (d, *J* = 11.1 Hz, 1 H), 4.14 (d, *J* = 9.3 Hz, 1 H), 3.80 (s, 3 H), 3.62 (s, 3 H), 3.15 (dd, *J* = 8.3, 6.2 Hz, 1 H), 3.12–3.19 (m, 1 H), 3.06 (s, 3 H), 2.36–2.45 (m, 1 H), 1.60 (d, *J* = 1.2 Hz, 3 H), 1.18 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.2 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), –0.02 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5, 159.0, 135.0, 131.2, 131.1, 129.2 (2C), 113.7, 80.6, 79.3, 70.7, 61.4, 55.3, 39.9, 39.0, 25.8, 18.2, 17.5, 17.1, 15.3, 11.2, –4.5, –5.0.

MS (EI): *m/z* (%) = 493 (0.1) $[M]^+$, 479 (0.3), 478 (0.9) $[M - CH_3]^+$, 462 (0.3), 436 (18), 392 (14), 328 (11), 234 (79), 200 (58), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{27}H_{48}N_1O_5Si_1$ $[M + H]^+$: 494.3302; found: 494.3308.

(*E*)-(2*R*,3*R*,6*S*,7*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]-2,4,6-trimethyloct-4-enal (34)

To a stirred solution (–78 °C) of amide **33** (1.00 g, 2.03 mmol) in THF (6 mL) was added DIBAL-H (5.1 mL, 1 M in heptane, 5.1 mmol) over 20 min. Upon complete addition, the reaction was stirred for further 15 min. Excess DIBAL-H was quenched by the addition of acetone (0.25 mL). The mixture was transferred via syringe to a second flask containing a vigorously stirred mixture (23 °C) of aqueous tartaric acid (1 M, 18 mL) and *n*-hexane (15 mL) and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 15:1) afforded aldehyde **34** (0.778 g, 1.79 mmol, 88%) as a colorless liquid. R_f = 0.65 (*n*-hexane–EtOAc, 2:1); $[\alpha]_D^{23}$ = +14.3 (*c* 1.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.64 (d, *J* = 2.2 Hz, 1 H), 7.26 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.22 (d, *J* = 9.9 Hz, 1 H), 4.52 (d, *J* = 11.3 Hz, 1 H), 4.33 (d, *J* = 11.3 Hz, 1 H), 4.21 (d, *J* = 6.6 Hz, 1 H), 3.80 (s, 3 H), 3.22 (dq, *J* = 7.0, 6.4 Hz, 1 H), 2.54 (dquin-like, *J* = 6.7, 2.2 Hz, 1 H), 2.49 (ddq, *J* = 9.9, 6.9, 6.7 Hz, 1 H), 1.60 (d, *J* = 1.1 Hz, 3 H), 1.09 (d, *J* = 6.2 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), –0.01 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.4, 159.0, 134.9, 131.1, 130.8, 129.2, 113.7, 78.6, 78.4, 70.5, 55.3, 51.1, 38.6, 25.7, 18.1, 17.4, 16.7, 12.4, 9.6, –4.4, –5.2.

MS (EI): *m/z* (%) = 434 (0.1) $[M]^+$, 416 (0.5), 377 (8) $[M - C_4H_9]^+$, 333 (16), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{25}H_{42}Na_1O_4Si_1$ $[M + Na]^+$: 457.2750; found: 457.2743.

(2*E*,8*E*)-(4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-hydroxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyldodeca-2,8-dienoic Acid Methyl Ester (22)

To a stirred solution (–78 °C) of aldehyde **34** (163 mg, 0.37 mmol) in Et_2O (5 mL) was added tris(pentafluorophenyl)borane monohydrate (230 mg, 0.43 mmol). Ketene acetal **1**[11] (185 mg, 0.81 mmol) and *i*-PrOH (25 mg, 0.42 mmol) were diluted with Et_2O (0.8 mL) and added via syringe pump over 2 h. The mixture was allowed to warm to –50 °C over 30 min and was then evaporated in vacuo at r.t.. Silica gel chromatography (*n*-hexane–EtOAc, 4:1) afforded ester **22** (188 mg, 0.34 mmol, 91%) as a colorless liquid. R_f = 0.29 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +6.7 (*c* 0.6, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 6.71 (dd, *J* = 15.7, 9.3 Hz, 1 H), 5.82 (dd, *J* = 15.7, 0.8 Hz, 1 H), 5.24 (d, *J* = 9.9 Hz, 1 H), 4.51 (d, *J* = 11.4 Hz, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 3.90 (d, *J* = 7.7 Hz, 1 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.32 (quin-like, *J* = 6.6 Hz, 1 H), 3.28–3.32 (m, 1 H), 2.61 (ddq, *J* = 9.9, 6.7, 6.7 Hz, 1 H), 2.41 (dddq, *J* = 9.4, 9.2, 6.7, 0.8 Hz, 1 H), 2.00 (d, *J* = 5.1 Hz, 1 H), 1.56–1.63 (m, 1 H), 1.54 (d, *J* = 1.2 Hz, 3 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.04 (s, 3 H), –0.03 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 159.0, 150.8, 136.2, 131.0, 129.7, 129.0, 120.8, 113.7, 82.4, 78.5, 75.2, 70.3, 55.3, 51.5, 41.0, 39.7, 37.7, 25.9, 18.1, 17.1, 16.6, 16.4, 12.0, 8.1, –4.4, –5.0.

MS (EI): *m/z* (%) = 548 (2) $[M]^+$, 491 (2), 447 (8), 377 (13), 355 (2), 333 (58), 121 (100).

HRMS: *m/z* calcd for $C_{31}H_{52}O_6Si_1$ $[M]^+$: 548.35333; found: 548.35176.

(2*E*,8*E*)-(4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodeca-2,8-dienoic Acid Methyl Ester

To a stirred solution (0 °C) of ester **22** (172 mg, 0.313 mmol) in CH_2Cl_2 (3.5 mL) was added 2,6-lutidine (91 μL, 0.78 mmol) and TESOTf (106 μL, 0.47 mmol) dropwise. After 15 min, the reaction was quenched by the addition of sat. aq $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) The combined organic layers were washed with sat. aq $NaHCO_3$ (5 mL), aq $NaHSO_4$ (1 M, 2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 15:1) afforded the ester (201 mg, 0.303 mmol, 97%) as a colorless liquid. R_f = 0.48 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +7.1 (*c* 1.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dm, *J* = 8.7 Hz, 2 H), 6.94 (dd, *J* = 15.8, 7.7 Hz, 1 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.76 (dd, *J* = 15.8, 1.4 Hz, 1 H), 5.16 (d, *J* = 9.9 Hz, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.3 Hz, 1 H), 3.80 (s, 3 H), 3.76 (d, *J* = 8.8 Hz, 1 H), 3.73 (s, 3 H), 3.55 (dd, *J* = 5.7, 2.5 Hz, 1 H), 3.25 (dq, *J* = 7.7, 6.2 Hz, 1 H), 2.56 (ddq, *J* = 9.9, 8.8, 6.7 Hz, 1 H), 2.41–2.49 (m, 1 H), 1.69 (ddq, *J* = 8.8, 6.7, 2.5 Hz, 1 H), 1.53 (d, *J* = 1.4 Hz, 3 H), 1.17 (d, *J* = 6.2 Hz, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.60 (q, *J* = 7.9 Hz, 6 H), 0.02 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 159.0, 152.3, 136.8, 131.2, 131.0, 129.0, 120.1, 113.7, 80.6, 78.7, 74.9, 70.5, 55.3, 51.4, 42.3, 39.3, 38.8, 25.9, 18.2, 17.4, 16.9, 15.0, 11.9, 10.8, 7.1, 5.7, –4.3, –4.9.

MS (EI): *m/z* (%) = 662 (3) $[M]^+$, 561 (2), 389 (3), 378 (15), 333 (76), 257 (30), 241 (29), 213 (13), 185 (27), 121 (100).

HRMS: *m/z* calcd for $C_{37}H_{66}O_6Si_2$ $[M]^+$: 662.43982; found: 662.43843.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,3-dihydroxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Methyl Ester (35)

To a stirred solution of AD-mix α (415 mg) in *t*-BuOH–H_2O (1:1, 2.5 mL) was added methanesulfonamide (21.5 mg, 0.226 mmol) at r.t. The suspension was cooled to 0 °C and (2*E*,8*E*)-(4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodeca-2,8-dienoic acid methyl ester (148 mg, 0.223 mmol) was added in *t*-BuOH (0.6 mL). After 5 d, the reaction was quenched by the addition of $Na_2S_2O_3$ (229 mg), warmed to r.t. and stirred for 1 h. H_2O (2 mL) was added, and the mixture was extracted with EtOAc (4 × 10 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 3:1) afforded diol **35** (147 mg, 0.202 mmol, 91%) as a mixture of diastereomers (d.r. 24:1).

Major Diastereomer (35)

R_f = 0.31 (*n*-hexane–EtOAc, 3:1); $[\alpha]_D^{23}$ = –10.9 (*c* 1.6, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.16 (dd-like, *J* = 9.7, 1.3 Hz, 1 H), 4.51 (d, *J* = 11.8 Hz, 1 H), 4.40 (d, *J* = 11.8 Hz, 1 H), 4.26 (dd, *J* = 5.6, 3.0 Hz, 1 H), 3.80 (s, 3 H), 3.80–3.84 (m, 1 H), 3.78 (s, 3 H), 3.74 (d, *J* = 9.2 Hz, 1 H), 3.61 (dd, *J* = 5.2, 2.2 Hz, 1 H), 3.29 (quin-like, *J* = 6.3 Hz, 1 H), 3.12 (dd, *J* = 5.5, 1.0 Hz, 1 H), 2.62 (dq-like, *J* = 9.8, 6.6 Hz, 1 H), 2.61 (d, *J* = 8.1 Hz, 1 H), 1.74–1.82 (m, 2 H), 1.58 (d, *J* = 1.4 Hz, 3 H), 1.12 (d, *J* = 6.2 Hz, 3 H), 0.97 (t, *J* = 7.9 Hz, 9 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.63 (q, *J* = 7.9 Hz, 6 H), 0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 159.1, 137.5, 130.8, 130.4, 129.1, 113.8, 81.2, 78.5, 73.4, 73.1, 72.1, 70.3, 55.3, 52.6, 42.4, 39.5, 37.8, 25.9, 18.2, 17.1, 16.5, 11.7, 11.2, 10.5, 7.1, 5.7, –4.3, –5.0.

