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Two-directional total synthesis of efomycine M and formal total synthesis of elaiolide

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Abstract

The anti-inflammatory agent efomycine M (**1**) has been synthesized from macrodilactone **38** and vinyliodide **42** by a two-directional total synthesis in 17 steps over the longest linear sequence with an overall yield of 7%. The C_2-symmetric macrodiolide **38** has been prepared by Yamaguchi macrolactonization of *seco*-acid **26**. The central stereopentad of **1** was obtained by a highly efficient *anti*-aldol reaction followed by a diastereoselective ketone reduction. Additionally, we have completed a formal total synthesis of elaiolide (**3**) by converting macrodiolide **37** into Paterson's methylketone **13**.

1. Introduction

Efomycines are a newly disclosed family of small molecules that structurally mimic the binding site of selectin ligands.[1] These *E*- and *P*-selectin is expressed in inflammatory skin diseases such as psoriasis, atopic dermatitis or contact dermatitis and mediates T cell rolling along blood vessels by their interaction with T cell epitopes, which are represented by the sialyl Lewis^x (sLe^x) tetrasaccharide.[2] This process results in the infiltration of T cells into the skin. The blockade of selectin ligands by small-molecule antagonists is a new therapeutic approach in dermatology to prevent the rolling of T cells and therefore to prevent the occurrence of skin inflammation.

The most promising representative of this family, efomycine M (**1**), is obtained semi-synthetically from naturally occurring elaiophylin (**2**) by a base-catalyzed β-elimination of the L-2-deoxyfucose moiety (Scheme 1).[3] Elaiophylin (**2**) was originally isolated from *Streptomyces melanosporus* in 1959 and one year later re-isolated from a related microorganism.[4] The structure of **2** was elucidated by chemical degradation,[5] spectroscopic methods[6] and by X-ray crystallographic analysis.[7] The natural product **2** itself has received much attention during the last years due to its antibiotic properties against Gram-positive bacteria.[4a] Furthermore, compound **2** was shown to possess anthelmintic activity against *Trichonomonas vaginalis*,[4a] apoptosis inducing activities,[8] immunosuppressive activity[9] and plant growth inhibitory activity.[10]

The demanding structure of elaiophylin (**2**) initiated several synthetic approaches[11] and total syntheses. Kinoshita et al. completed the only total synthesis of the natural product **2** in 1986.[12] One year before, Seebach et al. described the first synthesis of 11,11′-di-*O*-methylelaiophylidene (**4**), the dimethyl aglycon of **2**.[13] Evans and Fitch[14] and Paterson et al.[15] reported the syntheses of elaiolide (**3**), the elaiophylin agylcon.

Before we started, there was no total synthesis of efomycine M (**1**), which was surprising in view of its interesting structure and promising biological profile. We are now pleased to report a route that was efficient enough to provide sufficient amounts of **1**. Furthermore, it appears suitable for the preparation of analogues for future SAR studies, which are indicated by the fact that von Bonin et al. recently strongly disputed the postulated mode of action of **1** via a pan-selectin antagonism, although they fully confirmed the anti-inflammatory profile of compound.[16]

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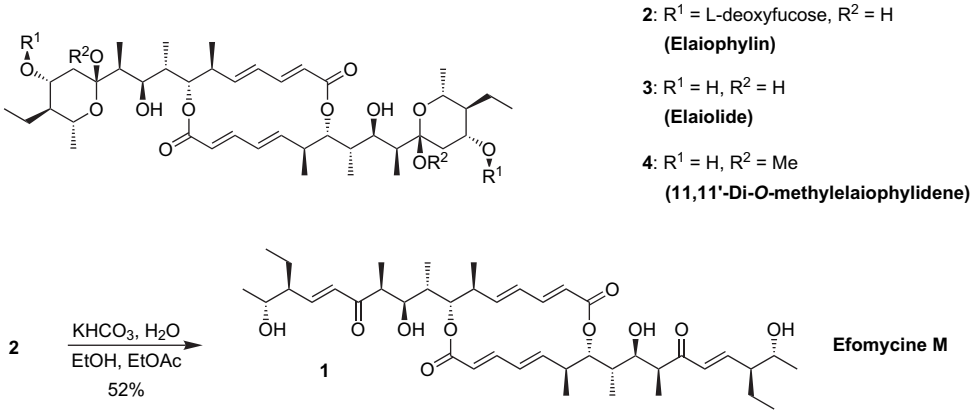


Scheme 1. Semi-synthetic origin of efomycine M (**1**) from elaiophylin (**2**) by base-catalyzed β-elimination.

2. Retrosynthetic considerations

The structure of efomycine M (**1**) features a 16-membered macrodiolide core, a labile α,β-enone moiety and seven stereogenic centres. The characteristic C_2-symmetry of **1** inspired us to aim for a two-directional strategy (Scheme 2).[17] The C11–C12 bond should be formed at a late stage of the synthesis by the nucleophilic attack of an organometallic species **5**, which should be obtained from methyl (*R*)-3-hydroxybutyrate **7**, to bis-aldehyde **6**. The central macrodiolide core of **6** should come from the dimerization of the corresponding *seco*-acid **8**, which would be formed from aldehyde **9** and phosphonate **10**.

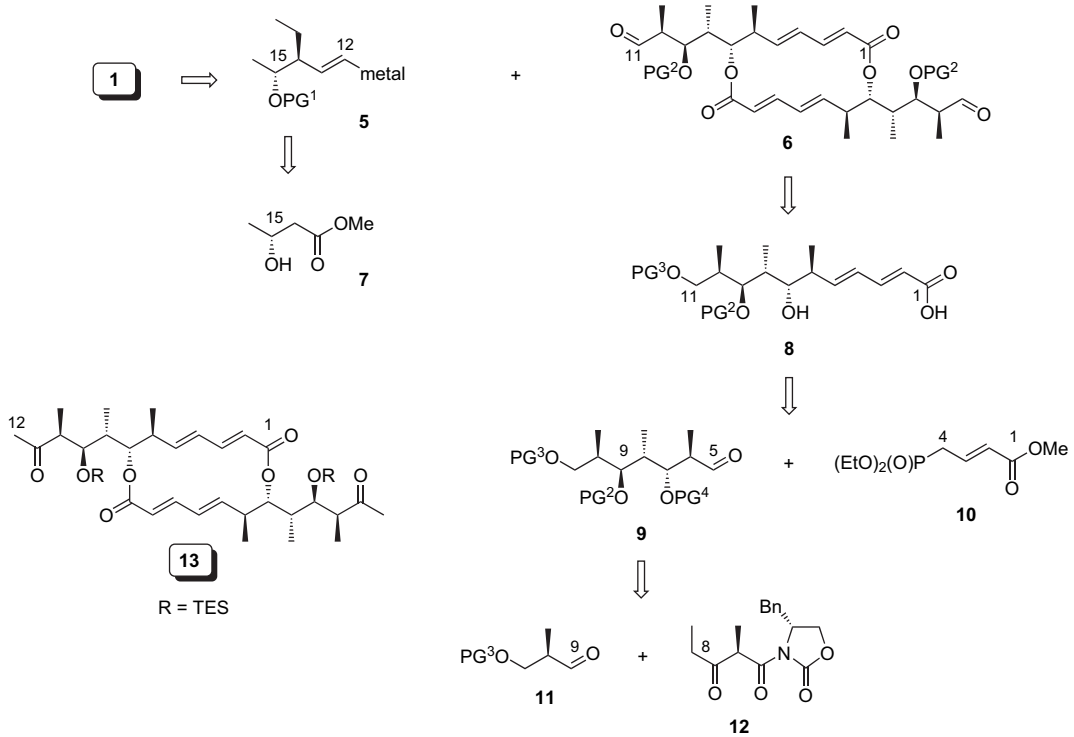
The central stereopentad **9** should be available by an aldol reaction between β-ketoimide **12** and aldehyde **11** followed by a diastereoselective ketone reduction.

We also performed a formal total synthesis of elaiolide (**3**) from bis-aldehyde **6** by a sequence of double Wittig olefination and double Wacker oxidation to generate bis-methylketone **13**, which has previously been elaborated into elaiolide (**3**) by the Paterson group.[15a]

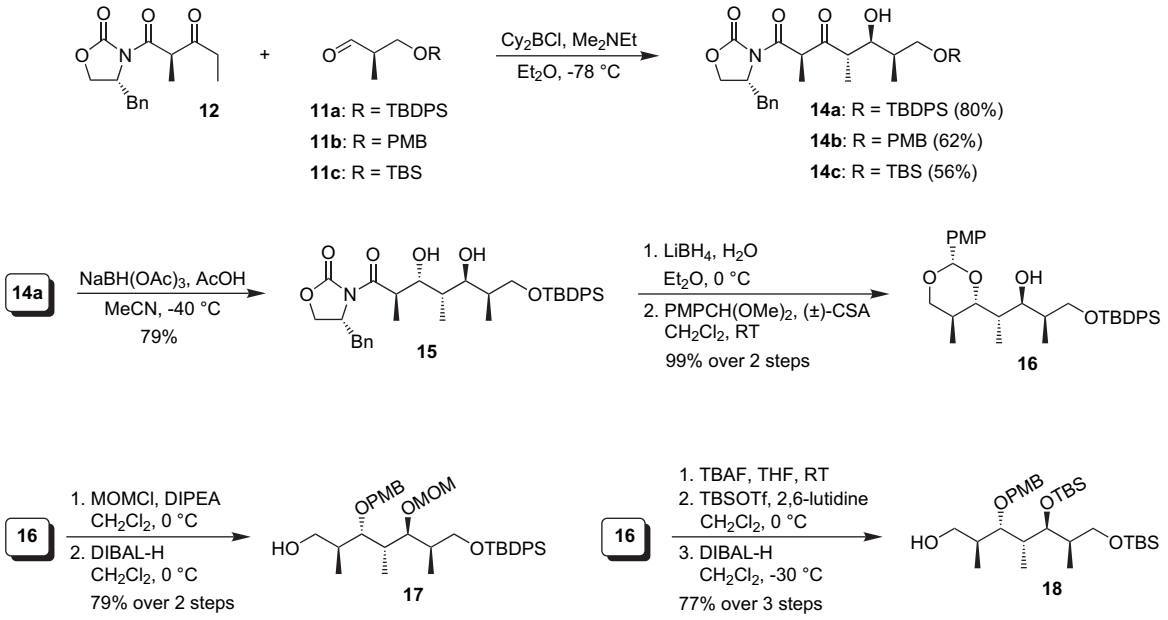
3. Results and discussion

3.1. First generation synthesis of stereopentads 17 and 18 and preparations of seco-acids 25 and 26

Our synthesis started with an *anti*-selective aldol reaction between β-ketoimide **12** and aldehyde **11a**, which gave β-hydroxyketone **14a** in 80% yield and a diastereomeric ratio of 95:5 as determined by HPLC (Scheme 3).[18] The TBDPS



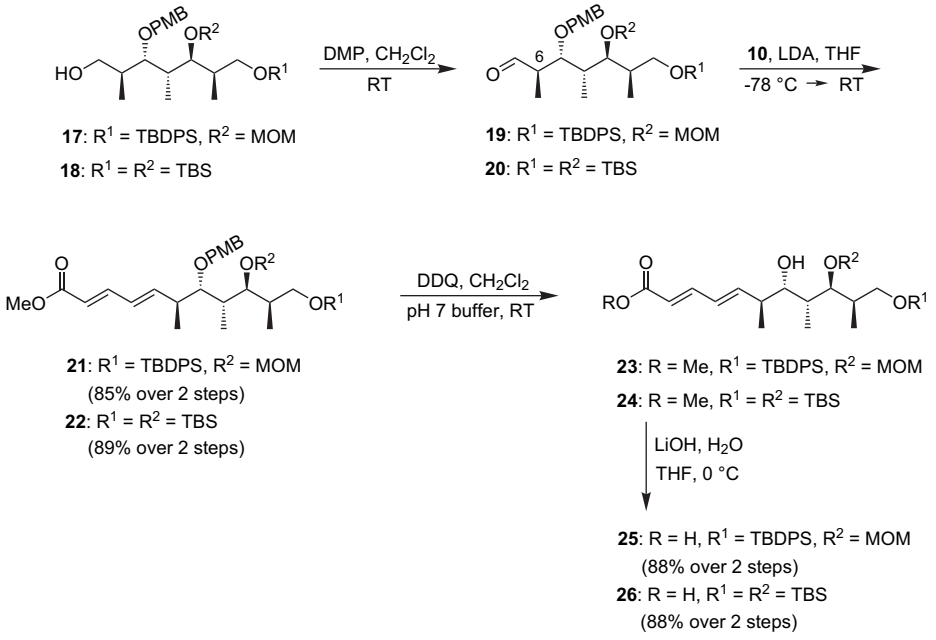
Scheme 2. Retrosynthetic anaylsis of efomycine M (**1**) and of elaiolide precursors **13**. PG=protecting group.