MS (EI): *m/z* (%) = 696 (0.1) $[M]^+$, 662 (0.2), 639 (0.2) $[M - C_4H_9]^+$, 606 (0.6), 461 (2), 377 (20), 333 (73), 185 (23), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{37}H_{68}Na_1O_8Si_2$ $[M + Na]^+$: 719.4350; found: 719.4334.

(2*S*,3*R*) Isomer (C2,C3-*epi*-35)

R_f = 0.40 (*n*-hexane–EtOAc, 3:1); $[\alpha]_D^{23}$ = –12.8 (*c* 0.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.6 Hz, 2 H), 6.87 (dm, *J* = 8.6 Hz, 2 H), 5.17 (d, *J* = 9.8 Hz, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.36 (br s, 1 H), 4.10 (d, *J* = 8.8 Hz, 1 H), 3.91 (ddd, *J* = 10.2, 3.4, 1.1 Hz, 1 H), 3.84 (dd, *J* = 3.0, 2.1 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.69 (d, *J* = 9.8 Hz, 1 H), 3.29 (quin-like, *J* = 6.4 Hz, 1 H), 2.90 (d, *J* = 8.5 Hz, 1 H), 2.62 (dq-like, *J* = 9.8, 6.7 Hz, 1 H), 1.94 (ddq, *J* = 10.4, 6.9, 3.6 Hz, 1 H), 1.83 (ddq, *J* = 9.8, 6.7, 1.8 Hz, 1 H), 1.55 (d, *J* = 1.2 Hz, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 0.97 (t, *J* = 7.9 Hz, 9 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.74 (d, *J* = 7.0 Hz, 3 H), 0.60–0.66 (m, 6 H), 0.03 (s, 3 H), –0.03 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 159.0, 136.9, 131.0, 130.9, 129.0, 113.7, 81.9, 78.4, 75.0, 74.8, 71.6, 70.2, 55.3, 52.5, 40.1, 37.8, 37.2, 29.7, 25.8, 18.2, 16.8, 16.5, 12.4, 11.5, 6.9, 5.1, –4.4, –5.0.

MS (EI): *m/z* (%) = 662 (0.1), 639 (0.2) $[M - C_4H_9]^+$, 461 (5), 377 (21), 333 (70), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{37}H_{68}Na_1O_8Si_2$ $[M + Na]^+$: 719.4350; found: 719.4349.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Methyl Ester

To a stirred solution (0 °C) of diol **35** (161 mg, 0.231 mmol) in DMF (2 mL) was added imidazole (95 mg, 1.4 mmol) and TBSCl (105 mg, 70 μmol). After 16 h, the reaction was quenched by the addition of sat. aq NH_4Cl (2 mL) and the mixture was extracted with *n*-hexane–EtOAc (5:1, 4 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 8:1) afforded the desired ester (187 mg, 0.230 mmol, 99%) as a colorless liquid. R_f = 0.38 (*n*-hexane–EtOAc, 10:1); $[\alpha]_D^{23}$ = +2.7 (*c* 1.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.13 (dd-like, *J* = 9.8, 1.2 Hz, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 4.08 (d, *J* = 6.9 Hz, 1 H), 3.80–3.83 (m, 1 H), 3.80 (s, 3 H), 3.74 (d, *J* = 10.0 Hz, 1 H), 3.72 (s, 3 H), 3.54 (d, *J* = 7.4 Hz, 1 H), 3.24 (dq, *J* = 7.1, 6.2 Hz, 1 H), 2.57 (dq-like, *J* = 6.9, 2.8 Hz, 1 H), 2.54 (d, *J* = 4.5 Hz, 1 H), 1.86 (dq-like, *J* = 10.0, 6.6 Hz, 1 H), 1.58 (d, *J* = 1.1 Hz, 3 H), 1.57–1.62 (m, 1 H), 1.15 (d, *J* = 6.2 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.96 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.88 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.57–0.65 (m, 6 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 159.0, 137.4, 131.2, 131.1, 129.0, 113.7, 81.5, 78.6, 75.8, 74.0, 71.6, 70.3, 55.2, 51.8, 40.0, 38.5, 25.8, 25.7, 25.6, 18.3, 18.2, 17.3, 17.0, 11.5, 10.3, 10.2, 7.2, 5.9, –4.3, –5.0 (2C), –5.3.

MS (EI): *m/z* (%) = 810 (0.5) $[M]^+$, 793 (22) $[M - OH]^+$, 751 (6), 736 (15) $[M - C_4H_9]^+$, 707 (13), 644 (23), 619 (100), 512 (1), 121 (13).

HRMS (ESI): *m/z* calcd for $C_{43}H_{83}Na_1O_8Si_3$ $[M + Na + H]^+$: 834.5294; found: 834.5303.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Methyl Ester (36)

To a stirred solution of trimethyloxonium tetrafluoroborate (815 mg, 5.54 mmol) in CH_2Cl_2 (10 mL) was added proton sponge (1.18 g, 5.51 mmol). The mixture was cooled to 0 °C and a solution of (*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic acid methyl ester (285 mg, 0.351 mmol) in CH_2Cl_2 (2 mL) was added slowly. The reaction was protected from light and stirred for 24 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with sat. aq $NaHCO_3$ (3 × 30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was filtered through a short pad of silica gel with EtOAc and evaporated. Silica gel chromatography (*n*-hexane–MTBE, 20:1) afforded ester **36** (238 mg, 0.288 mmol, 82%) as a colorless liquid. R_f = 0.28 (*n*-hexane–EtOAc, 10:1); $[\alpha]_D^{23}$ = +4.6 (*c* 2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.17 (dd-like, *J* = 9.6, 1.3 Hz, 1 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 4.34 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 6.6 Hz, 1 H), 3.80 (s, 3 H), 3.78 (d, *J* = 10.0 Hz, 1 H), 3.71 (s, 3 H), 3.46 (dd, *J* = 8.8, 0.7 Hz, 1 H), 3.41 (s, 3 H), 3.34 (dd, *J* = 6.6, 1.4 Hz, 1 H), 3.22 (dq, *J* = 8.0, 6.1 Hz, 1 H), 2.49 (ddq, *J* = 9.6, 7.9, 6.7 Hz, 1 H), 1.82 (ddq, *J* = 10.1, 6.7, 0.6 Hz, 1 H), 1.64 (ddq, *J* = 8.7, 7.3, 1.3 Hz, 1 H), 1.60 (d, *J* = 1.3 Hz, 3 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.83 (d, *J* = 7.0 Hz, 3 H), 0.55–0.66 (m, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 159.0, 136.8, 131.7, 131.2, 129.0, 113.7, 82.5, 81.2, 78.7, 75.3, 74.3, 70.5, 60.4, 55.2, 51.6, 39.3, 39.2, 39.0, 25.9, 25.7, 18.3, 18.2, 17.8, 16.7, 11.6, 11.2, 10.0, 7.2, 6.2, –4.2, –4.9, –5.1, –5.2.

MS (EI): *m/z* (%) = 809 (0.1) $[M - CH_3]^+$, 767 (0.4) $[M - C_4H_9]^+$, 659 (0.6), 589 (3), 377 (21), 333 (44), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{44}H_{84}Na_1O_8Si_3$ $[M + Na]^+$: 847.5372; found: 847.5371.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-11-hydroxy-3-methoxy-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Methyl Ester

To a stirred solution (0 °C) of ester **36** (237 mg, 0.287 mmol) in CH_2Cl_2–pH7 buffer (10:1, 1 mL) was added DDQ (81.5 mg, 0.359 mmol). After 1.5 h, the reaction was diluted with CH_2Cl_2 (10 mL) and sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 5:1) afforded the alcohol

(195 mg, 0.277 mmol, 96%) as a colorless liquid. R_f = 0.32 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = –8.2 (*c* 1.3, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.20 (dd-like, *J* = 9.6, 1.4 Hz, 1 H), 4.28 (d, *J* = 6.7 Hz, 1 H), 3.80 (d, *J* = 10.0 Hz, 1 H), 3.71 (s, 3 H), 3.56–3.62 (m, 1 H), 3.46 (dd, *J* = 8.7, 0.8 Hz, 1 H), 3.42 (s, 3 H), 3.33 (dd, *J* = 6.7, 1.3 Hz, 1 H), 2.41 (ddq, *J* = 9.6, 6.7, 6.7 Hz, 1 H), 1.81 (ddq, *J* = 6.8, 3.2, 0.8 Hz, 1 H), 1.61–1.68 (m, 1 H), 1.61 (d, *J* = 1.2 Hz, 3 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.55–0.67 (m, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 137.5, 131.0, 82.6, 81.1, 75.3, 74.4, 71.7, 60.4, 51.7, 40.0, 39.4, 38.9, 25.8, 25.7, 21.3, 18.3, 18.2, 15.7, 11.7, 11.2, 10.1, 7.2, 6.2, –4.3, –4.9, –5.1, –5.2.

MS (EI): *m/z* (%) = 675 (0.3) $[M - Et]^+$, 647 (0.5), 589 (0.9), 515 (1), 471 (5), 257 (100), 213 (23), 115 (3).

HRMS (ESI): *m/z* calcd for $C_{36}H_{76}Na_1O_7Si_3$ $[M + Na]^+$: 727.4797; found: 727.4802.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-4,6,8,10-tetramethyl-11-oxo-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Methyl Ester (21)

To a stirred solution (0 °C) of (*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-bis{[*tert*-butyl(dimethyl)silyl]oxy}-11-hydroxy-3-methoxy-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic acid methyl ester (124 mg, 0.176 mmol) in CH_2Cl_2 (3 mL) was added powdered molecular sieves (3 Å, 100 mg) and *N*-methylmorpholine-*N*-oxide (31.0 mg, 0.265 mmol). TPAP (3.1 mg, 8.8 μmol) was added after 20 min and the reaction was warmed to r.t.. After 4 h, the mixture was filtered through a short pad (5 × 30 mm) of silica gel with CH_2Cl_2 (10 mL) and the solvent was evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 10:1) afforded methyl ketone **21** (123 mg, 0.175 mmol, 99%) as a colorless liquid. R_f = 0.47 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +69.7 (*c* 1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.25 (dq, *J* = 9.4, 1.4 Hz, 1 H), 4.28 (d, *J* = 6.7 Hz, 1 H), 3.82 (d, *J* = 10.0 Hz, 1 H), 3.71 (s, 3 H), 3.44 (s, 3 H), 3.39–3.45 (m, 2 H), 3.32 (dd, *J* = 6.7, 1.4 Hz, 1 H), 2.12 (s, 3 H), 1.81 (ddq, *J* = 10.1, 6.7, 0.9 Hz, 1 H), 1.69 (d, *J* = 1.4 Hz, 3 H), 1.62 (ddq, *J* = 8.6, 7.0, 1.4 Hz, 1 H), 1.15 (d, *J* = 6.7 Hz, 3 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.51–0.65 (m, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.9, 172.4, 139.9, 127.4, 82.6, 80.7, 75.4, 74.1, 60.5, 51.7, 46.8, 39.6, 39.0, 28.2, 25.8, 25.7, 18.3, 18.2, 16.1, 11.6, 11.2, 9.9, 7.2, 6.1, –4.3, –4.9, –5.1, –5.2.

MS (EI): *m/z* (%) = 703 (0.02), 688 (0.1), 673 (0.8), 645 (6) $[M - C_4H_9]^+$, 589 (1), 387 (9), 354 (7), 255 (100), 212 (10) 72 (12).

HRMS (ESI): *m/z* calcd for $C_{36}H_{74}Na_1O_7Si_3$ $[M + Na]^+$: 725.4640; found: 725.4641.

(*R*)-4-Benzyl-3-{(2*S*,3*R*,4*S*)-3-hydroxy-5-[(4-methoxybenzyl)oxy]-2,4-dimethylpentanoyl}oxazolidin-2-one

To a stirred solution (–78 °C) of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (945 mg, 4.05 mmol) in CH_2Cl_2 was added di-*n*-butylboryltrifluoromethanesulfonate (4.45 mL, 1 M in CH_2Cl_2, 4.45 mmol) and Et_3N (0.78 mL, 5.6 mmol). The mixture was warmed to 0 °C, stirred for 1 h and then cooled back down to –78 °C. A solution of aldehyde **37**[36] (1.04 g, 5.00 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 5 min. After 20 min, the reaction was warmed to 0 °C and stirred for 1 h. The reaction was quenched by dropwise addition of pH7 phosphate buffer (4.2 mL), MeOH (12.5 mL) and a mixture of MeOH and 30% aq H_2O_2 (2:1, 12.5 mL) and stirred for 1 h. H_2O (15 mL) was added, the organic layer was separated and the aqueous layer was extracted with MTBE (4 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 2:1) afforded the desired compound (1.39 g, 3.15 mmol, 78%) as a colorless solid. R_f = 0.32 (*n*-hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ = +41.7 (*c* 2.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.36 (m, 2 H), 7.24–7.30 (m, 3 H), 7.19–7.22 (m, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 4.67 (dddd, *J* = 9.7, 6.8, 3.4, 3.3 Hz, 1 H), 4.43 (s, 2 H), 4.20 (dd, *J* = 9.0, 7.2 Hz, 1 H), 4.17 (dd, *J* = 9.0, 3.4 Hz, 1 H), 3.94–4.02 (m, 2 H), 3.80 (s, 3 H), 3.47 (dd, *J* = 9.3, 4.5 Hz, 1 H), 3.45 (dd, *J* = 9.3, 5.2 Hz, 1 H), 3.24 (dd, *J* = 13.5, 3.3 Hz, 1 H), 3.01 (br s, 1 H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1 H), 1.85–1.93 (m, 1 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.0, 159.1, 152.8, 135.1, 130.3, 129.4, 129.2, 128.9, 127.4, 113.7, 74.0, 73.9, 72.9, 66.0, 55.2, 55.1, 40.6, 37.7, 36.2, 12.8, 12.4.

MS (EI): *m/z* = 441 (8), 374 (2), 320 (2), 303 (14), 287 (20), 233 (42), 121 (100).

HRMS: *m/z* calcd for $C_{25}H_{31}O_6N_1$ $[M]^+$: 441.21515; found: 441.21733.

(2*S*,3*R*,4*S*)-3-Hydroxy-*N*-methoxy-5-[(4-methoxybenzyl)oxy]-*N*,2,4-trimethylpentanamide (38)

To a stirred solution (0 °C) of *N*,*O*-dimethylhydroxylamine hydrochloride (0.48 g, 5.0 mmol) in CH_2Cl_2 (7 mL) was added Me_3Al (2.4 mL, 2 M in heptane, 4.8 mmol) over 5 min. The mixture was warmed to r.t.. After 1 h, the clear solution was cooled to –20 °C and (*R*)-4-benzyl-3-{(2*S*,3*R*,4*S*)-3-hydroxy-5-[(4-methoxybenzyl)oxy]-2,4-dimethylpentanoyl}oxazolidin-2-one (1.00 g, 2.26 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction was allowed to warm to r.t. for 3 h and was stirred overnight. The mixture was transferred via syringe to a second flask containing a vigorously stirred aq soln of tartaric acid (1 M, 20 mL) at 0 °C. After 1 h, H_2O (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 1:1) afforded amide **38** (0.730 g, 2.24 mmol, 99%) as a colorless liquid. R_f = 0.08 (*n*-hexane–EtOAc, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (dm, *J* = 8.7 Hz, 2 H), 6.85 (dm, *J* = 8.7 Hz, 2 H), 4.41 (dd-like, *J* = 22.4, 11.5 Hz, 2 H), 3.86 (dd-like, *J* = 5.5, 1.8 Hz, 1 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 3.49 (dd, *J* = 9.2, 4.1 Hz, 1 H), 3.40 (dd, *J* = 9.2, 4.5 Hz, 1 H), 3.15 (s, 3 H), 3.13–3.18 (m, 1 H), 1.81–1.89 (m, 1 H), 1.21 (d, *J* = 7.0 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 159.1, 130.2, 129.8, 129.0, 113.7, 74.9, 74.5, 73.0, 61.5, 55.2, 37.5, 35.7, 12.6, 12.3.

MS (EI): *m/z* = 325 (6) $[M]^+$, 279 (1), 204 (2), 177 (13), 121 (100).

HRMS: *m/z* calcd for $C_{17}H_{27}O_5N_1$ $[M]^+$: 325.18893; found: 325.18755.

(2*S*,3*R*,4*S*)- *N*-Methoxy-5-[(4-methoxybenzyl)oxy]-*N*,2,4-trimethyl-3-[(triethylsilyl)oxy]pentanamide

To a stirred solution (0 °C) of amide **38** (730 mg, 2.24 mmol) in CH_2Cl_2 (15 mL) was slowly added 2,6-lutidine (0.46 mL, 4.0 mmol) and TESOTf (0.68 mL, 3.0 mmol). The mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with MeOH (0.12 mL), diluted with CH_2Cl_2 (15 mL) and successively washed with sat. aq $NaHCO_3$ (10 mL), $NaHSO_4$ (1 M, 2 × 20 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 4:1) afforded the product amide (847 mg, 1.92 mmol, 85%) as a colorless liquid. R_f = 0.28 (*n*-hexane–EtOAc, 2:1); $[\alpha]_D^{23}$ = –1.8 (*c* 1.9, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.85 (dm, *J* = 8.7 Hz, 2 H), 4.40 (s, 2 H), 4.04 (dd, *J* = 8.8, 2.1 Hz, 1 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.40 (dd, *J* = 9.1, 6.5 Hz, 1 H), 3.22 (dd, *J* = 8.9, 7.7 Hz, 1 H), 3.14 (s, 3 H), 3.07 (br s, 1 H), 1.80–1.89 (m, 1 H), 1.16 (d, *J* = 7.0 Hz, 3 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.55–0.65 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6, 159.0, 130.7, 129.3, 113.6, 74.4, 73.1, 72.3, 61.4, 55.2, 39.4, 37.5, 32.1, 15.3, 10.8, 7.0, 5.4.

MS (EI): *m/z* = 439 (5) $[M]^+$, 410 (34), 383 (1), 251 (9), 121 (100).

HRMS: *m/z* calcd for $C_{23}H_{41}N_1O_5Si_1$ $[M]^+$: 439.27539; found: 439.26820.

(2*S*,3*R*,4*S*)-5-[(4-Methoxybenzyl)oxy]-2,4-dimethyl-3-[(triethylsilyl)oxy]pentanal (39)

To a stirred solution of (–78 °C) of (2*S*,3*R*,4*S*)-*N*-methoxy-5-[(4-methoxybenzyl)oxy]-*N*,2,4-trimethyl-3-[(triethylsilyl)oxy]pentanamide (205 mg, 0.467 mmol) in THF (5 mL) was added DIBAL-H (1.17 mL, 1 M in heptane, 1.17 mmol) over 10 min. Upon complete addition, the reaction was stirred for 15 min. Excess DIBAL-H was quenched by the addition of acetone (60 μL). The mixture was transferred via syringe to second flask containing a vigorously stirred mixture (23 °C) of aqueous tartaric acid (1 M, 4 mL) and *n*-hexane (4 mL) and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 10:1) afforded aldehyde **39** (152 mg, 0.40 mmol, 86%) as a colorless liquid. R_f = 0.37 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +43.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.81 (d, *J* = 1.2 Hz, 1 H), 7.24 (dm, *J* = 8.7 Hz, 2 H), 6.88 (dm, *J* = 8.7 Hz, 2 H), 4.42 (d, *J* = 11.5 Hz, 1 H), 4.38 (d, *J* = 11.5 Hz, 1 H), 4.22 (dd, *J* = 5.0, 4.2 Hz, 1 H), 3.80 (s, 3 H), 3.37 (dd, *J* = 9.1, 7.1 Hz, 1 H), 3.24 (dd, *J* = 9.1, 5.8 Hz, 1 H), 2.53 (ddq, *J* = 6.9, 5.2, 1.2 Hz, 1 H), 1.92 (ddq-like, *J* = 12.7, 6.9, 4.1 Hz, 1 H), 1.06 (d, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.60 (q, *J* = 7.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.1, 159.2, 130.5, 129.2, 113.7, 72.7 (2C), 72.6, 55.2, 51.3, 37.2, 12.3, 9.3, 6.9, 5.2.