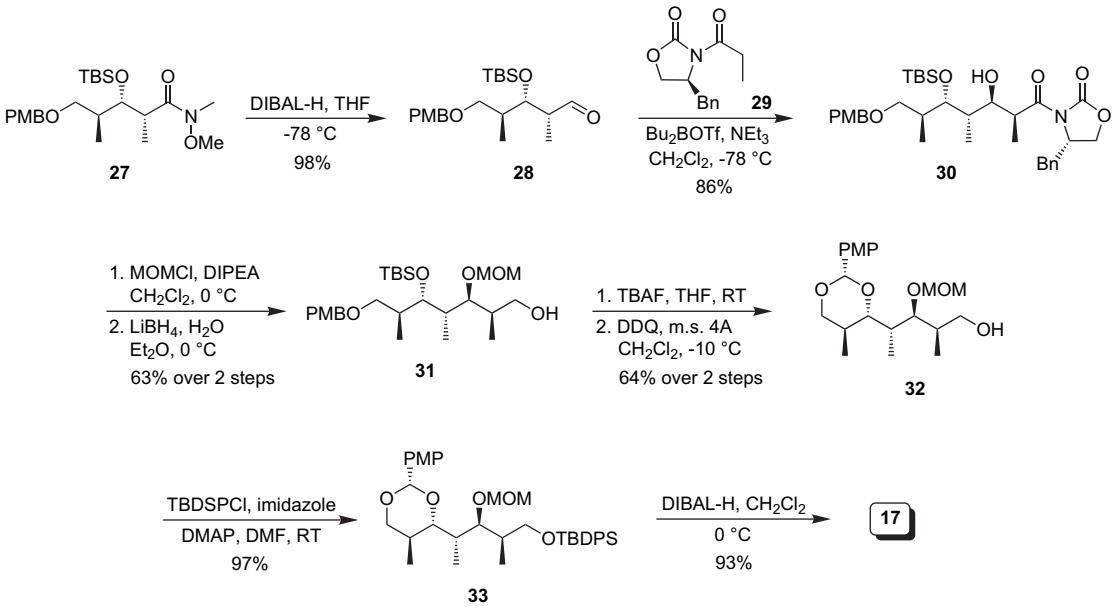
Scheme 3. Preparation of stereopentads **17** and **18**.

protecting group gave the highest yields in comparison to PMB (**14b**: 62%) and TBS (**14c**: 56%). β-Hydroxyketone **14a** was selectively reduced to the *anti*-1,3-diol **15** with $NaBH(OAc)_3$ (79%, dr 96:4).[19] The reductive removal of the auxiliary with $LiBH_4$ furnished a triol, which was protected regioselectively as PMP-acetal **16** with $PMPCH(OMe)_2$ (99% over two steps). For the protection of the free 9-OH function, we examined both an MOM and a TBS group. The MOM group was introduced under standard conditions with MOMCl/DIPEA. Before introducing the 9-OTBS group, the primary TBDPS group was removed and the resulting diol was di-TBS-protected (90% over two steps). Finally, both PMP-acetals were reductively opened with DIBAL-H to give fully protected stereopentads **17** (94%) and **18** (85%, based on recovered starting material).

The primary alcohols **17** and **18** were oxidized with Dess–Martin periodinane as the corresponding Swern oxidation resulted in a partial epimerization of the *C*6-methyl group of aldehydes **19** and **20** (Scheme 4). The (2*E*,4*E*)-diene moiety was formed in a single olefination step. Best results were obtained from a Horner–Wadsworth–Emmons reaction with phosphonate **10**[20] and aldehydes **19** and **20**, which gave the desired *E*-olefins **21** and **22** in excellent yields (**21**: 85% and **22**: 89%, over two steps) and 4*E*/4*Z* ratios of >50:1. The corresponding Wittig olefination required repeated column chromatography and resulted generally in lower yields.



Scheme 4. Preparation of *seco*-acids **25** and **26**.



Scheme 5. Second generation synthesis of stereopentad **17**.

The preparation of both *seco*-acids **25** and **26** was completed by a sequence of PMB cleavage with DDQ and hydrolysis of the methyl ester with LiOH in THF/H_2O (**25**: 88%, **26**: 88%, over two steps, Scheme 4).

3.2. Second generation synthesis of stereopentad *17*

To obtain an independent structural confirmation of fragment **17**, we performed a second synthesis from Weinreb amide **27**,[21] which was reduced to aldehyde **28** (Scheme 5).[22] A stereoselective *syn*-aldol addition with imide **29** afforded stereopentad **30** in 86% yield, diastereomerically pure as determined by ^{1}H NMR.[23] MOM protection and reductive removal of the auxiliary afforded **31** (63% over two steps). Cleavage of the TBS group and formation of the 1,3-PMP-acetal gave **32** in 64% yield over two steps. The remaining primary hydroxyl group was protected as TBDPS-ether **33** (97%). Finally, reductive opening of the PMP-acetal with DIBAL-H gave primary alcohol **17** (93%), identical in all respects with the material obtained from the first synthesis (cf. Scheme 3).

3.3. Yamaguchi dimerization and preparation of macrodiolide cores *37* and *38*

Initial attempts to dimerize *seco*-ester **23** or **24** with Otera's catalyst (**34**) failed to give the desired macrodiolides **35** and **36** and led to the corresponding *seco*-acids **25** and **26**, exclusively.[24]

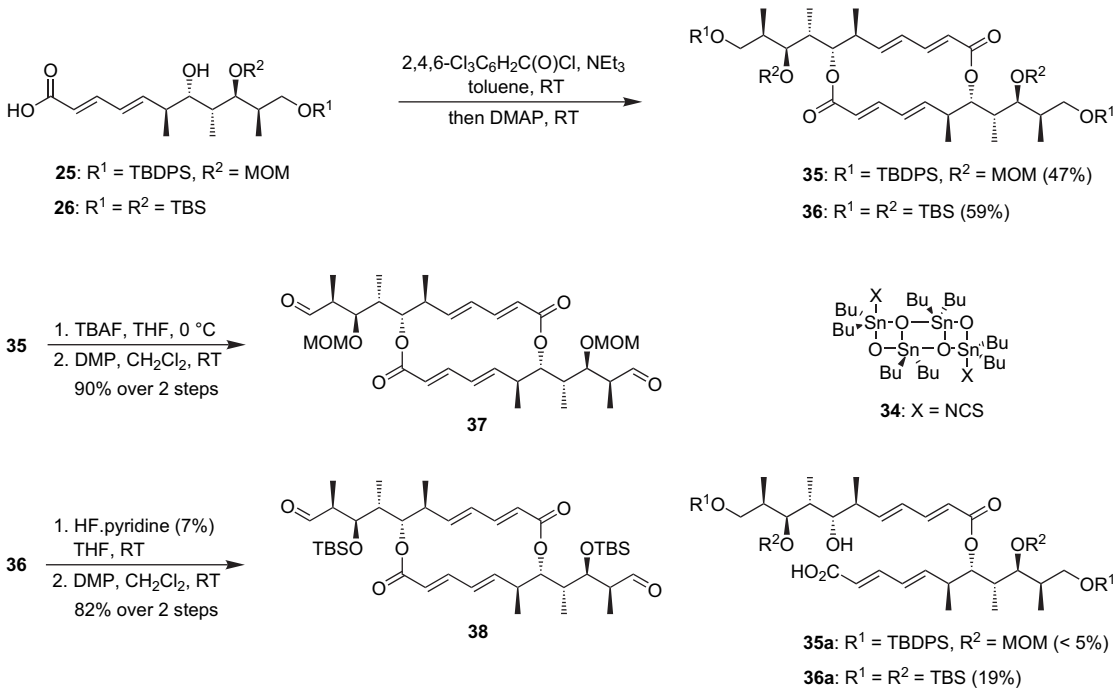
In contrast, the dimerization of *seco*-acids **25** and **26** via the modified Yonemitsu–Yamaguchi protocol gave the desired dimers **35** and **36** in 47% and 59% yield, respectively (Scheme 6).[25,14] In both cases, only minor amounts of the acyclic dimer were isolated (**35a**: <5% and **36a**: 19%) and it could be easily reconverted into **25** and **26** by treatment with LiOH. The yields of the formation of dimer **35** were depending on the scale of the reaction and varied between 23% (**25**: 1.0 mmol) and 78% (**25**: 0.1 mmol). The TBDPS groups of **35** were removed with TBAF and the resulting primary bis-alcohol was oxidized to the bis-aldehyde **37** in 90% over two steps. In the case of macrolactone **36**, the two primary TBS ethers were cleaved with a diluted solution of HF·pyridine in THF and the resulting bis-alcohol was oxidized with Dess–Martin periodinane to bis-aldehyde **38** in 82% over two steps.

3.4. Preparation of the C12–C16 fragments *42* and *43*

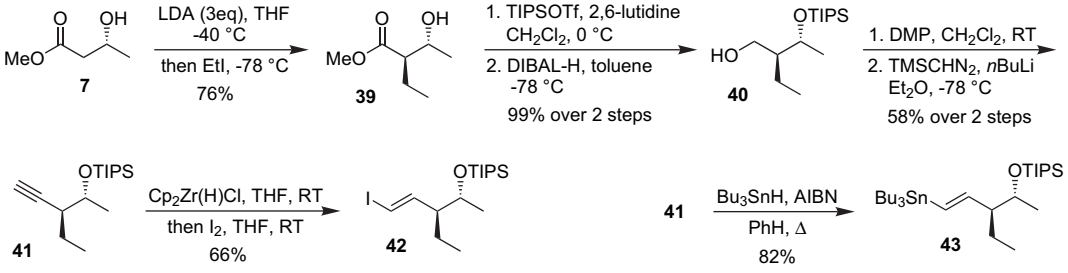
Methyl (*R*)-3-hydroxybutanoate (**7**) was alkylated with ethyl iodide by a diastereoselective Fráter–Seebach reaction in 76% yield and a diastereomeric ratio of 97:3 after distillation (Scheme 7).[26] The secondary alcohol was protected and the methyl ester was reduced to alcohol **40** with DIBAL-H (99%). Among several protecting groups tested (i.e., PMB, MOM, TBS), the TIPS group was the best choice for the preparation of the C12–C16 fragment and for a late stage cleavage. After oxidation of alcohol **40** with Dess–Martin periodinane, a C_1-homologation with $TMSCHN_2$/*n*-BuLi gave alkyne **41** in 58% yield over two steps.[27] Hydrozirconation/iodination furnished (*E*)-vinyliodide **42** (66%).[28] Alternatively, alkyne **41** was converted into stannane **43** by an AIBN-mediated hydrostannylation in 82% yield. Direct formation of vinyliodide **42** via a Takai iodoolefination proceeded with an excellent *E*/*Z* ratio (>40:1),[29] though in low yield (18%).

3.5. C11–C12 bond formation and completion of the synthesis of efomycine M (*1*)

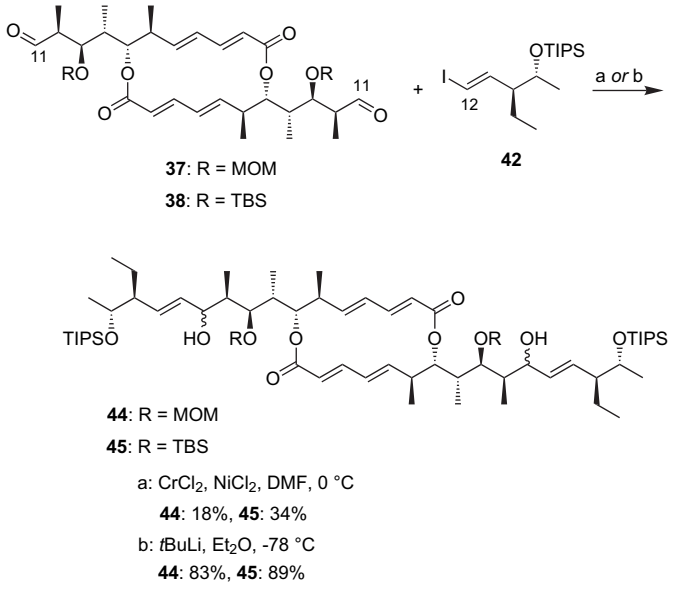
Our initial strategy envisaged a $CrCl_2$/$NiCl_2$-mediated Nozaki–Hiyama–Kishi coupling between vinyliodide **42** and bis-aldehydes **37** and **38**, respectively (Scheme 8).[30] Although



Scheme 6. Yonemitsu–Yamaguchi macrolactonization and preparation of bis-aldehydes **37** and **38**.



Scheme 7. Preparation of vinyliodide **42**.



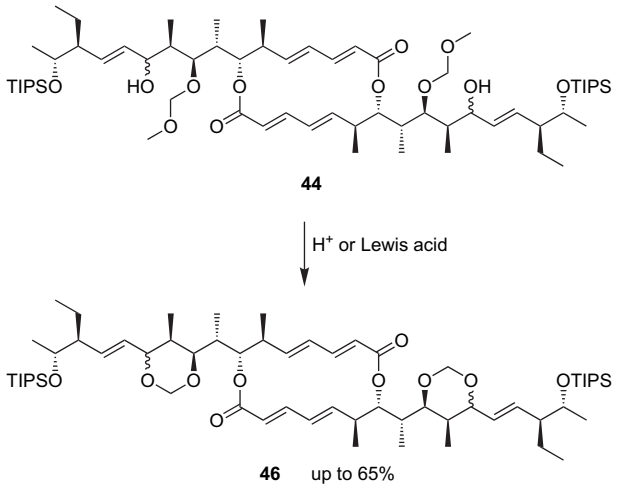
Scheme 8. Two-directional C11–C12 bond formation.

a test reaction of **42** with isobutyraldehyde in DMSO gave the corresponding allylic alcohol in 82% yield as a 1:1 mixture of diastereomers, all additions of vinyliodide **42** to bis-aldehydes **37** or **38** proceeded in disappointingly low yields. The best result (34%) was achieved when bis-aldehyde **38** and iodide **42** were treated with a 20-fold excess of $CrCl_2$ in DMF.

Next, we examined the addition of the corresponding organozinc derivative. Thus, following a protocol by Wipf et al. alkyne **41** was hydrozirconated and the organozirconium species was transmetallated with Et_2Zn.[31] The organozinc compound was added to **38**. However, only traces (<5%) of the bis-allylic alcohol **45** were obtained.

A satisfactory solution was finally achieved by halogen–lithium exchange of **42** with *t*-BuLi in Et_2O and adding the resulting vinyllithium species to bis-aldehyde **37** or **38**, respectively. The vinyllithium intermediate did not attack at the macrocycle carbonyls even in the presence of a large excess so that the bis-allylic alcohols **44** and **45** were isolated in excellent yields (**44**: 83%, **45**: 89%).

No stereoinduction was observed, as we obtained an inseparable yet inconsequential mixture of all three diastereomers



Scheme 9. Attempted cleavage of the MOM-protecting group.

of **44** and **45** in a 1:1:2 ratio for both the Nozaki–Hiyama–Kishi reaction and the vinyllithium addition.

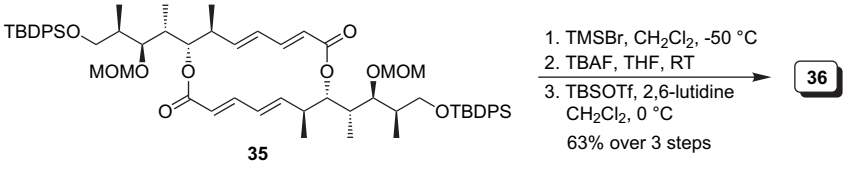
The final steps of the total synthesis envisaged the cleavage of the protecting groups and oxidation of the bis-allylic alcohol to the enone moiety. In the case of **44**, it was possible to perform the oxidation step with Dess–Martin periodinane or MnO_2 and to cleave the TIPS protecting groups with TBAF. However, all attempts to remove the MOM groups under Brønsted or Lewis acid conditions failed. The free allylic alcohol trapped the intermediate oxonium species under formation of the cyclic methylene acetal **46** in up to 65% yield (Scheme 9). Prior protection of the free alcohol as TBS ether or prior oxidation to the enone did not help. In both cases decomposition of the starting material during the attempted MOM cleavage was observed.