MS (EI): *m/z* = 380 (0.3) $[M]^+$, 362 (2), 323 (0.4), 291 (0.4), 279 (0.4), 251 (2), 121 (100).

HRMS: *m/z* calcd for $C_{21}H_{36}O_4Si_1$ $[M]^+$: 380.23828; found: 380.23666.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-13-hydroxy-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enoic Acid Methyl Ester (43)

To a stirred solution of methyl ketone **21** (30 mg, 43 μmol) in THF (0.8 mL) were added powdered molecular sieves (3 Å, 20 mg) at r.t. After 1 h, the mixture was cooled to –78 °C and NaHMDS (47 μL, 1M in THF) was added dropwise. Aldehyde **39** (25 mg, 67 μmol) was dissolved in THF (50 μL) and a small grain of CaH_2 was placed into the flask. After 1 h, the aldehyde solution was rapidly added to the enolate solution. The reaction was quenched after 1 min by rapid addition of pH7 buffer (2 mL). MTBE (3 mL) was added, and the vessel was warmed to r.t.. The mixture was extracted with MTBE (4 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 15:1) afforded aldol **43** (28 mg, 26 μmol, 61%) as a colorless liquid.

Major Diasteromer (43)[45]

R_f = 0.44 (*n*-hexane–EtOAc, 4:1), R_f = 0.30 (2 × *n*-hexane–EtOAc, 8:1); $[\alpha]_D^{23}$ = +22.7 (*c* 0.4, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.34 (dq, *J* = 9.1, 1.3 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 4.25 (d, *J* = 6.7 Hz, 1 H), 4.09–4.14 (m, 1 H), 3.85 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.82 (d, *J* = 9.8 Hz, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.42 (s, 3 H), 3.38–3.45 (m, 3 H), 3.33 (dd, *J* = 6.7, 1.4 Hz, 1 H), 3.23 (dd, *J* = 8.9, 7.0 Hz, 1 H), 2.78 (d, *J* = 2.7 Hz, 1 H), 2.58 (dd, *J* = 17.5, 7.9 Hz, 1 H), 2.54 (dd, *J* = 17.5, 4.6 Hz, 1 H), 2.08 (dq, *J* = 6.8, 2.7 Hz, 1 H), 1.78 (ddq, *J* = 9.8, 6.7, 0.8 Hz, 1 H), 1.64 (d, *J* = 1.4 Hz, 3 H), 1.58 (ddq, *J* = 8.4, 7.0, 1.4 Hz, 1 H), 1.50 (ddq, *J* = 7.0, 3.2, 0.8 Hz, 1 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 7.0 Hz, 3 H), 0.53–0.65 (m, 12 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 172.4, 159.1, 139.6, 130.8, 129.2, 126.8, 113.7, 82.5, 80.6, 75.7, 74.9, 73.4, 72.6, 68.1, 60.6, 55.2, 51.7, 46.4, 46.3, 41.4, 39.4, 39.3, 36.8, 29.7, 25.8 (2C), 18.3, 18.2, 16.6, 11.7, 11.5, 11.2, 9.9 (2C), 7.2, 7.1, 6.1, 5.5, –4.3, –4.9, –5.1 (2C).

MS (EI): *m/z* (%) = 921 (10), 613 (2), 482 (9), 460 (13), 308 (100).

HRMS (ESI): *m/z* calcd for $C_{57}H_{110}Na_1O_{11}Si_4$ $[M + Na]^+$: 1105.7023; found: 1105.7030.

(13*R*) Isomer (C13-*epi*-43)[45]

R_f = 0.14 (2 × *n*-hexane–EtOAc, 8:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.23 (dq, *J* = 9.6, 1.2 Hz, 1 H), 4.42 (dd-like, *J* = 11.3, 15.0 Hz, 2 H), 4.26 (d, *J* = 6.9 Hz, 1 H), 4.15 (dq, *J* = 9.7, 2.8 Hz, 1 H), 3.86 (dd, *J* = 6.5, 2.7 Hz, 1 H), 3.80 (s, 3 H), 3.80 (d, *J* = 9.9 Hz, 1 H), 3.72 (s, 3 H), 3.43 (s, 3 H), 3.39–3.47 (m, 3 H), 3.26 (dd, *J* = 6.9, 1.2 Hz, 1 H), 3.23 (dd, *J* = 8.9, 7.0 Hz, 1 H), 2.78 (d, *J* = 3.0 Hz, 1 H), 2.67 (dd, *J* = 17.5, 9.5 Hz, 1 H), 2.50 (dd, *J* = 17.5, 2.6 Hz, 1 H), 2.08 (dq-like, *J* = 6.8, 2.8 Hz, 1 H), 1.77 (dq-like, *J* = 7.0, 3.0 Hz, 1 H), 1.20 (d, *J* = 1.4 Hz, 3 H) 1.58–1.66 (m, 1 H), 1.50–1.55 (m, 1 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.91 (d, *J* = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.86 (s, 9 H), 0.86 (d, *J* = 7.0 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H) 0.84 (d, *J* = 7.0 Hz, 3 H), 0.55–0.68 (m, 12 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.02 (s, 3 H), –0.09 (s, 3 H).

HRMS (ESI): *m/z* calcd for $C_{57}H_{110}Na_1O_{11}Si_4$ $[M + Na]^+$: 1105.7023; found: 1105.7025.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7,13-Tris-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enoic Acid Methyl Ester

To a stirred solution (0 °C) of alcohol **43** (44.0 mg, 40.6 μmol) in CH_2Cl_2 (0.9 mL) was added 2,6-lutidine (24.0 μL, 206 μmol) and TBSOTf (37.0 μL, 161 μmol). After 45 min, the reaction was quenched by the addition of MeOH (10 μL). Sat. aq $NaHCO_3$ (2 mL) was added and the mixture was extracted with MTBE (4 × 10 mL). The combined organic layers were washed with sat. aq $NaHSO_4$ (10 mL), sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 30:1) afforded the ester (42.4 mg, 35.4 μmol, 87%) as a colorless liquid. R_f = 0.61 (*n*-hexane–EtOAc, 4:1); $[\alpha]_D^{23}$ = +37.0 (*c* 1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dm, *J* = 8.7 Hz, 2 H), 6.86 (dm, *J* = 8.7 Hz, 2 H), 5.33 (dd-like, *J* = 9.2, 1.2 Hz, 1 H), 4.44 (d, *J* = 11.4 Hz, 1 H), 4.37 (d, *J* = 11.4 Hz, 1 H), 4.25 (d, *J* = 6.9 Hz, 1 H), 4.19 (ddd, *J* = 8.5, 4.7, 1.8 Hz, 1 H), 3.81 (d, *J* = 10.4 Hz, 1 H), 3.80 (s, 3 H), 3.77 (dd, *J* = 8.8, 1.8 Hz, 1 H), 3.71 (s, 3 H), 3.42 (s, 3 H), 3.32–3.46 (m, 4 H), 3.22 (dd, *J* = 8.8, 6.9 Hz, 1 H), 2.82 (dd, *J* = 16.0, 8.5 Hz, 1 H), 2.38 (dd, *J* = 16.0, 4.7 Hz, 1 H), 2.09 (ddq,

J = 6.9, 6.9, 1.6 Hz, 1 H), 1.75–1.83 (m, 1 H), 1.65 (d, *J* = 1.2 Hz, 3 H), 1.55–1.61 (m, 1 H), 1.54 (ddq, *J* = 6.9, 1.9, 1.8 Hz, 1 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 8.1 Hz, 9 H), 0.93 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.87 (s, 9 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H), 0.83 (s, 9 H), 0.81 (d, *J* = 6.9 Hz, 3 H), 0.52–0.65 (m, 12 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H), –0.01 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.1, 172.4, 159.0, 139.3, 130.8, 129.5, 129.4, 126.8, 113.6, 82.4, 80.6, 75.8, 74.0, 73.7, 73.5, 72.6, 68.8, 60.6, 55.3, 51.7, 47.3, 46.8, 41.0, 39.3 (2C), 36.2, 26.3, 25.9 (2C), 25.8, 25.7, 18.3, 18.2, 17.9, 16.7, 11.7, 11.2, 10.4, 10.1, 9.8, 7.2 (2C), 6.0, 5.6, –4.1, –4.3, –4.7, –4.9, –5.1.

HRMS: *m/z* calcd for $C_{63}H_{124}Na_1O_{11}Si_5$ [M + Na]$^+$: 1219.7888; found: 1219.7916.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7,13-Tris-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-5,15-bis[(triethylsilyl)oxy]-heptadec-8-ene-1,11-diol

To a stirred solution (–78 °C) of the above-described ester (9.6 mg, 8.0 μmol) in CH_2Cl_2 (0.5 mL) was added DIBAL-H (65 μL, 1 M in heptane, 65 μmol). After 90 min, Et_2O (3 mL) was added slowly and the mixture was warmed to r.t.. H_2O (20 μL) was added, followed by aq 2 N NaOH (40 μL) after 10 min. A white solid was formed after additional 10 min of stirring. The mixture was dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (*n*-hexane–EtOAc, 15:1) afforded the desired diol (5.7 mg, 4.9 μmol, 61%, inseparable 6:1 mixture of C11 diastereomers) along with the corresponding hydroxyaldehyde (1.6 mg, 1.4 μmol, 17%) as a colorless liquid. R_f = 0.21 (*n*-hexane–EtOAc, 10:1); $[\alpha]_D^{23}$ = –11.1 (*c* 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dm, *J* = 8.7 Hz, 2 H), 6.86 (dm, *J* = 8.7 Hz, 2 H), 5.44 (dd-like, *J* = 9.3, 1.3 Hz, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H), 4.38 (d, *J* = 11.4 Hz, 1 H), 3.82–3.86 (m, 1 H), 3.82 (d, *J* = 9.8 Hz, 1 H), 3.80 (s, 3 H), 3.78 (dd, *J* = 7.1, 3.6 Hz, 1 H), 3.70–3.75 (m, 1 H), 3.63 (dd, *J* = 11.3, 4.4 Hz, 1 H), 3.49–3.53 (m, 1 H), 3.49 (d-like, *J* = 8.2 Hz, 1 H), 3.41 (dd, *J* = 8.7, 6.4 Hz, 1 H), 3.35 (d, *J* = 7.3 Hz, 1 H), 3.33 (s, 3 H), 3.20 (dd, *J* = 8.7, 7.4 Hz, 1 H), 3.13 (dd, *J* = 7.3, 1.2 Hz, 1 H), 2.35–2.42 (m, 1 H), 2.12 (br s, 1 H), 2.03 (ddq, *J* = 13.8, 6.7, 2.6 Hz, 1 H), 1.94 (br s, 1 H), 1.81 (ddq, *J* = 6.7, 3.0, 1.0 Hz, 1 H), 1.70–1.75 (m, 2 H), 1.60–1.68 (m, 1 H), 1.58 (d, *J* = 1.2 Hz, 3 H), 1.53–1.58 (m, 1 H), 0.98 (t, *J* = 7.9 Hz, 9 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.91 (s, 9 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.88–0.90 (m, 6 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.86 (d, *J* = 7.0 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.64 (q-like, *J* = 7.7 Hz, 6 H), 0.57 (q-like, *J* = 7.8 Hz, 6 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), 0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 137.3, 130.8, 130.7, 129.3, 113.7, 81.5, 81.0, 77.2, 74.3, 74.0, 73.6, 73.3, 72.7, 71.8, 71.0, 64.2, 60.3, 55.3, 41.0, 39.8, 39.0, 38.7, 38.1, 37.8, 29.7, 26.0 (2C), 25.9, 18.2, 18.1, 18.0, 13.6, 11.7, 11.6, 11.5, 11.3, 10.5, 7.3, 7.1, 6.1, 5.6, –4.1, –4.2, –4.3, –4.4, –4.7, –4.9.

HRMS (ESI): *m/z* calcd for $C_{62}H_{126}Na_1O_{10}Si_5$ [M + Na]$^+$: 1193.8095; found: 1193.8069.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7,13-Tris-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enal

To a stirred solution of (*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,-15*R*,16*S*)-2,7,13-tris{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-5,15-bis[(triethylsilyl)oxy]heptadec-8-ene-1,11-diol (5.6 mg, 4.8 μmol) in CH_2Cl_2 (0.5 mL) was added powdered molecular sieves (3 Å, 15 mg) and *N*-methylmorpholine-*N*-oxide (1.7 mg, 14.5 μmol) at r.t., followed by TPAP (0.3 mg, 0.8 μmol) after 5 min. The reaction was stirred for 4 h and then filtered through a short pad of silica (5 × 25 mm) with CH_2Cl_2 (10 mL). Evaporation of the solvent in vacuo followed by silica gel chromatography (*n*-hexane–EtOAc, 20:1) afforded the aldehyde (3.9 mg, 3.3 μmol, 70%) as a colorless liquid. R_f = 0.54 (*n*-hexane–EtOAc, 10:1); $[\alpha]_D^{23}$ = +30.5 (*c* 0.4, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.69 (d, *J* = 1.6 Hz, 1 H), 7.24 (dm, *J* = 8.5 Hz, 2 H), 6.86 (dm, *J* = 8.5 Hz, 2 H), 5.31 (d-like, *J* = 9.1 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 4.37 (d, *J* = 11.4 Hz, 1 H), 4.18 (ddd, *J* = 8.4, 4.9, 1.8 Hz, 1 H), 4.14 (dd, *J* = 6.0, 1.6 Hz, 1 H), 3.80 (s, 3 H), 3.79 (d, *J* = 8.5 Hz, 1 H), 3.76 (dd, *J* = 8.8, 1.8 Hz, 1 H), 3.44 (dd, *J* = 6.1, 1.4 Hz, 1 H), 3.41 (dd, *J* = 7.9, 1.3 Hz, 1 H), 3.38 (s, 3 H), 3.32–3.38 (m, 2 H), 3.21 (dd, *J* = 8.7, 7.0 Hz, 1 H), 2.81 (dd, *J* = 16.1, 8.4 Hz, 1 H), 2.38 (dd, *J* = 15.9, 4.9 Hz, 1 H), 2.08 (dq-like, *J* = 7.0, 1.5 Hz, 1 H), 1.79–1.88 (m, 1 H), 1.77 (dq-like, *J* = 6.8, 2.6 Hz, 1 H), 1.62 (d, *J* = 1.2 Hz, 3 H), 1.48–1.56 (m, 1 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 8.1 Hz, 9 H), 0.93 (t, *J* = 8.0 Hz, 9 H), 0.92 (s, 9 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.82 (s, 9 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.80 (d, *J* = 7.1 Hz, 3 H), 0.51–0.64 (m, 12 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H), –0.02 (s, 3 H), –0.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.2, 202.4, 159.0, 139.2, 130.8, 129.5, 129.4, 126.8, 113.6, 81.7, 80.7, 78.7, 73.9, 73.6, 73.4, 72.6, 68.8, 59.5, 55.3, 47.2, 46.9, 41.0, 39.1, 39.0, 36.2, 29.7, 26.3, 25.8, 18.2 (2C), 17.9, 16.6, 11.7, 11.6, 10.4, 10.2, 10.1, 7.2, 5.9, 5.5, –4.1, –4.3, –4.6, –4.7, –4.9, –5.0.

HRMS (ESI): *m/z* calcd for $C_{62}H_{122}Na_1O_{10}Si_5$ [M + Na]$^+$: 1189.7782; found: 1189.7765.

7,13-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-hydroxy-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enoic Acid

To a stirred solution of the heptadec-8-enal (5.0 mg, 4.3 μmol) in *t*-BuOH (0.25 mL) was added 2-methyl-2-butene (75 μL, 1.6 mmol), followed by NaH_2PO_4 (29.4 mg, 188 μmol) and $NaClO_2$ (4.4 mg, 49 μmol) in H_2O (0.2 mL). The mixture was stirred at r.t. for 3 d. The reaction was quenched by the addition of $Na_2S_2O_3$ (0.15 mL, sat. soln in pH7 buffer). EtOAc (20 mL) was added and the solution was washed with sat. aq NH_4Cl, H_2O and brine (5 mL each). The aqueous layers were reextracted with EtOAc (15 mL), the combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. Silica gel chromatography (EtOAc; then EtOAc–MeOH, 1:1) afforded the carboxylic acid (4.6 mg, 4.3 μmol, 99%) as a viscous liquid. The product was used directly in the next reaction. R_f = 0.41 (CH_2Cl_2–MeOH, 10:1)

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-7,13-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-17-hydroxy-3-methoxy-4,6,8,10,14,-16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enoic Acid (44)

To a stirred solution of the above-described heptadec-8-enoic acid (2.0 mg, 1.7 μmol) in CH_2Cl_2 (1 mL) was added pH7 buffer (0.1 mL) and DDQ (1.0 mg, 4.4 μmol) in two portions over 15 min at r.t.. After 2.5 h, the reaction was quenched with sat. aq $NaHCO_3$ (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The organic layers were washed with sat. aq $NaHCO_3$ and brine (3 mL each). The aqueous phases were treated with sat. aq NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Silica gel chromatography (CH_2Cl_2–MeOH, 10:1; then MeOH) afforded carboxylic acid **44** (0.8 mg, 0.84 μmol, 50%) as a viscous liquid. The product was used directly in the next reaction. R_f = 0.37 (CH_2Cl_2–MeOH, 10:1).

(*E*)-(3*S*,4*S*,5*S*,6*R*,7*S*,8*R*,11*S*,14*S*,15*R*,16*R*,17*S*)-8,14-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-4-methoxy-5,7,9,11,15,17-hexamethyl-6,16-bis[(triethylsilyl)oxy]oxacyclooctadec-9-ene-2,12-dione (45)

To a stirred solution of PPh_3 (1.7 mg, 6.5 μmol) in toluene (1.5 mL) was added DEAD (1.1 μL, 7 μmol). After 20 min, carboxylic acid **44** (0.7 mg, 0.7 μmol, azeotropically dried by 3 × evaporation of toluene in vacuo) was added in toluene (1.5 mL) and the reaction was stirred at r.t.. After 24 h, the mixture was evaporated. Silica gel chromatography (*n*-hexane–EtOAc, 30:1) afforded lactone **45** (0.6 mg, 0.6 μmol, 86%) as a colorless liquid. R_f = 0.44 (*n*-hexane–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.35 (dq, *J* = 8.6, 1.2 Hz, 1 H), 4.10 (d, *J* = 6.1 Hz, 1 H), 4.06 (dd, *J* = 10.0, 5.4 Hz, 1 H), 3.96 (d, *J* = 10.2 Hz, 1 H), 3.78 (dd, *J* = 6.5, 2.5 Hz, 1 H), 3.70 (d, *J* = 10.0 Hz, 1 H), 3.48 (dd, *J* = 2.2, 2.2 Hz, 1 H), 3.41 (dq, *J* = 8.5, 7.0 Hz, 1 H), 3.32 (s, 3 H), 3.29 (d, *J* = 10.3 Hz, 1 H), 2.76 (dd, *J* = 17.3, 4.3 Hz, 1 H), 2.67 (d, *J* = 10.2 Hz, 1 H), 2.54 (dd, *J* = 17.2, 5.2 Hz, 1 H), 2.34–2.43 (m, 1 H), 1.97–2.03 (m, 1 H), 1.73–1.82 (m, 2 H), 1.59 (d, *J* = 1.2 Hz, 3 H), 1.57–1.62 (m, 1 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 0.99 (t, *J* = 7.9 Hz, 9 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.98 (t, *J* = 8.0 Hz, 9 H), 0.96 (d, *J* = 7.2 Hz, 3 H), 0.92 (d, *J* = 7.2 Hz, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.85 (d, *J* = 7.1 Hz, 3 H), 0.60–0.66 (m, 12 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.03 (s, 3 H), –0.05 (s, 3 H).