The MOM protected macrodiolide core **35** could be, however, converted into the corresponding TBS protected macrocycle **36** (Scheme 10). This was performed by a three-step sequence of TMSBr-mediated MOM cleavage, followed by cleavage of the primary TBDPS groups with TBAF and perprotection as TBS ether with TBSOTf in 63% yield over three steps. It should be mentioned that in this case the cleavage of the MOM group proceeded smoothly at low temperature without the formation of side products. Additionally, the use of TMSBr at low temperature gave by far the best results for the MOM cleavage reaction.[31]

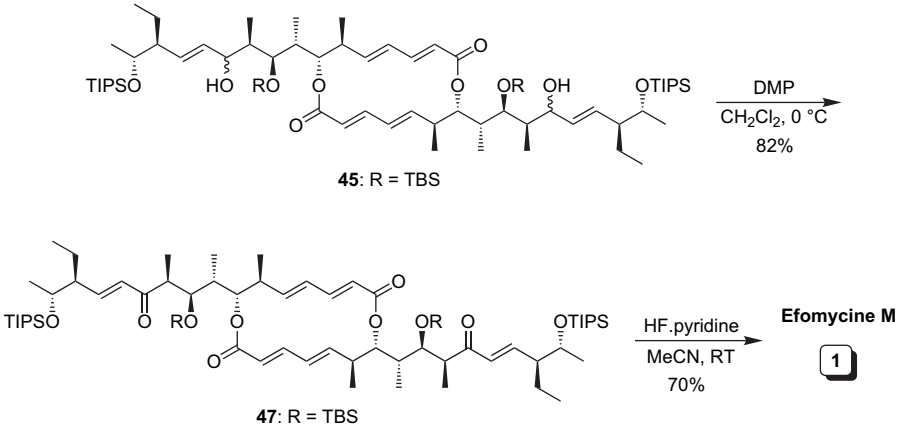
This failure of the MOM route turned our attention to the TBS-protected bis-allylic alcohol **45**. The allylic hydroxyl groups were oxidized with Dess–Martin periodinane to the bis-enone **47** in 82% yield (Scheme 11). The attempted global deprotection with TBAF resulted in the elimination of the OTBS group and gave the (10*E*,12*E*)-bis-dieneone. AcOH-buffered TBAF gave no reaction. Eventually, the global deprotection step was smoothly effected with a 70% solution of HF·pyridine in MeCN to provide efomycine M (**1**) in 17 steps over the longest linear sequence in a total yield of 7%. All spectroscopic data of our synthetic material, i.e., ^{1}H NMR, ^{13}C NMR, IR, HRMS and the optical rotation were in complete agreement with the data obtained from an authentic efomycine M (**1**) sample.[33]

4. Formal total synthesis of elaiolide (3)

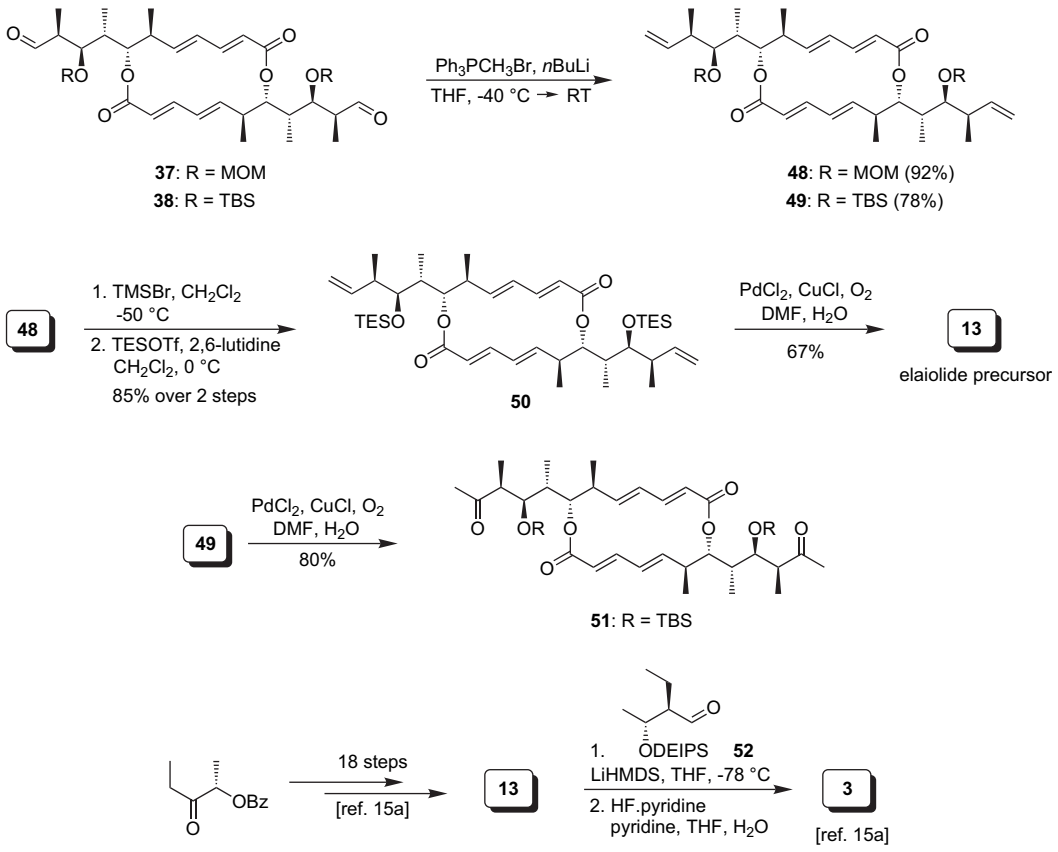
The successful syntheses of macrodiolide aldehydes **37** and **38** encouraged us to tackle the formal total synthesis of elaiolide (**3**, Scheme 12). The synthesis of methylketones **13** and **51** should also allow an additional access towards the preparation



Scheme 10. Conversion of macrodilactone **35** into macrodiolide **36**.



Scheme 11. Completion of the total synthesis of efomycine M (**1**).



Scheme 12. Formal total synthesis of elaiolide (**3**) by a double Wacker oxidation.

of efomycine M (**1**) analogues in future. Our syntheses started from macrocycles **37** and **38**, which were homologated by a Wittig olefination with methylene triphenylphosphorane in excellent yields (**48**: 92% and **49**: 78%, respectively). The MOM protecting group of **48** was then exchanged for a TES group.

In this respect, the use of TMSBr for the MOM cleavage gave best results.[32] The TES group was introduced via the corresponding triflate to give **50** in 85% yield over two steps. Finally, a double Wacker oxidation furnished bis-methylketone **13** in 67% yield.[34] Additionally, TBS-protected olefin **49** was directly oxidized to bis-methylketone **51** by means of a double Wacker oxidation in 80% yield.[34] Our formal total synthesis of elaiolide (**3**) was achieved in 16 steps in an overall yield of 9%. The analytical data of bis-methylketone **13** were in complete agreement with those described for Paterson's intermediate.[15a]

5. Conclusion

In conclusion, we completed the first total synthesis of efomycine M (**1**) in 17 steps over the longest linear sequence in 7% overall yield. This two-directional convergent approach was also applied to a formal total synthesis of elaiolide (**3**). Our synthesis should also allow the preparation of simplified analogues, which is currently underway in our laboratories. In this connection, side-chain modifications as well as stereochemical variations are considered and will be reported in due course.

6. Experimental

6.1. General experimental procedures

^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 K on a Bruker Avance DRX 400 or DRX 600 at 400.1 MHz (100.6 MHz) or 600.1 MHz (150.9 MHz), respectively. Chemical shifts were referenced to residual $CHCl_3$ (δ_H=7.26) and $CDCl_3$ (δ_C=77.0). All chemical shifts are given in parts per million and all coupling constants in hertz. Assignment of proton resonances was confirmed by correlated spectroscopy. IR spectra were recorded as thin films on a silicon disc on a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra were measured on a Micro mass, trio 200 Fisions Instruments. High-resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10,000. Optical rotations were measured on a Perkin–Elmer 351 polarimeter in a 1 dm cell. Melting points were measured on a Reichert Thermovar and were uncorrected. Analytical HPLC was performed on a Jasco System (PU-980 pump, UV 975 and RI 930) using a Nucleosil 50 column (5 μm, Ø 4 mm×250 mm) at ambient temperature. Preparative HPLC was performed on a Dynamix Model SD-1 equipped with a Model UV-1 absorbance detector using a Supersphere (60 Å pore size, 4 μm particle size, Ø 25 mm×250 mm) at ambient temperature.

The reaction progress was checked on precoated TLC plates (Merck Kieselgel 60 F_{254}). Spots were visualized under 254 nm UV light and/or by dipping the TLC plate into

a solution of 20 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.5 g $CeSO_4\cdot 7H_2O$ in 400 mL 10% H_2SO_4 followed by heating with a hot gun. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). All solvents (hexane, ethyl acetate, CH_2Cl_2, Et_2O) were distilled prior to use. All reactions were performed under an atmosphere of argon using oven-dried glassware and standard syringe/septa techniques. THF and Et_2O were distilled from sodium/benzophenone and toluene from sodium. CH_2Cl_2 was dried over P_2O_5. CH_3CN, DMF, NEt_3, Me_2NEt, *i*-Pr_2NH, *i*-Pr_2NEt and 2,6-lutidine were distilled from CaH_2.

6.2. Total synthesis of efomycine M (**1**)

6.2.1. (2R,4S,5S,6R)-1-[(R)-4-Phenylmethyl-2-oxo-oxazolidin-3-yl]-7-(tert-butyldiphenylsilanyloxy)-5-hydroxy-2,4,6-trimethylheptane-1,3-dione (**14a**)

To a stirred solution of β-ketoimide **12** (5.77 g, 19.94 mmol) in 95 mL Et_2O was added a solution of chlorodicyclohexylborane (1.0 M in hexane, 23.0 mL, 23.0 mmol) at 0 °C. Me_2NEt (3.05 mL, 28.15 mmol) was added dropwise and the resulting yellow suspension was stirred at 0 °C for 90 min. After cooling to −78 °C, a solution of freshly prepared aldehyde **14a** (6.46 g, 19.78 mmol) in 12 mL Et_2O was added dropwise. The reaction mixture was stirred at −78 °C for 6 h and was then allowed to warm up to +4 °C within 12 h. The reaction was quenched with 80 mL of a saturated solution of NH_4Cl. The organic phase was separated and concentrated under reduced pressure. The remaining yellow oil was dissolved in 80 mL MeOH and 80 mL of pH 7 phosphate buffer and cooled to 0 °C. H_2O_2 (16 mL, 30%) was added cautiously and the reaction mixture was stirred for 60 min at 0 °C. After dilution with CH_2Cl_2, the organic phase was separated and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane/ethyl acetate, 3:1) provided β-hydroxyketone **14a** (10.83 g, 89%) as a colourless highly viscous oil, which still contained 9% of **12** as determined by ^1H NMR. A sample was additionally purified by preparative HPLC (hexane/*i*-PrOH, 97.5:2.5, flow: 80 mL×min^{-1}, t_R=7.0 min). R_f=0.28 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −51.6 (*c* 1.13, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.63–7.67 (m, 4H, H_{arom}), 7.18–7.45 (m, 11H, H_{arom}), 4.91 (q, *J*=7.3 Hz, 1H, *CH*CH_3), 4.75 (m, 1H, NCH), 4.22 (t, *J*=9.1 Hz, 1H, CH_AH_BPh), 4.16 (dd, *J*=9.1, 2.9 Hz, 1H, CH_BH_APh), 4.07 (ddd, *J*=9.5, 3.0, 2.0 Hz, 1H, *CH*OH), 3.75 (dd, *J*=10.1, 4.2 Hz, 1H, CH_AH_BOSi), 3.65 (dd, *J*=10.1, 5.9 Hz, 1H, CH_BH_AOSi), 3.31 (dd, *J*=13.3, 3.0 Hz, 1H, CH_AH_BO), 2.92 (dq, *J*=9.5, 7.0 Hz, 1H, *CH*CH_3), 2.79 (dd, *J*=13.3, 9.6 Hz, 1H, CH_BH_AO), 2.59 (d, *J*=3.1 Hz, 1H, OH), 1.76 (m, 1H, *CH*CH_3), 1.49 (d, *J*=7.3 Hz, 3H, CH_3CH), 1.05 (s, 12H, CH_3CH overlapped by *t*-Bu), 0.90 (d, *J*=7.0 Hz, 3H, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=211.1 (C), 170.9 (C), 153.4 (C), 135.7 (CH), 135.6 (CH), 135.2 (C), 133.2 (C), 133.0 (C), 129.8 (CH), 129.7 (CH), 129.4 (CH), 129.0 (CH), 127.8 (2×CH), 127.4 (CH), 75.0 (CH), 68.3 (CH_2), 66.3 (CH_2), 55.4 (CH), 53.0 (CH), 47.4 (CH), 38.0 (CH_2), 35.9 (CH), 26.9 (3×CH_3), 19.2 (C), 13.8 (CH_3), 12.8 (CH_3), 8.9 (CH_3); IR (thin film): 3503, 2931, 2858, 1780, 1718, 1696, 1359, 702 cm^{-1}; HRMS [MNa^+] calcd: 638.2914, found: 638.2922.

6.2.2. (R)-4-Methylphenyl-3-[(2R,3R,4S,5S,6R)-7-(tert-butyldiphenylsilanyloxy)-3,5-dihydroxy-2,4,6-trimethylheptanoyl]-oxazolidin-2-one (**15**)

To a stirred suspension of $NaBH(OAc)_3$ (24.0 g, 146.4 mmol) in 120 mL MeCN under argon atmosphere at −45 °C was added 80 mL AcOH. After stirring for 10 min at −45 °C, a solution of β-hydroxyketone **14a** (10.83 g, 17.59 mmol) in 35 mL MeCN was added dropwise. The reaction mixture was allowed to warm up to −15 °C within 4 h and was stirred at this temperature until TLC indicated complete consumption of the starting material. The reaction was quenched by the slow addition of 50 mL of a saturated solution of $NaHCO_3$ and was neutralized with solid $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted four times with ethyl acetate. The combined organic layers were washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 2:1) to give diol **15** (8.62 g, 79%) as a highly viscous oil. R_f=0.23 (hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}$ −52.7 (*c* 0.77, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.67 (m, 4H, H_{arom}), 7.21–7.47 (series of m, 11H, H_{arom}), 4.74 (m, 1H, NCH), 4.27 (m, 1H, *CH*OH), 4.21 (dd∼t, *J*=9.1 Hz, 1H, CH_AH_BPh), 4.16 (dd, *J*=9.1, 3.0 Hz, 1H, CH_BH_APh), 4.04 (dq, *J*=9.5, 6.9 Hz, 1H, *CH*CH_3), 3.87 (br d, *J*=7.5 Hz, 1H, *CH*OH), 3.78 (dd, *J*=10.1, 3.9 Hz, 1H, CH_AH_BOSi), 3.69 (dd, *J*=10.1, 4.5 Hz, 1H, CH_BH_AOSi), 3.27 (dd, *J*=13.4, 3.3 Hz, 1H, CH_AH_BO), 3.00 (br s, 1H, OH), 2.81 (br s, 1H, OH), 2.80 (dd, *J*=13.3, 9.6 Hz, 1H, CH_BH_AO), 1.74–1.87 (m, 2H, 2×*CH*CH_3), 1.12 (d, *J*=6.9 Hz, 3H, CH_3CH), 1.07 (s, 9H, *t*-Bu), 1.04 (d, *J*=7.0 Hz, 3H, CH_3CH), 0.90 (d, *J*=7.0 Hz, 3H, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.8 (C), 153.5 (C), 135.7 (CH), 135.6 (CH), 135.3 (C), 133.1 (C), 132.9 (C), 129.8 (CH), 129.8 (CH), 129.4 (CH), 128.9 (CH), 127.8 (2×CH), 127.3 (CH), 75.8 (CH), 73.5 (CH), 68.9 (CH_2), 66.1 (CH_2), 55.3 (CH), 40.0 (CH), 38.0 (CH_2), 36.7 (CH), 36.7 (CH), 26.9 (3×CH_3), 19.2 (C), 14.3 (CH_3), 10.3 (CH_3), 10.0 (CH_3); IR (thin film): 3480 (br), 2963, 1931, 2858, 1783, 1699, 1472, 1455, 1428, 1390, 1350, 1212, 1112, 1019, 972, 738, 702 cm^{-1}; HRMS [MNa^+] calcd: 640.3070, found: 640.3043.

6.2.3. (2S,3S,4R,5S,6R)-7-(tert-Butyldiphenylsilanyloxy)-2,4,6-trimethylheptane-1,3,5-triol

$LiBH_4$ (300 mg, 13.77 mmol) was added in small portions over a period of 3 h to a stirred solution of diol **15** (7.13 g, 11.54 mmol) in 120 mL Et_2O and H_2O (0.27 mL, 14.98 mmol) at 0 °C. The reaction was quenched with 30 mL H_2O. The organic layer was separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by

flash column chromatography (hexane/ethyl acetate, 1:1) to give the triol (4.48 g, 87%) as a colourless, highly viscous gel. R_f=0.21 (hexane/ethyl acetate, 1:1); $[\alpha]_D^{20}$ +2.9 (*c* 1.23, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.63–7.68 (m, 4H, H_{arom}), 7.37–7.47 (m, 6H, H_{arom}), 3.93 (dd, *J*=9.7, 1.7 Hz, 1H, CHO), 3.81 (m, 1H, CHO), 3.76 (dd, *J*=10.0, 4.0 Hz, 1H, CHO), 3.64–3.70 (m, 3H, 3×CHO), 3.48 (br s, 2H, 2×OH), 3.30 (d, *J*=2.7 Hz, 1H, OH), 1.68–1.94 (series of m, 3H, 3×*CH*CH_3), 1.06 (s, 9H, *t*-Bu), 1.05 (d, *J*=7.2 Hz, 3H, *CH*$_3$CH), 0.88 (d, *J*=7.0 Hz, 3H, *CH*$_3$CH), 0.68 (d, *J*=6.9 Hz, 3H, *CH*$_3$CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.8 (CH), 135.5 (CH), 133.0 (C), 132.8 (C), 129.9 (CH), 129.8 (CH), 127.8 (CH), 127.8 (CH), 77.2 (CH), 76.9 (CH), 69.5 (CH_2), 68.9 (CH_2), 37.1 (CH), 36.9 (CH), 36.9 (CH), 26.9 (3×CH_3), 19.2 (C), 13.2 (CH_3), 10.8 (CH_3), 10.2 (CH_3); IR: (thin film) 3392 (br), 2962, 2931, 2856, 1780, 1428, 1166, 1113, 702 cm^{-1}; HRMS [M$^+$–*t*-Bu] calcd: 387.1992, found: 387.1999.

6.2.4. (2R,3S,4S)-1-(tert-Butyldiphenylsilanyloxy)-4-[(2S,4S,5S)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxan-4-yl]-2-methylpentan-3-ol (**16**)

Triol (2.10 g, 4.72 mmol) was dissolved in 50 mL CH_2Cl_2. Freshly distilled PMPCH(OMe)$_2$ (1.0 mL, 5.86 mmol) was added followed by the addition of (±)-CSA (49 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 60 min and then quenched by the addition of 20 mL of a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to give **16** quantitatively. As it was not possible to separate the remaining *p*-methoxybenzaldehyde from PMP-acetal **16** by flash column chromatography, the crude product was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (m, 4H, H_{arom}), 7.33–7.45 (series of m, 8H, H_{arom}), 6.88 (m, 2H, H_{arom}), 5.50 (s, 1H, OCHO), 4.09 (dd, *J*=11.1, 4.6 Hz, 1H, *CH*$_A$H$_B$O), 3.93 (dt, *J*=8.5, 3.1 Hz, 1H, *CH*OH), 3.88 (dd, *J*=10.3, 1.8 Hz, 1H, CHO), 3.80 (s, 3H, OCH_3), 3.75 (dd, *J*=10.0, 4.4 Hz, 1H, *CH*$_A$H$_B$OSi), 3.67 (dd, *J*=10.0, 5.5 Hz, 1H, *CH*$_B$H$_A$OSi), 3.52 (dd∼t, *J*=11.1 Hz, 1H, *CH*$_B$H$_A$O), 2.62 (d, *J*=4.0 Hz, 1H, OH), 2.07 (m, 1H, *CH*CH_3), 1.77–1.86 (m, 2H, 2×*CH*CH_3), 1.05 (s, 9H, *t*-Bu), 0.96 (d, *J*=7.0 Hz, 3H, *CH*$_3$CH), 0.92 (d, *J*=7.0 Hz, 3H, *CH*$_3$CH), 0.71 (d, *J*=6.7 Hz, 3H, *CH*$_3$CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.8 (C), 135.6 (CH), 133.2 (C), 132.0 (CH), 131.6 (C), 129.7 (CH), 127.7 (CH), 113.5 (CH), 100.9 (CH), 81.8 (CH), 73.3 (CH_2), 68.5 (CH_2), 55.3 (CH_3), 36.7 (CH), 36.2 (CH), 30.4 (CH), 26.9 (*t*-Bu), 19.2 (C), 11.9 (CH_3), 10.0 (CH_3), 9.6 (CH_3).

6.2.5. (2R,3S,4S)-4-[(2S,4S,5S)-2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentane-1,3-diol

Crude PMP-acetal **16** (2.94 g, calcd as 4.72 mmol) was dissolved in 35 mL THF. A solution of TBAF (1.0 M in THF, 9.40 mL, 9.40 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 24 h. After quenching with 30 mL of a saturated solution of NH_4Cl and dilution with 30 mL of CH_2Cl_2, the organic layer was separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification with flash column chromatography gave the diol (1.51 g, 99% over two steps) as viscous oil. R_f=0.17 (hexane/ethyl acetate, 1:1); $[\alpha]_D^{20}$ +43.8 (*c* 1.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38 (m, 2H, H_{arom}), 6.88 (m, 2H, H_{arom}), 5.47 (s, 1H, OCHO), 4.11 (dd, *J*=11.2, 4.7 Hz, 1H, *CH*$_A$H$_B$O), 3.88 (dd, *J*=10.1, 2.0 Hz, 1H, CHO), 3.87 (m, 1H, *CH*OH), 3.80 (s, 3H, OCH_3), 3.75 (dd, *J*=10.5, 3.9 Hz, 1H, *CH*$_A$H$_B$OH), 3.70 (m, 1H, *CH*$_B$H$_A$OH), 3.53 (t, *J*=11.1 Hz, 1H, *CH*$_B$H$_A$O), 2.74 (br d, *J*=2.8 Hz,1H, OH), 2.07–2.17 (m, 2H, OH, *CH*CH_3), 1.89 (ddq, *J*=10.4, 7.1, 2.1 Hz, 1H, *CH*CH_3), 1.82 (m, 1H, *CH*CH_3), 0.98 (d, *J*=7.0 Hz, 3H, *CH*$_3$CH), 0.96 (d, *J*=7.1 Hz, 3H, *CH*$_3$CH), 0.77 (d, *J*=7.7 Hz, 3H, *CH*$_3$CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.9 (C), 131.3 (C), 127.4 (CH), 113.6 (CH), 101.1 (CH), 82.3 (CH), 74.6 (CH), 73.2 (CH_2), 67.9 (CH_2), 55.3 (CH_3), 36.7 (CH), 36.5 (CH), 30.4 (CH), 12.0 (CH_3), 10.5 (CH_3), 9.2 (CH_3); IR (thin film): 3402 (br), 2967, 1518, 1250, 1032 cm^{-1}; HRMS [M$^+$] calcd: 324.1937, found: 324.1942.

6.2.6. (2S,4S,5S)-4-[(1R,2S,3R)-2,4-Bis-(tert-butyldimethylsilanyloxy)-1,3-dimethylbutyl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxinane

2,6-Lutidine (2.40 mL, 20.60 mmol) and TBSOTf (1.95 mL, 8.49 mmol) were added to a stirred solution of the diol (1.02 g, 3.14 mmol) in 30 mL CH_2Cl_2 at 0 °C. After 90 min, the reaction was quenched by the addition of 20 mL of a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 30:1) to give the di-TBS ether (1.59 g, 91%) as a colourless oil. R_f=0.65 (hexane/ethyl acetate, 7:1); $[\alpha]_D^{20}$ +22.4 (*c* 1.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (m, 2H, H_{arom}), 6.87 (m, 2H, H_{arom}), 5.47 (s, 1H, OCHO), 4.12 (dd, *J*=10.9, 4.5 Hz, 1H, *CH*$_A$H$_B$O), 4.01 (dd, *J*=8.7, 1.0 Hz, 1H, CHO), 3.80 (s, 3H, OCH_3), 3.75 (br d, *J*=9.9 Hz, 1H, CHO), 3.49 (t, *J*=11.1, CHO), 3.47 (dd, *J*=9.7, 8.3 Hz, 1H, *CH*$_A$H$_B$O), 3.39 (dd, *J*=9.8, 6.9 Hz, 1H, *CH*$_B$H$_A$O), 2.05 (m, 1H, *CH*CH_3), 1.79–1.90 (m, 2H, 2×*CH*CH_3), 0.92 (s, 9H, *t*-Bu), 0.91 (d, *J*=7.1 Hz, 3H, *CH*$_3$CH), 0.88 (s, 9H, *t*-Bu), 0.80 (d, *J*=6.8 Hz, 3H, *CH*$_3$CH), 0.74 (d, *J*=6.7 Hz, 3H, *CH*$_3$CH), 0.07 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si), 0.03 (s, 6H, 2×CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.7 (C), 131.7 (C), 127.2 (CH), 113.4 (CH), 100.3 (CH), 80.8 (CH), 73.3 (CH_2), 71.4 (CH), 66.1 (CH_2), 55.3 (CH_3), 38.4 (CH), 38.3 (CH), 30.4 (CH), 26.4 (3×CH_3), 25.9 (3×CH_3), 18.6 (C), 18.2 (C), 12.3 (CH_3), 9.9 (CH_3), 9.1 (CH_3), −3.4 (CH_3), −4.1 (CH_3), −5.2 (CH_3), −5.3 (CH_3); IR (thin film): 2956, 2930, 2857, 1519, 1472, 1463, 1386, 1250, 1109, 1093, 1039, 835, 775 cm^{-1}; HRMS [M$^+$–*t*-Bu] calcd: 495.2962, found: 495.2967.

*6.2.7. (2S,3S,4R,5S,6R)-5,7-Bis-(tert-butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylheptan-1-ol (**18**)*

A solution of DIBAL-H (1.5 M in toluene, 5.0 mL, 7.50 mmol) was added to a stirred solution of the PMP-acetal (1.40 g, 2.53 mmol) in 24 mL CH_2Cl_2 at −30 °C under argon atmosphere. The reaction mixture was allowed to warm up to −10 °C within 3 h and was then quenched by the addition of a saturated solution of Na/K/tartrate. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography to give alcohol **18** (0.97 g, 69%, 85% based on the recovered starting material) as colourless oil together with 0.26 g of recycled starting material. R_f=0.26 (hexane/ethyl acetate, 7:1); $[\alpha]_D^{20}$ −6.2 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26 (m, 2H, H_{arom}), 6.87 (m, 2H, H_{arom}), 4.60, 4.54 (AB system, *J*=10.2 Hz, 2H, OCH_2Ph), 4.00 (br d, *J*=6.3 Hz, 1H, CHO), 3.83 (ddd∼dt, 11.0, 3.9 Hz, 1H, CH_AH_BOH), 3.80 (s, 3H, OCH_3), 3.59 (ddd∼dt, *J*=11.0, 5.8 Hz, 1H, CH_BH_AOH), 3.47 (dd∼t, *J*=5.4 Hz, 1H, CHOSi), 3.42 (t, *J*=9.6 Hz, 1H, CH_AH_BOSi), 3.34 (dd, *J*=9.6, 5.6 Hz, 1H, CH_BH_AOSi), 2.90 (dd, *J*=6.2, 5.1 Hz, 1H, OH), 1.91−2.02 (m, 2H, 2×$CHCH_3$), 1.75 (m, 1H, $CHCH_3$), 1.08 (d, *J*=7.3 Hz, 3H, CH_3CH), 1.06 (d, *J*=7.3 Hz, 3H, CH_3CH), 0.91 (s, 9H, *t*-Bu), 0.89 (s, 9H, *t*-Bu), 0.84 (d, *J*=6.8 Hz, 3H, CH_3CH), 0.10 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si), 0.04 (s, 6H, 2×CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.3 (C), 130.5 (C), 129.3 (CH), 113.9 (CH), 86.6 (CH), 75.3 (CH_2), 71.5 (CH), 66.0 (CH_2), 65.5 (CH_2), 55.3 (CH_3), 42.8 (CH), 37.7 (CH), 37.2 (CH), 26.1 (3×CH_3), 25.9 (3×CH_3)18.5 (C), 18.2 (C), 15.6 (CH_3), 11.7 (CH_3), 10.7 (CH_3), −3.4 (CH_3), −4.4 (CH_3), −5.4 (2×CH_3); IR (thin film): 3448 (br), 2956, 2929, 2857, 1515, 1473, 1465, 1251, 1086, 1043, 836, 774 cm^{-1}; HRMS [M^+] calcd: 554.3823, found: 554.3814.