HRMS (ESI): *m/z* calcd for $C_{48}H_{98}Na_1O_9Si_4$ [M + Na]$^+$: 953.6186; found: 953.6188.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Allyl Ester

A mixture of methyl ester **36** (230 mg, 0.279 mmol), bis[(dibutyl)chlorotin] oxide (77.4 mg, 0.14 mmol) and allyl alcohol (5 mL) was heated to 160 °C in a sealed tube under argon for 4 d. The excess allyl alcohol was evaporated and the residue was dissolved in MTBE and filtered through celite. The solvent was evaporated again, and the crude product was used in the next step without further purification. R_f = 0.16 (*n*-hexane–MTBE, 19:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.92 (ddt, *J* = 17.0, 10.4, 6.1 Hz, 1 H), 5.36 (ddd, *J* = 17.0, 2.9, 1.5 Hz, 1 H), 5.26 (ddd, *J* = 10.4, 2.5, 1.1 Hz, 1 H), 5.18 (dd-like, *J* = 9.7, 1.0 Hz, 1 H), 4.59 (ddddd, *J* = 19.6, 13.0, 6.0, 1.3, 1.1 Hz, 2 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.35 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 6.7 Hz, 1 H), 3.80 (s, 3 H), 3.76–3.81 (m, 1 H), 3.46 (d, *J* = 8.8 Hz, 1 H), 3.41 (s, 3 H), 3.33 (dd, *J* = 6.7, 1.0 Hz, 1 H), 3.23 (dq, *J* = 7.9, 6.0 Hz, 1 H), 2.43–2.54 (m, 1 H), 1.81 (dq-like, *J* = 10.1, 6.6 Hz, 1 H), 1.57–1.70 (m, 1 H), 1.60 (d, *J* = 1.3 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.85 (d, *J* = 6.9 Hz, 6 H), 0.56–0.65 (m, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), –0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 159.0, 136.8, 131.7, 131.6, 131.2, 129.0, 119.2, 113.7, 82.5, 81.2, 78.7, 75.5, 74.2, 70.5, 65.5, 60.5, 55.3, 39.3 (2C), 39.0, 25.8 (2C), 18.2 (2 C), 17.8, 16.7, 11.6, 11.2, 10.0, 7.2, 6.1, –4.2, –4.9, –5.0, –5.2.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-11-hydroxy-3-methoxy-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Allyl Ester

To a solution of (*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,11*S*)-2,7-bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-11-[(4-methoxybenzyl)oxy]-4,6,8,10-tetramethyl-5-[(triethylsilyl)oxy]dodec-8-enoic acid allyl ester (0.279 mmol; from the previous reaction) in CH_2Cl_2 (2.8 mL) was added pH7 buffer soln (0.28 mL) followed by DDQ (0.698 mmol, 158 mg). The resulting mixture was stirred for 1 h. Sat. aq $NaHCO_3$ solution was added. The organic layer was washed twice with sat. aq $NaHCO_3$, dried over $MgSO_4$ and evaporated. The crude product was used in the next step without further purification. R_f = 0.15 (*n*-hexane–MTBE, 4:1); $[\alpha]_D^{23}$ = –3.8 (*c* 0.52, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1 H), 5.36 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1 H), 5.26 (ddd, *J* = 10.4, 2.5, 1.1 Hz, 1 H), 5.20 (dd-like, *J* = 9.7, 1.0 Hz, 1 H), 4.59 (ddddd, *J* = 17.8, 13.0, 6.1, 1.3, 1.1 Hz, 2 H), 4.28 (d, *J* = 6.8 Hz, 1 H), 3.79 (d, *J* = 10.2 Hz, 1 H), 3.59 (qui-like, *J* = 6.4 Hz, 1 H), 3.46 (d, *J* = 8.8 Hz, 1 H), 3.42 (s, 3 H), 3.33 (dd, *J* = 6.7, 1.1 Hz, 1 H), 2.41 (ddq, *J* = 9.7, 6.7, 6.7 Hz, 1 H), 1.80 (dq-like, *J* = 10.0, 6.6 Hz, 1 H), 1.58–1.68 (m, 1 H), 1.61 (d, *J* = 1.3 Hz, 3 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.96 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.85 (d, *J* = 6.9 Hz, 6 H), 0.58–0.66 (m, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), –0.04 (s, 3 H), OH proton not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 137.5, 131.6, 131.0, 119.2, 82.6, 81.1, 75.6, 74.3, 71.6, 65.6, 60.5, 40.0, 39.5, 39.0, 25.8 (2C), 21.3, 18.2 (2C), 15.6, 11.7, 11.2, 10.1, 7.2, 6.2, –4.3, –4.9, –5.0, –5.2

HRMS (ESI): *m/z* calcd for $C_{38}H_{78}NaO_7Si_3$ [M + Na]$^+$: 753.4953; found: 753.4970.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-4,6,8,10-tetramethyl-11-oxo-5-[(triethylsilyl)oxy]dodec-8-enoic Acid Allyl Ester (46)

To a mixture of the above crude product (0.279 mmol), powdered molecular sieves (4 Å, 140 mg) and NMO (82.0 mg, 0.698 mmol) in CH_2Cl_2 (2.8 mL), was added TPAP (2.0 mg, 56 μmol). After 15 min, no starting material was detectable. The solvent was removed and the crude product was purified by chromatography (*n*-hexane–MTBE, 9:1) to afford the methyl ketone **46** (187 mg, 0.257 mmol, 92% over 3 steps) as a colorless oil. R_f = 0.22 (*n*-hexane–MTBE, 9:1); $[\alpha]_D^{23}$ = +51.3 (*c* 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (ddt, *J* = 17.1, 10.4, 6.0 Hz, 1 H), 5.36 (ddd, *J* = 17.1, 2.9, 1.4 Hz, 1 H), 5.23–5.28 (m, 2 H), 4.59 (ddddd, *J* = 19.0, 12.9, 6.0, 1.3, 1.2 Hz, 2 H), 4.27 (d, *J* = 6.9 Hz, 1 H), 3.81 (d, *J* = 9.9 Hz, 1 H), 3.38–3.47 (m, 2 H), 3.43 (s, 3 H), 3.31 (dd, *J* = 6.8, 1.2 Hz, 1 H), 2.11 (s, 3 H), 1.78 (dq-like, *J* = 9.7, 6.9 Hz, 1 H), 1.57–1.72 (m, 1 H), 1.68 (d, *J* = 1.3 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.86 (s, 9 H), 0.85 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H), 0.49–0.66 (m, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9, 171.6, 139.9, 131.5, 127.4, 119.3, 82.6, 80.7, 75.7, 74.1, 65.6, 60.6, 46.7, 39.7, 39.1, 28.2, 25.8, 25.7, 18.2 (2 C), 16.1, 11.6, 11.2, 9.9, 7.2, 6.1, –4.3, –4.9, –5.0, –5.1.

HRMS (ESI): *m/z* calcd for $C_{38}H_{76}NaO_7Si_3$ [M + Na]$^+$: 751.4797; found: 751.4781.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-13-hydroxy-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enoic Acid Allyl Ester (47)

A 25-mL flask was charged with powdered molecular sieves (4 Å, 257 mg) and heated while being evacuated. The flask was flushed with argon and after cooling to r.t., (*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*)-2,7-bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-4,6,8,10-tetramethyl-11-oxo-5-[(triethylsilyl)oxy]dodec-8-enoic acid allyl ester (**46**, 187 mg, 0.257 mmol) in THF (9 mL) was added. The mixture was cooled to –78 °C and KHMDS (0.36 mmol, 0.72 mL, 0.5 M solution in toluene) was added dropwise. Aldehyde **39** (0.310 mmol, 118 mg) was dissolved in THF (1 mL), dried with a small piece of CaH_2 for 1 h and then added to the reaction mixture. After 5 min, the reaction was quenched by the addition of pH7 buffer solution (10 mL). The aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic phase was washed with brine, dried over

$MgSO_4$ and evaporated. The crude product was purified by chromatography (*n*-hexane–MTBE, 85:15) to afford the aldol product **47** (153 mg, 0.151 mmol, 59%) as a colorless oil. R_f = 0.2 (*n*-hexane–MTBE, 85:15); $[\alpha]_D^{23}$ = +21.6 (*c* 0.12, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dm, *J* = 8.7 Hz, 2 H), 6.87 (dm, *J* = 8.7 Hz, 2 H), 5.91 (ddt, *J* = 17.2, 10.4, 6.1 Hz, 1 H), 5.36 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1 H), 5.32–5.37 (dm, *J* = 1.3 Hz, 1 H), 5.26 (ddd, *J* = 10.4, 2.5, 1.1 Hz, 1 H), 4.59 (ddddd, *J* = 18.2, 12.8, 5.9, 1.2, 1.2 Hz, 2 H), 4.39–4.46 (m, 2 H), 4.25 (d, *J* = 6.8 Hz, 1 H), 4.11 (ddd, *J* = 7.4, 4.7, 3.1 Hz, 1 H), 3.84 (dd, *J* = 6.7, 2.5 Hz, 1 H), 3.79–3.83 (m, 1 H), 3.80 (s, 3 H), 3.38–3.44 (m, 3 H), 3.41 (s, 3 H), 3.32 (dd, *J* = 6.8, 1.3 Hz, 1 H), 3.23 (dd, *J* = 8.8, 6.9 Hz, 1 H), 2.53–2.58 (m, 2 H), 2.08 (dq, *J* = 6.8, 2.5 Hz, 1 H), 1.73–1.79 (m, 1 H), 1.50–1.70 (m, 2 H), 1.64 (d, *J* = 1.1 Hz, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.83–0.91 (m, 12 H), 0.53–0.64 (m, 12 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), –0.05 (s, 3 H), OH proton not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 171.6, 159.1, 139.6, 131.6, 130.7, 129.2 (2 C), 126.8, 119.3, 113.7, 82.5, 80.5, 77.2, 76.0, 74.9, 74.0, 73.4, 72.7 (2 C), 72.6, 68.1, 65.6, 60.7, 55.2, 46.4, 46.3, 41.4, 39.5, 39.4, 37.2, 36.7, 25.8 (2 C), 18.2 (2 C), 16.7, 11.7, 11.5, 11.2 (2C), 9.9, 9.8, 7.2, 7.1, 6.0, 5.5, –4.3, –4.9, –5.0, –5.1.