*6.2.8. (2R,3R,4R,5S,6R)-5,7-Bis-(tert-butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylheptanal (**20**) and (2E,4E)-(6S,7S,8R,9S,10R)-9,11-bis-(tert-butyldimethylsilanyloxy)-7-(4-methoxybenzyloxy)-6,8,10-trimethylundeca-2,4-dienoic acid methyl ester (**22**)*

Dess−Martin periodinane (3.54 g, 8.35 mmol) was added in one portion to a stirred solution of alcohol **18** (2.57 g, 4.63 mmol) in 50 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and for 4 h at room temperature. The reaction was quenched by the addition of 20 mL of a 1.0 M solution of $Na_2S_2O_3$ and neutralized with 30 mL of a saturated solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered over a short column of silica gel and concentrated in vacuo. The crude product **20** (2.56 g) was used in the next step without any further purification.

A solution of LDA was prepared by adding a solution of *n*-BuLi (2.5 M in hexane, 2.65 mL, 6.63 mmol) to a solution of *i*-Pr_2NH (0.93 mL, 6.64 mmol) in 15 mL THF under argon atmosphere at 0 °C and stirred for 30 min. Phosphonate **10** (1.55 g, 6.56 mmol) was dissolved in 30 mL THF and cooled to −78 °C under argon atmosphere. The freshly prepared solution of LDA was added dropwise at −78 °C and the reaction mixture was allowed to warm up to −20 °C within 3 h. The reaction mixture was re-cooled to −78 °C and a solution of aldehyde **20** (2.56 g, 4.63 mmol) in 15 mL THF was added dropwise. The reaction mixture was allowed to warm up to room temperature overnight and was quenched by the addition of 40 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 15:1) gave diene **22** (2.61 g, 89% over two steps) as a colourless viscous oil. R_f=0.29 (hexane/ethyl acetate, 10:1); $[\alpha]_D^{20}$ −2.0 (*c* 0.82, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24−7.31 (m, 3H, H_{arom}, C_3−H), 6.88 (m, 2H, H_{arom}), 6.24 (m, 2H, C_4−H, C_5−H), 5.78 (d, *J*=15.4 Hz, 1H, C_2−H), 4.57, 4.52 (AB system, *J*=10.4 Hz, 2H, OCH_2Ph), 4.01 (br d, *J*=5.6 Hz, 1H, C_9−H), 3.81 (s, 3H, OCH_3), 3.74 (s, 3H, C_1−OCH_3), 3.41 (t, *J*=9.6 Hz, 1H, C_{11}−H_A), 3.32 (dd, *J*=9.6, 5.3 Hz, 1H, C_{11}−H_B), 3.25 (dd, *J*=7.5, 3.3 Hz, 1H, C_7−H), 2.71 (m, 1H, C_6−H), 1.84 (m, 1H, C_8−H), 1.72 (m, 1H, C_{10}−H), 1.13 (d, *J*=6.8 Hz, 3H, C_6−CH_3), 1.05 (d, *J*=7.1 Hz, 3H, C_8−CH_3), 0.93 (s, 9H, *t*-Bu), 0.88 (s, 9H, *t*-Bu), 0.84 (d, *J*=6.8 Hz, 3H, C_{10}−CH_3), 0.08 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si), −0.03 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.6 (C), 159.1 (C), 146.5 (CH), 145.3 (CH), 131.0 (CH), 129.1 (CH), 128.7 (CH), 119.1 (CH), 113.8 (CH), 85.2 (CH), 75.0 (CH_2), 70.0 (CH), 66.4 (CH_2), 55.3 (CH_3), 51.4 (CH_3), 43.4 (CH), 40.5 (CH), 37.4 (CH), 26.0 (6×CH_3), 18.3 (C), 18.3 (C), 18.2 (CH_3), 11.8 (CH_3), 11.2 (CH_3), −3.7 (CH_3), −4.7 (CH_3), −5.2 (CH_3), −5.3 (CH_3); IR (thin film): 2955, 2930, 2857, 1722 (br), 1516, 1250, 1142, 1072, 1042, 836, 774 cm^{-1}; HRMS [M^+−*t*-Bu] calcd: 577.3381, found: 577.3394.

*6.2.9. (2E,4E)-(6S,7S,8R,9S,10R)-9,11-Bis-(tert-butyldimethylsilanyloxy)-7-hydroxy-6,8,10-trimethylundeca-2,4-dienoic acid methyl ester (**24**)*

DDQ (581 mg, 2.559 mmol) was added in small portions to a vigorously stirred solution of PMB-ether **22** (935 mg, 1.472 mmol) in 40 mL DCM and 15 mL of a 1.0 M pH 7 phosphate buffer over a period of 4 h. Stirring was continued until TLC indicated complete consumption of the starting material. The reaction was quenched with 50 mL of a saturated solution of $NaHCO_3$ and the organic layer was separated. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 10:1) to give *seco*-ester **24** (741 mg, 98%) as a slightly yellow oil. R_f=0.20 (hexane/ethyl acetate, 10:1); $[\alpha]_D^{20}$ −20.6 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30 (dd, *J*=15.4, 10.0 Hz, 1H, C_3−H), 6.17−6.29 (m, 2H, C_4−H, C_5−H), 5.80 (d, *J*=15.4 Hz, 1H, C_2−H), 3.87 (t, *J*=4.2 Hz, 1H,

C_9–H), 3.73 (s, 3H, OCH_3), 3.71 (m, 1H, C_7–H), 3.50 (dd, J=9.8, 6.4 Hz, 1H, C_{11}–H_A), 3.45 (dd, J=9.8, 6.0 Hz, 1H, C_{11}–H_B), 3.04 (d, J=1.7 Hz, OH), 2.41 (m, 1H, C_6–H), 1.89 (m, 1H, C_{10}–H), 1.77 (m, 1H, C_8–H), 0.97 (d, J=7.1 Hz, 3H, C_8–CH_3), 0.96 (d, J=6.8 Hz, 3H, C_6–CH_3), 0.93 (d, J=6.9 Hz, 3H, C_{10}–CH_3), 0.91 (s, 9H, *t*-Bu), 0.98 (s, *t*-Bu), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.6 (C), 147.8 (CH), 145.4 (CH), 128.2 (CH), 119.2 (CH), 77.6 (CH), 74.9 (CH), 66.0 (CH_2), 51.4 (CH_3), 40.7 (CH), 39.5 (CH), 37.9 (CH), 26.2 (3×CH_3), 25.9 (3×CH_3), 18.4 (C), 18.2 (C), 16.4 (CH_3), 13.0 (CH_3), 11.1 (CH_3), −3.8 (CH_3), −4.0 (CH_3), −5.4 (2×CH_3); IR (thin film): 3503, 2956, 2930, 2885, 2858, 1723 (br), 1645, 1258, 1142, 1091, 1045, 1004, 837, 775 cm^{-1}; HRMS [M^+−*t*-Bu] calcd: 457.2806, found: 457.2798.

*6.2.10. (2E,4E)-(6S,7S,8R,9S,10R)-9,11-Bis-(tert-butyldimethylsilanyloxy)-7-hydroxy-6,8,10-trimethylundeca-2,4-dienoic acid (**26**)*

A solution of $LiOH\cdot H_2O$ (170 mg, 4.051 mmol) in 11 mL H_2O was added to a solution of **24** (741 mg, 1.493 mmol) in 24 mL THF at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for 24 h. The reaction was quenched by the dropwise addition of AcOH (0.37 mL, 6.65 mmol) at 0 °C. The organic layer was separated and the aqueous layer was four times extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 3:1) gave *seco*-acid **26** (649 mg, 90%) as a slightly yellow, highly viscous gum. R_f=0.17 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −24.3 (*c* 1.08, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.37 (m, 1H, C_3–H), 6.27 (m, 2H, C_4–H, C_5–H), 5.79 (d, J=15.3 Hz, 1H, C_2–H), 3.87 (t, J=4.1 Hz, 1H, C_9–H), 3.74 (dd, J=8.7, 2.1 Hz, 1H, C_7–H), 3.51 (dd, J=9.8, 6.4 Hz, 1H, C_{11}–H_A), 3.46 (dd, J=9.8, 5.9 Hz, 1H, C_{11}–H_B), 2.43 (m, 1H, C_6–H), 1.90 (m, 1H, C_{10}–H), 1.78 (m, 1H, C_8–H), 0.98 (d, J=6.9 Hz, C_8–CH_3), 0.97 (d, J=6.6 Hz, C_6–CH_3), 0.94 (d, J=6.9 Hz, C_{10}–CH_3), 0.91 (s, 9H, *t*-Bu), 0.89 (s, 9H, *t*-Bu), 0.10 (CH_3Si), 0.09 (CH_3Si), 0.04 (CH_3Si), 0.04 (CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.1 (C), 148.9 (CH), 147.4 (CH), 128.1 (CH), 118.8 (CH), 77.9 (CH), 75.0 (CH), 66.0 (CH_2), 40.8 (CH), 39.5 (CH), 37.8 (CH), 26.2 (3×CH_3), 25.9 (3×CH_3), 18.4 (C), 18.2 (C), 16.4 (CH_3), 13.1 (CH_3), 11.2 (CH_3), −3.8 (CH_3), −4.0 (CH_3), −5.4 (2×CH_3); IR (thin film): 3470 (v br), 2956, 2929, 2858, 1691, 1639, 1257, 1089, 1048, 1004, 836, 774 cm^{-1}; HRMS [M^+−*t*-Bu] calcd: 443.2649, found: 443.2657.

*6.2.11. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-[(1R,2S,3R)-2,4-bis-(tert-butyldimethylsilanyloxy)-1,3-dimethylbutyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**36**)*

NEt_3 (160 μL, 1.148 mmol) and 2,4,6-trichlorobenzoylchloride (110 μL, 0.704 mmol) were added to a stirred solution of *seco*-acid **26** (285 mg, 0.569 mmol) in 35 mL toluene. The cloudy solution was stirred at room temperature for 4 h. A solution of *N*,*N*-dimethylaminopyridine (140 mg, 1.146 mmol) in 6 mL toluene was added over a period of 8 h with a syringe pump and stirring was continued overnight. The resulting slightly yellow suspension was quenched with 10 mL of a 1.0 M solution of $KHSO_4$. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification with flash column chromatography (hexane/ethyl acetate, 30:1) gave macrodiolide **36** (161 mg, 59%) as colourless needles together with uncyclized dimer **36a** (51 mg, 19%). R_f=0.22 (hexane/ethyl acetate, 15:1); $[\alpha]_D^{20}$ +46.4 (*c* 1.30, CH_2Cl_2); mp: 174–175 °C; ^1H NMR (400 MHz, $CDCl_3$): δ=6.93 (dd, J=15.3, 11.1 Hz, 2H, C_3–H), 5.98 (dd, J=15.0, 11.1 Hz, 2H, C_4–H), 5.63 (dd, J=15.0, 9.9 Hz, 2H, C_5–H), 5.58 (d, J=15.3 Hz, 2H, C_2–H), 4.94 (br d, J=10.1 Hz, 2H, C_7–H), 3.74 (dd, J=6.8, 1.7 Hz, 2H, C_9–H), 3.47 (dd, J=9.8, 7.6 Hz, 2H, C_{11}–H_A), 3.38 (dd, J=9.8, 6.9 Hz, 2H, C_{11}–H_B), 2.42 (m, 2H, C_6–H), 1.93 (m, 2H, C_8–H), 1.76 (m, 2H, C_{10}–H), 1.05 (d, J=6.6 Hz, 6H, C_6–CH_3), 0.96 (d, J=7.2 Hz, 6H, C_8–CH_3), 0.91 (s, 18H, *t*-Bu), 0.86 (s, 18H, *t*-Bu), 0.84 (d, J=6.8 Hz, 6H, C_{10}–CH_3), 0.15 (s, 6H, CH_3Si), 0.05 (s, 6H, CH_3Si), 0.02 (s, 6H, CH_3Si), 0.01 (s, 6H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.6 (C), 145.2 (CH), 144.5 (CH), 130.7 (CH), 121.3 (CH), 76.9 (CH), 73.7 (CH), 66.0 (CH_2), 42.5 (CH), 39.0 (CH), 38.7 (CH), 26.3 (3×CH_3), 25.9 (3×CH_3), 18.7 (C), 18.2 (C), 16.3 (CH_3), 10.4 (CH_3), 10.2 (CH_3), −3.6 (CH_3), −4.3 (CH_3), −5.3 (CH_3), −5.3 (CH_3); IR (thin film): 2956, 2943, 2930, 2885, 2856, 1709 (br), 1643, 1472, 1385, 1251, 1225, 1150, 1123, 1118, 1106, 1044, 1006, 849, 837, 776 cm^{-1}; HRMS [MNa^+] calcd: 987.6393, found: 987.6381.

6.2.12. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-[(1R,2S,3R)-2-(tert-butyldimethylsilanyloxy)-4-hydroxy-1,3-dimethylbutyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione

A solution of HF·pyridine (70%, 1.17 mL, 6.54 mmol) in 1.40 mL pyridine was added to a solution of compound **36** (243 mg, 0.252 mmol) in 6.0 mL THF under argon atmosphere at 0 °C. The reaction mixture was stirred at room temperature until TLC indicated complete consumption of the starting material (approximately 3 days). The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ and diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification with flash column chromatography (hexane/ethyl acetate, 3:1) gave the bis-diol (159 mg, 86%) as colourless needles. R_f=0.32 (hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}$ +19.8 (*c* 0.43, CH_2Cl_2); mp: 159–161 °C; ^1H NMR (400 MHz, $CDCl_3$): δ=6.93 (dd, J=15.3, 11.1 Hz, 2H, C_3–H), 6.01 (dd, J=15.0, 11.2 Hz, 2H, C_4–H), 5.61 (dd, J=15.0, 9.9 Hz, 2H, C_5–H), 5.61 (d, J=15.4 Hz, 2H, C_2–H), 4.87 (d, J=10.2 Hz, 2H, C_7–H), 3.86 (dd, J=5.8, 1.5 Hz, 2H, C_9–H), 3.45 (m, 4H, C_{11}–H), 2.43 (m, 2H, C_6–H), 2.03 (m,

2H, C_{10}–H), 1.63–1.84 (br m, 4H, C_8–H, OH), 1.06 (d, J=6.6 Hz, 6H, C_6–CH_3), 1.01 (d, J=7.2 Hz, 6H, C_{10}–CH_3), 0.91 (s, 18H, *t*-Bu), 0.85 (d, J=6.9 Hz, 6H, C_8–CH_3), 0.13 (s, 6H, CH_3Si), 0.06 (s, 6H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.0 (C), 145.4 (CH), 144.5 (CH), 131.0 (CH), 121.4 (CH), 77.6 (CH), 74.3 (CH), 66.2 (CH_2), 42.4 (CH), 39.1 (CH), 38.5 (CH), 26.1 (3×CH_3), 18.4 (C), 16.2 (CH_3), 11.3 (CH_3), 9.2 (CH_3), −3.9 (CH_3), −4.5 (CH_3); IR (thin film): 3483 (br), 2928, 1716, 1636, 1473, 1387, 1301, 1252, 1221, 1184, 1047, 998, 866, 837, 773 cm^{-1}; HRMS [M^+−*t*-Bu] calcd: 679.4062, found: 679.4076.

*6.2.13. (2S,3R,4R)-3-(tert-Butyldimethylsilanyloxy)-4-{(4E,6E,12E,14E)-(2S,3S,10S,11S)-10-[(1R,2R,3S)-2-(tert-butyldimethylsilanyloxy)-1,3-dimethyl-4-oxobutyl]-3,11-dimethyl-8,16-dioxo-1,9-dioxacyclohexadeca-4,6,12,14-tetraen-2-yl}-2-methylpentanal (**38**)*

Dess–Martin periodinane (320 mg, 0.754 mmol) was added in one portion to a stirred solution of the bis-alcohol (122 mg, 0.165 mmol) in 5 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred at room temperature for 4 h before being quenched with 4 mL of a 1.0 M solution of $Na_2S_3O_3$ and 10 mL of a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 5:1) gave bis-aldehyde **38** (114 mg, 94%) as colourless crystals. R_f=0.23 (hexane/ethyl acetate, 5:1); $[\alpha]_D^{20}$ +124.8 (*c* 0.99, CH_2Cl_2); mp: 126 °C; ^1H NMR (250 MHz, $CDCl_3$): δ=9.70 (s, 2H, C_{11}–H), 6.95 (dd, J=15.3, 11.1 Hz, 2H, C_3–H), 6.00 (dd, J=15.1, 11.1 Hz, 2H, C_4–H), 5.63 (dd, J=15.0, 10.0 Hz, 2H, C_5–H), 5.60 (d, J=15.4 Hz, 2H, C_2–H), 4.99 (d, J=10.2 Hz, 2H, C_7–H), 4.17 (dd, J=7.1, 2.1 Hz, 2H, C_9–H), 2.42 (m, 4H, C_6–H, C_{10}–H), 2.00 (m, 2H, C_8–H), 1.14 (d, J=7.0 Hz, 6H, C_{10}–CH_3), 1.06 (d, J=6.6 Hz, 6H, C_6–CH_3), 0.98 (d, J=7.1 Hz, 6H, C_8–CH_3), 0.87 (s, 18H, *t*-Bu), 1.14 (s, 6H, CH_3Si), −0.03 (s, 6H, CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): δ=204.9 (CH), 167.6 (C), 145.6 (CH), 144.5 (CH), 130.9 (CH), 121.2 (CH), 76.5 (CH), 72.8 (CH), 50.1 (CH), 42.4 (CH), 38.8 (CH), 26.1 (3×CH_3), 18.4 (C), 16.2 (CH_3), 10.0 (CH_3), 7.4 (CH_3), −4.2 (2×CH_3); IR (thin film): 2930, 2885, 2857, 1721, 1717, 1642, 1258, 1220, 1146, 1107, 1028, 999, 838; HRMS [M^+−*t*-Bu] calcd: 675.3749, found: 675.3738.

*6.2.14. (2R,3R)-2-Ethyl-3-hydroxybutyric acid methyl ester (**39**), (2R,3R)-2-ethyl-3-triisopropylsilanyloxybutyric acid methyl ester and (2S,3R)-2-ethyl-3-triisopropylsilanyl-oxybutan-1-ol (**40**)*

A solution of LDA was prepared by adding a solution of *n*-BuLi (2.5 M in hexane, 32.30 mL, 80.75 mmol) to a solution of *i*-Pr_2NH (11.40 mL, 81.34 mmol) in 70 mL THF at 0 °C and stirred for 30 min. A solution of (*R*)-3-hydroxybutyric acid methyl ester (**7**, 3.16 g, 26.75 mmol) in 15 mL THF was added at −50 °C and stirred for 3.5 h. During that period, the slightly yellow reaction mixture was allowed to warm up to −20 °C. The reaction mixture was re-cooled to −78 °C and a solution of EtI (7.50 mL, 93.77 mmol) in 15 mL THF was added dropwise. The reaction was stirred at −78 °C for 4 h and then allowed to warm up to room temperature overnight. After quenching with 70 mL of a saturated solution of NH_4Cl, the organic layer was separated and the aqueous layer was extracted four times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by bulb-to-bulb distillation (bp 72 °C at 3 mmHg) gave compound **39** (2.99 g, 76%) as a colourless liquid. $[\alpha]_D^{20}$ −4.5 (*c* 1.63, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=3.92 (m, 1H, *CH*OH), 3.72 (s, 3H, OCH_3), 2.46 (d, J=6.9 Hz, 1H, OH), 2.32 (dt, J=8.5, 6.0 Hz, 1H, *CH*CH_2), 1.59–1.75 (m, 2H, *CH*$_2CH_3$), 1.22 (d, J=6.3 Hz, 3H, *CH*$_3$CH), 0.92 (t, J=7.5 Hz, 3H, *CH*$_3CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.8 (C), 68.1 (CH), 54.3 (CH_3), 51.5 (CH), 22.6 (CH_2), 21.5 (CH_3), 11.7 (CH_3); IR (thin film): 3401 (br), 2972, 1737 (br), 1456, 1171, 995, 799 cm^{-1}; HRMS [M^+−Me] calcd: 131.0708, found: 131.0711.

2,6-Lutidine (6.00 mL, 51.51 mmol) and TIPSOTf (6.20 mL, 23.06 mmol) were added to a stirred solution of alcohol **39** (2.99 g, 20.45 mmol) in 21 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 2 h and then quenched by the addition of 20 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was used in the next step without any further purification.

A solution of DIBAL-H (1.5 M in toluene, 48.0 mL, 72.0 mmol) was added to a stirred solution of the TIPS-protected ester (calcd as 20.45 mmol) in 80 mL toluene at −78 °C. The reaction mixture was allowed to warm up to −50 °C within 2 h. After quenching with 50 mL of a saturated solution of Na/K/tartrate, the organic layer was separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 7:1) followed by vacuum distillation (bp: 125 °C at 4 mmHg) to give alcohol **40** (5.58 g, 99% over two steps) as a colourless liquid. R_f=0.20 (hexane/ethyl acetate, 7:1); $[\alpha]_D^{20}$ −8.0 (*c* 1.34, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=4.16 (dq, J=6.3, 3.8 Hz, 1H, CHOSi), 3.94 (dt, J=11.2, 3.3 Hz, 1H, *CH*$_A$H$_B$O), 3.63 (m, 1H, *CH*$_B$H$_A$O), 2.87 (dd, J=7.2, 3.8 Hz, 1H, OH), 1.43–1.62 (m, 2H, *CH*$_2CH_3$), 1.29 (d, J=6.3 Hz, *CH*$_3$CH), 1.09 (s, 21H, 3×CH(CH_3)$_2$), 0.96 (t, J=7.5 Hz, 3H, *CH*$_3CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=72.9 (CH), 62.5 (CH_2), 48.6 (CH), 22.3 (CH_3), 21.7 (CH_2), 18.2 (3×CH(CH_3)$_2$), 12.7 (CH_3); IR (thin film): 3429, 2962, 2944, 2868, 1053, 1032, 1013, 883, 678 cm^{-1}; HRMS [M^+−Me] calcd: 259.2093, found: 259.2084.

*6.2.15. (2R,3R)-2-Ethyl-3-triisopropylsilanyloxybutyraldehyde and [(1R,2S)-2-ethyl-1-methylbut-3-ynyloxy]-triisopropylsilane (**41**)*

Dess–Martin periodinane (5.50 g, 12.97 mmol) was added to a stirred solution of alcohol **40** (2.57 g, 9.36 mmol) in 25 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred at

room temperature for 3 h. After quenching with 25 mL of a 1.0 M solution of $Na_2S_2O_3$, the reaction mixture was neutralized with 40 mL of a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered over a short column of silica gel and concentrated under reduced pressure. The crude product was used in the next step without any further purification.

A solution of $TMSCHN_2$ (2.0 M in Et_2O, 5.80 mL, 11.60 mmol) was diluted with 20 mL Et_2O at −78 °C. A solution of *n*-BuLi (2.5 M in hexane, 4.70 mL, 11.75 mmol) was added dropwise over a period of 10 min and stirring was continued for 3 h. A solution of crude aldehyde (calcd as 9.36 mmol) in 5 mL THF was added dropwise. The reaction mixture was first stirred at −78 °C for 30 min and then at 0 °C overnight. The reaction was quenched with 20 mL of a saturated solution of NH_4Cl. The organic phase was separated and the aqueous phase was extracted with hexane/Et_2O (1:1). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification with flash column chromatography (hexane) gave alkyne **41** (1.46 g, 58% over two steps) as a colourless liquid. R_f=0.63 (hexane); $[\alpha]_D^{20}$ +13.3 (*c* 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.12 (dq, *J*=6.2, 3.9 Hz, 1H, CHOSi), 2.38 (ddt, *J*=10.5, 3.8, 2.5 Hz, 1H, *CH*CH_2), 2.06 (d, *J*=2.5 Hz, 1H, HCC), 1.75 (ddq, *J*=13.0, 7.4, 3.8 Hz, 1H, $CH_AH_BCH_3$), 1.36−1.47 (m, 1H, $CH_BH_ACH_3$), 1.23 (d, *J*=6.2 Hz, 3H, CH_3CH), 1.06 (s, 21H, 3×CH$(CH_3)_2$), 1.04 (t, *J*=7.4 Hz, 3H, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=85.7 (C), 70.4 (CH), 70.0 (CH), 41.9 (CH), 21.3 (CH_2), 19.5 (CH_3), 18.1 (3×CH$(CH_3)_2$), 12.5 (CH_3); IR (thin film): 3314, 2964, 2944, 2892, 2868, 1464, 1109, 998, 883, 680, 636 cm^{-1}; HRMS [M^+−*i*-Pr] calcd: 225.1675, found: 225.1670.

6.2.16. [(E)-(1R,2S)-2-Ethyl-4-iodo-1-methylbut-3-enyloxy]-triisopropylsilane (**42**)

Cp_2ZrCl_2 (1.04 g, 3.56 mmol) was dissolved in 10 mL THF at 0 °C. A solution of DIBAL-H (2.30 mL, 3.45 mmol) was added dropwise and the resulting suspension was stirred for 1 h at 0 °C. The supernatant liquid was removed with a syringe. The remaining white solid was washed with 5 mL THF and taken up in 10 mL THF. A solution of alkyne **41** (795 mg, 2.961 mmol) in 5 mL THF was added to the stirred suspension of Schwartz reagent resulting in a homogenous orange solution after stirring for 1 h at room temperature. A solution of I_2 (960 mg, 3.782 mmol) in 5 mL THF was added dropwise and stirring was continued for 5 min. The reaction was quenched with 6 mL of a 1.0 M solution of $Na_2S_2O_3$. Hexane (10 mL) was added and the organic phase was separated. The aqueous phase was extracted two times with hexane. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (hexane) gave (*E*)-vinyliodide **42** (776 mg, 66%) as colourless oil. R_f=0.78 (hexane); $[\alpha]_D^{20}$ +3.7 (*c* 1.84, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.38 (dd, *J*=14.4, 9.7 Hz, 1H, *CH*=CHI), 5.97 (d, *J*=14.4 Hz, 1H, *CHI*=CH), 3.94 (dq, *J*=6.2, 3.6 Hz, 1H, CHOSi), 1.95 (ddt, *J*=9.8, 6.1, 3.8 Hz, 1H, *CH*CH_2), 1.54−1.64 (m, 1H, $CH_AH_BCH_3$), 1.29−1.40 (m, 1H, $CH_BH_ACH_3$), 1.11 (d, *J*=6.2 Hz, 3H, CH_3CH), 1.06 (s, 21H, 3×CH$(CH_3)_2$), 0.86 (t, *J*=7.4 Hz, 3H, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.5 (CH), 75.3 (CH), 70.6 (CH), 56.8 (CH), 22.4 (CH_2), 21.1 (CH_3), 18.2 (3×CH$(CH_3)_2$), 12.7 (CH_3); IR (thin film): 2961, 2943, 2866, 1463, 1155, 1131, 1108, 1054, 998, 951, 882, 677 cm^{-1}; HRMS [M^+−*i*-Pr] calcd: 353.0798, found: 353.0807.