HRMS (ESI): *m/z* calcd for $C_{59}H_{112}NaO_{11}Si_4$ $[M + Na]^+$: 1131.7179; found: 1131.7181.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7,13-Tris-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methoxy-17-[(4-methoxybenzyl)oxy]-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]heptadec-8-enoic Acid Allyl Ester

To a solution of **47** (153 mg, 0.138 mmol) in CH_2Cl_2 (6.9 mL) was added 2,6-lutidine (0.16 mL, 1.38 mmol) at 0 °C. TBSOTf (0.16 mL, 0.69 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C. The organic phase was washed with 1 M $NaHSO_4$ solution (3 × 10 mL) and dried over $MgSO_4$. After removal of the solvent, the crude product was purified by chromatography (*n*-hexane–MTBE, 19:1) to afford the protected product (147 mg, 0.120 mmol, 87%) as colorless oil. R_f = 0.18 (*n*-hexane–MTBE, 19:1); $[\alpha]_D^{23}$ = +37.4 (*c* 0.305, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dm, *J* = 8.8 Hz, 2 H), 6.85 (dm, *J* = 8.8 Hz, 2 H), 5.92 (ddt, *J* = 17.1, 10.4, 6.1 Hz, 1 H), 5.36 (ddd, *J* = 17.1, 2.9, 1.4 Hz, 1 H), 5.30–5.36 (dm, *J* = 1.3 Hz, 1 H), 5.26 (ddd, *J* = 10.4, 2.4, 1.1 Hz, 1 H), 4.59 (ddddd, *J* = 20.3, 13.0, 6.1, 1.3, 1.1 Hz, 2 H), 4.44 (d, *J* = 11.4 Hz, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 4.25 (d, *J* = 6.8 Hz, 1 H), 4.18 (ddd, *J* = 8.4, 4.6, 1.6 Hz, 1 H), 3.81 (d, *J* = 9.4 Hz, 1 H), 3.80 (s, 3 H), 3.76 (dd, *J* = 8.9, 1.6 Hz, 1 H), 3.29–3.44 (m, 3 H), 3.41 (s, 3 H), 3.21 (dd, *J* = 8.5, 7.3 Hz, 1 H), 2.83 (dd, *J* = 15.9, 8.6 Hz, 1 H), 2.37 (dd, *J* = 15.9, 4.6 Hz, 1 H), 2.09 (dq-like, *J* = 6.9, 1.4 Hz, 1 H), 1.72–1.81 (m, 1 H), 1.50–1.70 (m, 3 H), 1.65 (d, *J* = 1.2 Hz, 3 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 0.93 (t, *J* = 8.0 Hz, 9 H), 0.79–0.92 (m, 12 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.82 (s, 9 H), 0.52–0.63 (m, 12 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), 0.01 (s, 3 H), –0.01 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 171.6, 159.1, 139.2, 131.6, 130.8, 129.5, 126.8, 119.3, 113.6, 82.5, 80.6, 76.0, 74.0, 73.7, 73.5, 72.7, 68.8, 65.5, 60.7, 55.3, 47.3, 46.8, 41.0, 39.5, 39.4, 36.2, 25.9, 25.8 (2 C), 18.2 (2 C), 17.9, 16.7, 11.7, 11.2, 10.4, 10.1, 9.8, 7.2, 7.1, 6.0, 5.6, –4.1, –4.2, –4.7, –5.0, –4.9, –5.1.

HRMS (ESI): *m/z* calcd for $C_{65}H_{126}NaO_{11}Si_5$ $[M + Na]^+$: 1245.8044; found: 1245.8038.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7,13-Tris-{[*tert*-butyl(dimethyl)silyl]oxy}-17-hydroxy-3-methoxy-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]-heptadec-8-enoic Acid Allyl Ester

To a solution of the previous PMB ether (118 mg, 96 μmol) in CH_2Cl_2 (5 mL) was added pH7 buffer solution (0.5 mL) followed by DDQ (54 mg, 0.24 mmol). The resulting mixture was stirred for 1 h. Sat. aq $NaHCO_3$ solution (5 mL) was added. The organic layer was diluted with CH_2Cl_2 (15 mL) and washed with sat. aq $NaHCO_3$ solution (3 × 10 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography (*n*-hexane–MTBE, 85:15) to afford the corresponding hydroxyl ester (91 mg, 83 μmol, 86%) as a colorless oil. R_f = 0.34 (*n*-hexane–MTBE, 85:15); $[\alpha]_D^{23}$ = +51.5 (*c* 0.65, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1 H), 5.36 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1 H), 5.31 (dd-like, *J* = 9.5, 1.1 Hz, 1 H), 5.26 (ddd, *J* = 10.4, 2.5, 1.1 Hz, 1 H), 4.59 (ddddd, *J* = 19.6, 12.8, 5.9, 1.3, 1.1 Hz, 2 H), 4.25 (d, *J* = 6.8 Hz, 1 H), 4.13 (qui-like, *J* = 3.8 Hz, 1 H), 3.83 (dd, *J* = 7.0, 3.3 Hz, 1 H), 3.81 (d, *J* = 9.5 Hz, 1 H), 3.55 (d, *J* = 6.7 Hz, 1 H), 3.54 (d, *J* = 6.1 Hz, 1 H), 3.37–3.48 (m, 3 H), 3.43 (s, 3 H), 3.33 (dd, *J* = 6.8, 1.3 Hz, 1 H), 2.86 (dd, *J* = 15.3, 7.8 Hz, 1 H), 2.41 (dd, *J* = 15.3, 4.2 Hz, 1 H), 1.92 (dq-like, *J* = 6.5, 3.2 Hz, 1 H), 1.77 (dq-like, *J* = 9.4, 6.8 Hz, 1 H), 1.55–1.70 (m, 2 H), 1.66 (d, *J* = 1.1 Hz, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 0.97 (t, *J* = 8.0 Hz, 9 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.81–0.93 (m, 12 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.53–0.66 (m, 12 H), 0.08 (s, 3 H), 0.07 (s, 6 H), 0.04 (s, 3 H), 0.03 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.1 171.6, 139.4, 131.6, 126.7, 119.3, 82.5, 80.6, 76.0, 74.0, 73.9, 69.7, 66.1, 65.6, 60.7, 47.1, 47.0, 40.5, 39.5, 39.4, 39.1, 25.9, 25.8 (2 C), 18.2 (2 C), 18.0, 16.6, 11.7, 11.2, 11.0, 10.4, 9.8, 7.2, 7.1, 6.1, 5.6, –4.0, –4.2, –4.6, –4.9, –5.0, –5.1.

HRMS (ESI): *m/z* calcd for $C_{57}H_{118}NaO_{10}Si_5$ $[M + Na]^+$: 1125.7469; found: 1125.7487.

(*E*)-(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,10*S*,13*S*,14*R*,15*R*,16*S*)-2,7,13-Tris-{[*tert*-butyl(dimethyl)silyl]oxy}-17-hydroxy-3-methoxy-4,6,8,10,14,16-hexamethyl-11-oxo-5,15-bis[(triethylsilyl)oxy]-heptadec-8-enoic Acid

To a solution of the previous allyl ester (63.5 mg, 57.5 μmol) and $Pd(PPh_3)_2Cl_2$ (4.0 mg, 5.7 μmol) in CH_2Cl_2 (2.3 mL) was added Bu_3SnH (230 μmol, 62 μl). After 10 min, the reaction was judged complete by TLC. The solvent was removed and the residue was purified by chromatography (gradient elution: *n*-hexane, then *n*-hexane–MTBE, 2:1) to afford the *seco*-acid (59.3 mg, 55.8 μmol, 97%) as a light-yellow foam. R_f = 0.16 (*n*-hexane–MTBE, 4:1)

^{1}H NMR (400 MHz, CD_3OD): δ = 5.38 (br d, *J* = 9.0 Hz, 1 H), 4.21–4.28 (m, 2 H), 3.88 (d, *J* = 9.8 Hz, 1 H), 3.80 (dd, *J* = 8.4, 2.0 Hz, 1 H), 3.46–3.57 (m, 4 H), 3.45 (s, 3 H), 3.40 (dd, *J* = 10.0, 8.2 Hz, 1 H), 2.98 (dd, *J* = 16.2, 8.3 Hz, 1 H), 2.47 (dd, *J* = 16.2, 4.5 Hz, 1 H), 1.92–2.00 (m, 1 H), 1.79–1.89 (m, 2 H), 1.71 (br s, 3 H), 1.58–1.69 (m, 2 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 0.99 (t, *J* = 8.0 Hz, 18 H), 0.85–0.97 (m, 12 H), 0.94 (s, 9 H), 0.90 (2 s, 18 H), 0.60–0.69 (m, 12 H), 0.10 (s, 6 H), 0.10 (s, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H), –0.01 (s, 3 H).

HRMS (ESI): *m/z* calcd for $C_{54}H_{113}O_{10}Si_5$ $[M - H]^-$ 1061.7180; found: 1061.7147.