6.2.17. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-[(E)-(1R,2S,3R,7S,8R)-2-(tert-butyldimethylsilanyloxy)-7-ethyl-4-hydroxy-1,3-dimethyl-8-triisopropylsilanyloxynon-5-enyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**45**) and (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-bis-[(E)-(1R,2R,3S,7S,8R)-2-(tert-butyldimethylsilanyloxy)-7-ethyl-1,3-dimethyl-4-oxo-8-triisopropylsilanyloxynon-5-enyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**47**)

t-BuLi (1.7 M in pentane, 0.54 mL, 0.918 mmol) was added dropwise to a stirred solution of vinyliodide **42** (180 mg, 0.454 mmol) in 4.5 mL Et_2O at −78 °C. The reaction mixture was stirred at −78 °C for 20 min and at 0 °C for 10 min before being re-cooled to −78 °C. A solution of bis-aldehyde **38** (128 mg, 0.175 mmol) in 6.0 mL Et_2O was added dropwise and the reaction mixture was stirred at −78 °C for 20 min and at 0 °C for 20 min. The reaction was quenched with 5.0 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted four times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 10:1) gave bis-allylic alcohol **45** (198 mg, 89%) as an inseparable mixture of diastereomers (dr=2:1:1); R_f=0.27 (hexane/ethyl acetate, 10:1).

Dess−Martin periodinane (362 mg, 0.854 mmol) was added in one portion to a stirred solution of the diastereomeric mixture of bis-allylic alcohol **45** (198 mg, 0.155 mmol) in 10 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred at room temperature for 6 h before being quenched with 4 mL of a 1.0 M solution of $Na_2S_3O_3$ and 10 mL of a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 15:1) gave bis-enone **47** (162 mg, 82%) as a highly viscous gum. R_f=0.20 (hexane/ethyl acetate, 15:1); $[\alpha]_D^{20}$ +96.6 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ=6.90 (dd, *J*=15.3, 11.2 Hz, 2H, C_3−H), 6.79 (dd, *J*=15.9, 9.4 Hz, 2H, C_{13}−H), 6.16 (d, *J*=15.9 Hz, 2H, C_{12}−H), 5.97 (dd, *J*=15.0, 11.2 Hz, 2H, C_4−H), 5.57 (d, *J*=15.3 Hz, 2H, C_2−H), 5.56 (dd, *J*=15.1, 11.3 Hz, 2H, C_5−H), 4.96 (d, *J*=10.0 Hz, 2H, C_7−H), 4.03 (m, 4H, C_9−H, C_{15}−H), 3.11 (m, 2H, C_{10}−H), 2.38 (m, 2H, C_6−H), 2.12 (m, 2H, C_{14}−H), 1.96 (m, 2H, C_8−H), 1.74 (m, 2H, C_{14}−CH_AH_B), 1.45 (m, 2H, C_{14}−CH_BH_A), 1.12 (d, *J*=7.0 Hz, 6H, C_{10}−CH_3), 1.10 (d, *J*=6.3 Hz, C_{15}−CH_3), 1.06

(s, 42H, 6×*i*-Pr), 1.03 (d, *J*=7.2 Hz, 6H, C_8−CH_3), 0.95 (d, *J*=6.6 Hz, 6H, C_6−CH_3), 0.86 (s, 18H, 2×*t*-Bu), 0.86 (t, *J*=7.3 Hz, 6H, C_{14}−CH_2CH_3), 0.09 (s, 6H, 2×CH_3Si), −0.02 (s, 6H, 2×CH_3Si); ^{13}C NMR (151 MHz, $CDCl_3$): δ=202.4 (C), 167.3 (C), 148.7 (CH), 145.0 (CH), 144.1 (CH), 131.0 (CH), 130.8 (CH), 121.6 (CH), 76.0 (CH), 75.9 (CH), 70.9 (CH), 53.1 (CH), 47.3 (CH), 42.4 (CH), 37.8 (CH), 26.2 (3×CH_3), 22.2 (CH_2), 21.0 (CH_3), 18.4 (C), 18.2 (6×CH_3), 16.1 (CH_3), 13.1 (CH_3), 12.6 (3×CH), 12.5 (CH_3), 10.9 (CH_3), −3.7 (CH_3), −3.9 (CH_3); IR (thin film): 2963, 2951, 2944, 2867, 1717, 1109, 1085, 1056, 998 cm^{-1}; HRMS [MNa^+] calcd: 1291.8779, found: 1291.8795.

*6.2.18. Efomycine M (**1**)*

Bis-enone **47** (57 mg, 44.8 μmol) was dissolved in 2.0 mL of THF and 3.0 mL of MeCN in a polyethylene vessel and the solution was cooled to 0 °C. HF·pyridine complex (70%, 0.15 mL, 5.77 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature. Stirring was continued for 72 h. The reaction was quenched by the addition of 0.5 mL of a saturated solution of $NaHCO_3$ and one spatula of solid $NaHCO_3$. The precipitate was filtered off over Celite and washed excessively with CH_2Cl_2. The crude product was concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 1:6) gave 23 mg (70%) efomycine M (**1**) as a colourless solid. R_f=0.33 (ethyl acetate); $[\alpha]_D^{20}$ +104.3 (*c* 1.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$, 7 mg): δ=6.95 (dd, *J*=15.3, 11.2 Hz, 2H, C_3−H), 6.72 (dd, *J*=15.8, 9.6 Hz, 2H, C_{13}−H), 6.23 (d, *J*=15.8 Hz, 2H, C_{12}−H), 6.04 (dd, *J*=15.0, 11.2 Hz, 2H, C_4−H), 5.64 (dd, *J*=15.0, 9.8 Hz, 2H, C_5−H), 5.60 (d, *J*=15.5 Hz, 2H, C_2−H), 5.08 (dd, *J*=10.3, 1.6 Hz, 2H, C_7−H), 3.81 (m, 2H, C_{15}−H), 3.74 (br dd, *J*=9.3, 2.6 Hz, 2H, C_9−H), 3.31 (br s, 2H, C_9−OH), 2.89 (dq, *J*=7.1, 2.7 Hz, 2H, C_{10}−H), 2.48 (tq, *J*=10.0, 6.6 Hz, 2H, C_6−H), 2.03 (m, 2H, C_{14}−H), 1.94 (m, 2H, C_8−H), 1.61 (m, 2H, C_{14}−CH_AH_B), 1.42 (br m, 2H, C_{14}−CH_BH_A), 1.17 (d, *J*=6.3 Hz, 6H, C_{15}−CH_3), 1.16 (d, *J*=7.1 Hz, 6H, C_{10}−CH_3), 1.03 (d, *J*=6.7 Hz, 6H, C_6−CH_3), 0.92 (d, *J*=7.0 Hz, 6H, C_8−CH_3), 0.86 (t, *J*=7.4 Hz, 6H, C_{14}−CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ=203.2 (C), 168.4 (C), 147.6 (CH), 145.2 (CH), 144.5 (CH), 131.3 (CH), 131.0 (CH), 121.1 (CH), 76.6 (CH), 71.5 (CH), 69.5 (CH), 52.4 (CH), 45.5 (CH), 41.5 (CH), 36.0 (CH), 23.5 (CH_2), 21.3 (CH_3), 15.3 (CH_3), 11.9 (CH_3), 9.3 (CH_3), 9.2 (CH_3); IR (thin film): 3470 (br), 2963, 1703, 1699, 1695, 1683, 1652, 1634, 1222, 1183, 1145, 997 cm^{-1}; HRMS [MNa^+] calcd: 751.4397, found: 751.4374.

*6.3. Formal total synthesis of elaiolide (**3**)*

6.3.1. tert-Butyl-(2R,3S,4S)-3-methoxymethoxy-4-(2S,4S,5S)-4-methoxyphenyl-5-methyl-[1,3]-dioxan-4-yl-2-methylpentyloxydiphenylsilane

DIPEA (1.62 mL, 9.30 mmol) and MOMCl (0.71 mL, 9.35 mmol) were added to a stirred solution of crude alcohol **16** (1.023 g, calcd as 1.55 mmol) in 10 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 36 h and the temperature was allowed to warm up to room temperature during that period. The reaction was quenched by the addition of 20 mL of a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 7:1) gave the MOM-ether (780 mg, 83% over two steps) as a colourless oil. R_f=0.36 (hexane/ethyl acetate, 5:1); $[\alpha]_D^{20}$ +20.3 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66 (m, 4H, H_{arom}), 7.32−7.43 (series of m, 8H, H_{arom}), 6.85 (m, 2H, H_{arom}), 5.46 (s, 1H, OCHO), 4.70, 4.62 (AB system, *J*=5.9 Hz, 1H, OCH_2O), 4.14 (dd, *J*=11.1, 4.6 Hz, 1H, CH_AH_BO), 3.95 (dd, *J*=10.1, 1.3 Hz, 1H, CHO), 3.81 (part A of dd, *J*=1.8 Hz, 0.5H, CHO), 3.79 (s, 3.5H, part B of dd, OCH_3), 3.64 (dd, *J*=9.9, 8.9 Hz, 1H, CH_AH_BOSi), 3.54 (dd, *J*=9.9, 5.1 Hz, 1H, CH_BH_AOSi), 3.52 (d, *J*=10.6 Hz, 1H, CH_BH_AO), 3.28 (s, 3H, OCH_3), 2.10 (m, 1H, $CHCH_3$), 1.86−1.98 (m, 2H, 2×$CHCH_3$), 1.03 (s, 9H, *t*-Bu), 0.90 (d, *J*=7.0 Hz, 3H, CH_3CH), 0.78 (d, *J*=7.1 Hz, 3H, CH_3CH), 0.76 (d, *J*=7.0 Hz, 3H, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.6 (C), 135.6 (CH), 135.6 (CH), 133.9 (C), 129.5 (CH), 127.6 (CH), 127.2 (CH), 113.5 (CH), 100.6 (CH), 99.0 (CH_2), 81.5 (CH), 79.2 (CH), 73.4 (CH_2), 66.4 (CH_2), 55.9 (CH_3), 55.3 (CH_3), 37.2 (CH), 36.2 (CH), 30.5 (CH), 26.8 (*t*-Bu), 19.2 (C), 12.0 (CH_3), 10.0 (CH_3), 9.1 (CH_3); IR (thin film): 2959, 2931, 2857, 1616, 1518, 1462, 1428, 1385, 1250, 1171, 1157, 1113, 1092, 1039, 972, 825, 703 cm^{-1}; HRMS [M^+−MeOH] calcd: 549.2672, found: 549.2665.

*6.3.2. (2S,3S,4R,5S,6R)-7-tert-Butyldiphenylsilanoxy-3-(4-methoxybenzyloxy)-5-methoxymethoxy-2,4,6-trimethylheptan-1-ol (**17**)*

DIBAL-H (1.5 M in toluene, 11.5 mL, 17.25 mmol) was added within 5 min to a stirred solution of the PMP-acetal (3.33 g, 5.49 mmol) in 65 mL CH_2Cl_2 at −5 °C. The reaction mixture was stirred at 0 °C for 50 min and then quenched by the addition of 40 mL of a saturated solution of Na/K/tartrate. The organic phase was separated and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 3:1) gave alcohol **17** (3.15 g, 94%) as a colourless oil. R_f=0.27 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +5.7 (*c* 1.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (m, 4H, H_{arom}), 7.35−7.45 (series of m, 6H, H_{arom}), 7.28 (m, 2H, H_{arom}), 6.85 (m, 2H, H_{arom}), 4.85, 4.65 (AB system, *J*=6.4 Hz, 2H, OCH_2O), 4.74, 4.60 (AB system, *J*=10.6 Hz, 2H, OCH_2Ar), 3.96 (dd, *J*=9.5, 1.5 Hz, 1H, CHO), 3.84 (dd, *J*=7.9, 1.5 Hz, 1H, CHO), 3.78 (s, 3H, OCH_3), 3.67 (dd, *J*=11.1, 7.2 Hz, 1H, CHO), 3.62 (dd, *J*=11.0, 3.5 Hz, 1H, CHO), 3.55 (m, 2H, 2×CHO), 3.39 (s, 3H, OCH_3), 3.02 (br s, 1H, OH), 1.91−1.97 (series of m, 2H, 2×$CHCH_3$), 1.82 (m, 1H, $CHCH_3$), 1.06 (s, 9H, *t*-Bu), 0.93 (2×d∼t, *J*=7.4 Hz, 6H, 2×CH_3), 0.75 (d, *J*=6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.1 (C), 135.5 (CH), 133.6 (C), 133.6 (C), 130.9 (C), 129.6 (CH), 129.2 (CH), 127.7 (CH), 113.8 (CH),

98.3 (CH_2), 83.5 (CH), 81.3 (CH), 74.2 (CH_2), 66.8 (CH_2), 66.1 (CH_2), 55.7 (CH_3), 55.2 (CH_3), 39.0 (CH), 38.9 (CH), 37.4 (CH), 26.9 (*t*-Bu), 19.2 (C), 14.9 (CH_3), 10.9 (CH_3), 9.1 (CH_3); IR (thin film): 3488 (br), 2931, 1514, 1472, 1428, 1248, 1141, 1112, 1085, 1035, 823 cm^{-1}; HRMS [M^+−*t*-Bu] calcd: 551.2829, found: 551.2818.

*6.3.3. (2R,3R,4R,5S,6R)-7-(tert-Butyldiphenylsilanyloxy)-3-(4-methoxybenzyloxy)-5-methoxymethoxy-2,4,6-trimethylheptanal (**19**) and (2E,4E)-(6S,7S,8R,9S,10R)-11-(tert-butyldiphenylsilanyloxy)-7-(4-methoxybenzyloxy)-9-methoxymethoxy-6,8,10-trimethylundeca-2,4-dienoic acid methyl ester (**21**)*

Dess–Martin periodinane (6.67 g, 15.73 mmol) was added in one portion to a stirred solution of alcohol **17** (3.012 g, 4.947 mmol) in 40 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and for 6 h at room temperature. The reaction was quenched with 40 mL of a 1.0 M solution of $Na_2S_2O_3$ and 20 mL of a saturated solution of $NaHCO_3$. Solid $NaHCO_3$ was added in small portions until two clear phases were obtained. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave aldehyde **19** (2.629 g, 88%) as a colourless oil. The product was used in the next step immediately. ^1H NMR (400 MHz, $CDCl_3$): δ=9.83 (d, *J*=2.7 Hz, 1H, HCO), 7.65 (m, 4H, H_{arom}), 7.34–7.45 (series of m, 6H, H_{arom}), 7.21 (m, 2H, H_{arom}), 6.82 (m, 2H, H_{arom}), 4.84, 4.64 (AB system, *J*=6.4 Hz, 2H, OCH_2O), 4.64, 4.49 (AB system, *J*=10.7 Hz, 2H, OCH_2O), 4.12 (dd, *J*=8.0, 1.6 Hz, 1H, CHO), 3.99 (dd, *J*=9.5, 1.7 Hz, 1H, CHO), 3.78 (s, 3H, OCH_3), 3.55 (m, 2H, CH_AH_BOSi), 3.38 (s, 3H, OCH_3), 2.72 (ddq, *J*=9.7, 7.0, 2.7 Hz, 1H, *CH*CH_3), 1.92 (m, 1H, *CH*CH_3), 1.79 (m, 1H, *CH*CH_3), 1.07 (d, *J*=7.0 Hz, 3H, *CH*$_3$CH), 1.04 (s, 9H, *t*-Bu), 0.93 (d, *J*=7.1 Hz, 3H, *CH*$_3$CH), 0.73 (d, *J*=6.9 Hz, 3H, *CH*$_3$CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.9 (CH), 159.0 (C), 135.6 (CH), 135.5 (CH), 133.7 (C), 133.7 (C), 130.9 (C), 129.7 (CH), 128.9 (CH), 127.7 (CH), 113.7 (CH), 98.7 (CH_2), 80.8 (CH), 79.7 (CH), 73.4 (CH_2), 66.0 (CH_2), 55.7 (CH_3), 55.2 (CH_3), 50.3 (CH), 38.8 (CH), 37.4 (CH), 26.9 (*t*-Bu), 19.2 (C), 11.8 (CH_3), 10.5 (CH_3), 9.1 (CH_3).