(*E*)-(3*S*,4*S*,5*S*,6*R*,7*S*,8*R*,11*S*,14*S*,15*R*,16*R*,17*S*)-3,8,14-Tris{[*tert*-butyl(dimethyl)silyl]oxy}-4-methoxy-5,7,9,11,15,17-hexamethyl-6,16-bis[(triethylsilyl)oxy]oxacyclooctadec-9-ene-2,12-dione (48)

To a solution of PPh_3 (109 mg, 0.42 mmol) in toluene (2.1 mL) was added DEAD (67 μL, 0.42 mmol). The solution was stirred for 20

min and then a solution of the previous *seco*-acid (45 mg, 42 μmol) in toluene (2.1 mL) was added. After a few minutes, the clear solution became turbid and no acid was detectable by TLC. The solvent was evaporated and the crude product was purified by chromatography (*n*-hexane–MTBE, 19:1) to afford macrolactone **48** (31.7 mg, 30.2 μmol, 72%) as inseparable mixture of two diastereomers (4:1). R_f = 0.52 (*n*-hexane–MTBE, 9:1).

^{1}H NMR (400 MHz, toluene-d_8, 360 K, major isomer): δ = 5.49 (dq, *J* = 9.2, 1.3 Hz, 1 H), 4.44 (d, *J* = 3.4 Hz, 1 H), 4.34 (ddq, *J* = 7.0, 5.8, 3.9 Hz, 1 H), 4.15 (dd, *J* = 11.2, 7.5 Hz, 1 H), 4.07 (dd, *J* = 11.2, 3.4 Hz, 1 H), 4.01 (d, *J* = 10.0 Hz, 1 H), 3.88 (t-like, *J* = 4.6 Hz, 1 H), 3.80 (dd, *J* = 4.3, 1.6 Hz, 1 H), 3.67 (dd, *J* = 6.6, 3.4 Hz, 1 H), 3.47 (s, 3 H), 3.39 (dq, *J* = 9.1, 6.9 Hz, 1 H), 2.84 (dd, *J* = 17.1, 3.9 Hz, 1 H), 2.76 (dd, *J* = 17.1, 5.8 Hz, 1 H), 2.23 (ddq, *J* = 11.0, 7.4, 3.6 Hz, 1 H), 1.99–2.12 (m, 3 H), 1.76 (d-like, *J* = 1.3 Hz, 3 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.23 (d, *J* = 6.8 Hz, 3 H), 1.17 (d, *J* = 7.2 Hz, 3 H), 1.12 (t, *J* = 8.0 Hz, 9 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.08 (t, *J* = 8.0 Hz, 9 H), 1.06 (s, 9 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.00 (s, 9 H), 0.99 (s, 9 H), 0.70–0.83 (m, 12 H), 0.30 (s, 3 H), 0.26 (s, 3 H), 0.23 (s, 3 H), 0.21 (s, 3 H), 0.17 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 172.3, 141.2, 126.5, 83.1, 81.3, 74.7, 73.4, 72.7, 71.4, 67.3, 60.2, 46.8, 46.0, 42.9 (2C), 41.1, 36.9, 26.2, 26.0, 25.8, 18.6, 18.3, 18.2, 15.5, 12.9, 12.8, 11.7, 11.4, 10.7, 7.2, 7.1, 5.8, 5.7, –4.2 (3C), –4.3, –4.9 (2C).

HRMS (ESI): *m/z* calcd for $C_{54}H_{112}NaO_9Si_5$ $[M + Na]^+$: 1067.7055; found: 1067.7177.

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References

(1) (a) Nettles, J. H.; Li, H.; Cornett, B.; Krahn, J. M.; Snyder, J. P.; Downing, K. H. *Science* **2004**, *305*, 866. (b) Altmann, K. H. *Org. Biomol. Chem.* **2004**, 2137.
(2) (a) Kalesse, M. *ChemBioChem* **2000**, *1*, 171. (b) Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193.
(3) Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981.
(4) (a) Shim, J. S.; Kwon, H. J. *Expert Opin. Ther. Targets* **2004**, *8*, 653. (b) Darvas, F.; Dorman, G.; Krajcsi, P.; Puskas, L. G.; Kovari, Z.; Lorincz, Z.; Urge, L. *Curr. Med. Chem.* **2004**, *11*, 3119.
(5) For an application to total synthesis in which all-syn stereotriades are generated, see: Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
(6) For a recent example of this strategy in the total synthesis of discodermolide, see: Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150.
(7) (a) Fischer, M.-R.; Kirschning, A.; Michel, T.; Schaumann, E. *Angew. Chem. Int. Ed.* **1994**, *33*, 217; *Angew. Chem.* **1994**, *106*, 220. (b) Smith, A. B. III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.
(8) (a) Marshall, J. A.; Fitzgerald, R. N. *J. Org. Chem.* **1999**, *64*, 4477. (b) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.
(9) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*, 2nd Suppl., Chap. 27; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **2000**.
(10) For a recent example of this strategy in the total synthesis of oleandolide, see: Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229.
(11) (a) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410. (b) Bode, J. W.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 2082; *Angew. Chem.* **2001**, *113*, 2128. (c) Brown, A. V.; Taylor, R. E. *Chemtracts* **2003**, *16*, 254.
(12) Hoffmann, H. M. R.; Hartung, I. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 1934; *Angew. Chem.* **2004**, *116*, 1968.
(13) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J.-M. *Org. Lett.* **2003**, *5*, 3159.
(14) First review covering the vinylogous principle: (a) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1. For excellent reviews covering the development until 2000, see: (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (d) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109. For vinylogous Mannich reactions see: (e) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem.*; **1998**, 110, 1096; Angew. Chem. Int. Ed.; **1998**, *37*: 1044. (f) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, 3221. For a review covering the vinylogous aldol reaction between 2000 and 2003 see: (g) Kalesse, M. In *Topics in Current Chemistry*, Vol. 244; Mulzer, J. H., Ed.; Springer Verlag: Heidelberg, **2004**, 43.
(15) For catalytic asymmetric vinylogous Mukaiyama aldol reactions via enolate activation, see: (a) Bluet, G.; Campagne, J.-M. *Tetrahedron Lett.* **1999**, *40*, 221. (b) Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, *66*, 4293.
(16) (a) Brennan, C. J.; Campagne, J.-M. *Tetrahedron Lett.* **2001**, *42*, 5195. (b) Bluet, G.; Campagne, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5507. (c) Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807.
(17) (a) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800. (b) Denmark, S. E.; Heemstra, J. R. Jr. *Synlett* **2004**, 2411.
(18) For pioneering contributions towards the catalytic asymmetric vinylogous aldol reaction, see: (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360. (c) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013. (d) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 3114; *Angew. Chem.* **1998**, *110*, 3312. (e) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (f) de Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3187. (g) Soriente, A.; de Rosa, M.; Stanzione, M.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2001**, *12*, 959. (h) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837.
(19) (a) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connel, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (c) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (d) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (e) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654. (f) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 603; *Angew. Chem.* **2001**, *113*, 623. (g) Paterson, I.; Collet, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187. (h) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem. Int. Ed.* **2000**, *39*, 377. (i) Braun, M.; Waldmüller, D. *Synthesis* **1989**, 856. (j) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (k) Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200. (l) Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H.

Synlett **2004**, 732. (m) Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604.

(20) (a) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4364; *Angew. Chem.* **2000**, *112*, 4535. (b) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885. (c) Christmann, M.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1269.

(21) Hassfeld, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, 3561.

(22) Hassfeld, J.; Kalesse, M. *unpublished results.*

(23) Bergquist, C.; Bridgewater, B. M.; Harlan, C. J.; Norton, J. R.; Friesner, R. A.; Parkin, G. *J. Am. Chem. Soc.* **2000**, *122*, 10581.

(24) Hassfeld, J.; Kalesse, M. *Tetrahedron Lett.* **2002**, *43*, 5093.

(25) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229.

(26) For a related approach to the C1–C11 segment of the tedanolides, see: Hassfeld, J.; Kalesse, M. *Synlett* **2002**, 2007.

(27) Tedanolide was isolated from *Tedania ignis*: Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

(28) 13-Deoxytedanolide was isolated from *Mycale adhaerens*: Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971.

(29) (a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385. (b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (c) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (d) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361. (e) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (f) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (g) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663. (h) Matsushima, T.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780. (i) Smith, A. B. III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. (j) Zheng, B.-Z.; Maeda, H.; Mori, M.; Kusaka, S.-i.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J. *Chem. Pharm. Bull.* **1999**, *47*, 1288. (k) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (l) Matsushima, T.; Nakajima, N.; Zheng, B.-Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855. (m) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.-i.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441. (n) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 1761. (o) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (p) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (q) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 6001. (r) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223. (s) Matsui, K.; Zheng, B.-Z.; Kusaka, S.-I.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. *Eur. J. Org. Chem.* **2001**, 3615. (t) Hearn, B. R.; Ciavarri, J. P.; Taylor, R. E. *Org. Lett.* **2002**, *4*, 2953. (u) Roush, W. R.; Newcom, J. S. *Org. Lett.* **2002**, *4*, 4739.

(30) (a) Smith, A. B. III; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (b) Smith, A. B. III; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12042.

(31) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(32) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.

(33) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447.

(34) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3461.

(35) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(36) Walkup, R. D.; Kahl, J. D.; Kane, R. R. *J. Org. Chem.* **1998**, *63*, 9113.

(37) Shimizu, S.; Nakamura, S.-i.; Nakada, M.; Shibasaki, M. *Tetrahedron* **1996**, *52*, 13363.

(38) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

(39) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Van Nieuwenhze, M. S.; Gustin, D. J.; Dilley, G. J.; Lane, G. C.; Scheidt, K. A.; Smith, W. J. III *J. Org. Chem.* **2002**, *67*, 4284.

(40) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(41) Nicolaou, K. C.; Li, J.; Zenke, G. *Helv. Chim. Acta* **2000**, *83*, 1977.

(42) For a representative protocol, see: Li, K. W.; Wu, J.; Xing, W.; Simon, J. *J. Am. Chem. Soc.* **1996**, *118*, 7237.

(43) (a) Baumhof, P.; Mazitschek, R.; Giannis, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3672; *Angew. Chem.* **2001**, *113*, 3784. (b) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.

(44) De la Torre, B. G.; Torres, J. L.; Bardaji, E.; Clapés, P.; Xaus, N.; Jorba, X.; Calvet, S.; Albericio, F.; Valencia, G. *J. Chem. Soc., Chem. Commun.* **1990**, 965.

(45) The C13 stereochemical assignment is based on analysis of the C12 ^{1}H NMR signals according to Ref. 39.