A solution of LDA was prepared by the addition of *n*-BuLi (2.5 M in hexane, 2.80 mL, 7.0 mmol) to a solution of DIPA (1.0 mL, 7.12 mmol) in 10 mL THF at 0 °C and stirred for 25 min. A solution of phosphonate **10** (1.7 g, 7.20 mmol) in 45 mL THF was cooled to −78 °C and the freshly prepared solution of LDA was added dropwise. The reaction mixture was stirred for 3.5 h and the temperature was allowed to warm up to −20 °C during that period. The reaction mixture was recooled to −78 °C and a solution of aldehyde **19** (2.629 g, 4.332 mmol) in 15 mL THF was added dropwise within 5 min. The reaction mixture was stirred overnight and the temperature was allowed to warm up to room temperature during that period. The reaction was quenched with 30 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography gave diene **21** (2.86 g, 96%, *E*/*Z* >50:1) as a highly viscous oil. R_f=0.55 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −38.6 (*c* 1.32, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.64–7.69 (m, 4H, H_{arom}), 7.34–7.45 (m, 6H, H_{arom}), 7.26–7.33 (m, 1H, C_3–H), 7.22 (m, 2H, H_{arom}), 6.82 (m, 2H, H_{arom}), 6.23 (m, 2H, C_4–H, C_5–H), 5.80 (d, *J*=15.3 Hz, 1H, C_2–H), 4.77, 4.62 (AB system, *J*=6.4 Hz, 2H, C_9–OCH_2), 4.57, 4.51 (AB system, *J*=10.7 Hz, 2H, C_7–OCH_2), 3.91 (dd, *J*=8.7, 1.5 Hz, 1H, C_9–H), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.65 (dd, *J*=6.7, 2.5 Hz, 1H, C_7–H), 3.57 (t, *J*=9.7 Hz, 1H, C_{11}–H_A), 3.51 (dd, *J*=10.1, 5.9 Hz, 1H, C_{11}–H_B), 3.35 (s, 3H, OCH_3), 2.60 (ddq∼tq, *J*=10.1, 6.8 Hz, 1H, C_6–H), 1.92 (m, 1H, C_{10}–H), 1.84 (m, 1H, C_8–H), 1.07 (d, *J*=6.8 Hz, 3H, C_6–CH_3), 1.06 (s, 9H, *t*-Bu), 0.91 (d, *J*=7.0 Hz, 3H, C_8–CH_3), 0.76 (d, *J*=6.9 Hz, 3H, C_{10}–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.7 (C), 158.9 (C), 147.1 (CH), 145.4 (CH), 135.6 (CH), 135.5 (CH), 133.7 (C), 133.7 (C), 131.3 (C), 129.6 (CH), 128.9 (CH), 127.9 (CH), 127.7 (CH), 119.0 (CH), 113.7 (CH), 98.4 (CH_2), 82.3 (CH), 80.5 (CH), 73.7 (CH_2), 66.4 (CH_2), 55.6 (CH_3), 55.2 (CH_3), 51.4 (CH_3), 41.6 (CH), 38.9 (CH), 37.2 (CH), 26.9 (*t*-Bu), 19.2 (C), 17.5 (CH_3), 10.9 (CH_3), 9.6 (CH_3); IR (thin film): 2931, 1718, 1642, 1614, 1514, 1429, 1302, 1248, 1143, 1112, 1035, 824, 741, 703 cm^{-1}; HRMS [M^+−MeOH] calcd: 656.3533, found: 656.3526.

*6.3.4. (2E,4E)-(6S,7S,8R,9S,10R)-11-(tert-Butyldiphenylsilanyloxy)-7-hydroxy-9-methoxymethoxy-6,8,10-trimethylundeca-2,4-dienoic acid methyl ester (**23**)*

DDQ (320 mg, 1.497 mmol) was added in small portions over a period of 3 h to a vigorously stirred solution of PMB-ether **21** (520 mg, 0.755 mmol) in 15 mL CH_2Cl_2 and 10 mL of a 0.5 M pH 7 phosphate buffer at room temperature. The reaction mixture was then stirred overnight. The reaction was quenched with 10 mL of a saturated solution of $NaHCO_3$ and diluted with 20 mL CH_2Cl_2 and 20 mL H_2O. Solid $NaHCO_3$ was added in small portions until two homogenous phases were obtained. The organic phase was separated and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 7:1) gave *seco*-ester **23** (398 mg, 91%) as a highly viscous oil. R_f=0.45 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +2.3 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.64 (m, 4H, H_{arom}), 7.35–7.45 (m, 6H, H_{arom}), 7.28–7.34 (m, 1H, C_3–H), 6.20–6.29 (m, 2H, C_4–H, C_5–H), 5.81 (d, *J*=15.3 Hz, 1H, C_2–H), 4.77, 4.61 (AB system, *J*=6.2 Hz, 2H, C_9–OCH_2O), 3.82 (dd, *J*=8.5, 2.9 Hz, 1H, C_9–H), 3.73 (s, 3H, OCH_3), 3.69 (m, 1H, C_7–H), 3.53 (br d, *J*=7.1 Hz, 2H, C_{11}–H_AH_B), 3.41 (br d, *J*=3.0 Hz, 1H, C_7–OH), 3.37 (s, 3H, OCH_3), 2.42 (m, 1H, C_6–H), 1.91 (m, 1H, C_{10}–H), 1.80 (m, 1H, C_8–H), 1.05 (s, 9H, *t*-Bu), 0.92 (d, *J*=6.9 Hz, 3H, C_6–CH_3), 0.85 (d, *J*=6.9 Hz, 3H, C_8–CH_3),

0.79 (d, J=6.9 Hz, 3H, C_{10}–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.7 (C), 149.0 (CH), 145.5 (CH), 135.6 (CH), 135.5 (CH), 133.6 (C), 133.6 (C), 129.7 (CH), 129.7 (CH), 127.7 (CH), 118.9 (CH), 99.0 (CH_2), 81.6 (CH), 73.0 (CH), 65.9 (CH_2), 56.2 (CH_3), 51.4 (CH_3), 40.3 (CH), 37.5 (CH), 36.3 (CH), 26.9 (*t*-Bu), 19.2 (C), 16.2 (CH_3), 10.2 (CH_3), 9.4 (CH_3); IR (thin film): 3503, 2962, 2931, 2858, 1718, 1642, 1429, 1262, 1142, 1112, 1090, 1028, 1005, 824, 741 cm^{-1}; HRMS [M^+–*t*-Bu] calcd: 479.2254, found:479.2243.

6.3.5. (2E,4E)-(6S,7S,8R,9S,10R)-11-(tert-Butyldiphenylsilanyloxy)-7-hydroxy-9-methoxymethoxy-6,8,10-trimethylundeca-2,4-dienoic acid (**25**)

A solution of LiOH·H_2O (99 mg, 2.359 mmol) in 4.8 mL H_2O was added to a stirred solution of methyl ester **23** (480 mg, 0.844 mmol) in 7.0 mL THF at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for 24 h. The reaction was quenched by the addition of AcOH (0.30 mL, 5.20 mmol) at 0 °C. The organic layer was separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 2:1) gave *seco*-acid **25** (455 mg, 97%) as a slightly yellow, highly viscous gum. R_f=0.22 (hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}$ +2.8 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64 (m, 4H, H_{arom}), 7.35–7.46 (m, 7H, H_{arom}, C_3–H), 6.23–6.33 (m, 2H, C_4–H, C_5–H), 5.80 (d, J=15.3 Hz, 1H, C_2–H), 4.77, 4.61 (AB system, J=6.2 Hz, 2H, C_9–OCH_2O), 3.82 (dd, J=8.5, 2.9 Hz, 1H, C_9–H), 3.71 (3.71, dd, J=9.6, 1.7 Hz, 1H, C_7–H), 3.53 (br d, J=7.1 Hz, 2H, C_{11}–H_AH_B), 3.38 (s, 3H, OCH_3), 2.45 (m, 1H, C_6–H), 1.92 (m, 1H, C_{10}–H), 1.81 (m, 1H, C_8–H), 1.06 (s, 9H, *t*-Bu), 0.93 (d, J=6.8 Hz, 3H, C_6–CH_3), 0.86 (d, J=6.9 Hz, 3H, C_8–CH_3), 0.79 (d, J=6.9 Hz, C_{10}–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.0 (C), 150.1 (CH), 147.6 (CH), 135.6 (CH), 135.5 (CH), 133.6 (C), 133.6 (C), 129.7 (CH), 129.7 (CH), 127.7 (CH), 127.7 (CH), 118.5 (CH), 99.0 (CH_2), 81.7 (CH), 73.1 (CH), 65.9 (CH_2), 56.2 (CH_3), 40.3 (CH), 37.5 (CH), 36.3 (CH), 26.9 (*t*-Bu), 19.2 (C), 16.2 (CH_3), 10.2 (CH_3), 9.4 (CH_3); IR (thin film): 3480, 2962, 2931, 2858, 1688, 1112, 1027, 702 cm^{-1}; HRMS [MNa^+] calcd: 577.2961, found: 577.2951.

6.3.6. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-[(1S,2S,3R)-4-(tert-butyldiphenylsilanyloxy)-2-methoxymethoxy-1,3-dimethylbutyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**35**)

NEt_3 (0.21 g, 1.507 mmol) and 2,4,6-trichlorobenzoylchloride (120 μL, 0.768 mmol) were added to a stirred solution of *seco*-acid **25** (290 mg, 0.523 mmol) in 18 mL toluene at room temperature. The reaction mixture was stirred for 2.5 h. A solution of 4-dimethylaminopyridine (300 mg, 2.456 mmol) in 4 mL toluene was added over a period of 3 h with a syringe pump and the reaction mixture was stirred overnight. The reaction was quenched by the addition of 12 mL of a 1.0 M solution of $KHSO_4$. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 5:1) gave macrodiolide **35** (130 mg, 47%) as a highly viscous oil. It should be mentioned that an up-scaling of the reaction was accompanied with a decrease of the yield. R_f=0.32 (hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}$ +29.0 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66 (m, 8H, H_{arom}), 7.34–7.43 (m, 12H, H_{arom}), 6.96 (dd, J=15.3, 11.2 Hz, 2H, C_3–H), 6.03 (dd, J=15.0, 11.2 Hz, 2H, C_4–H), 5.70 (dd, J=15.0, 9.9 Hz, 2H, C_5–H), 5.57 (d, J=15.4 Hz, 2H, C_2–H), 5.08 (d, J=10.3 Hz, 2H, C_7–H), 4.72, 4.57 (AB system, J=6.3 Hz, 4H, C_9–OCH_2), 3.72 (dd, J=9.9, 8.6 Hz, 2H, C_{11}–H_A), 3.54 (m, 4H, C_9–H, C_{11}–H_B), 3.28 (s, 6H, C_9–OCH_3), 2.50 (ddq, J=10.2, 9.9, 6.3 Hz, 2H, C_6–H), 1.98 (m, 2H, C_8–H), 1.89 (m, 2H, C_{10}–H), 1.05 (d, J=6.6 Hz, 6H, C_6–CH_3), 1.03 (s, 18H, *t*-Bu), 0.91 (d, J=7.0 Hz, 6H, C_8–CH_3), 0.83 (d, J=6.9 Hz, 6H, C_{10}–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.7 (C), 145.5 (CH), 144.8 (CH), 135.6 (CH), 135.6 (CH), 134.1 (C), 134.0 (C), 130.7 (CH), 129.5 (2×CH), 127.6 (2×CH), 121.2 (CH), 99.6 (CH_2), 80.4 (CH), 76.3 (CH), 66.4 (CH_2), 55.8 (CH_3), 42.1 (CH), 37.5 (CH), 36.3 (CH), 26.8 (*t*-Bu), 19.2 (C), 16.0 (CH_3), 10.2 (CH_3), 9.6 (CH_3); IR (thin film): 2964, 2931, 1715, 1221, 1140, 1112, 1034, 999, 877, 744, 702 cm^{-1}; HRMS [MNa^+] calcd: 1095.5814, found: 1095.5821.

6.3.7. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-((1S,2S,3R)-4-hydroxy-2-methoxymethoxy-1,3-dimethylbutyl)-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione

A solution of TBAF (1.0 M in THF, 0.50 mL, 0.50 mmol) was added to a stirred solution of bis-TBDPS ether **35** (122 mg, 1.136 mmol) in 4 mL THF at 0 °C. The reaction mixture was stirred for 3 days and the temperature was allowed to warm up to room temperature during that period. The reaction was quenched by the addition of 5 mL of a saturated solution of NH_4Cl and diluted with Et_2O. The organic phase was separated and the aqueous phase was extracted four times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 1:1.25) gave the bis-diol (64 mg, 94%) as white needles. R_f=0.14 (hexane/ethyl acetate, 1:1); $[\alpha]_D^{20}$ +27.5 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.91 (dd, J=15.2, 11.2 Hz, 2H, C_3–H), 6.02 (dd, J=15.0, 11.2 Hz, 2H, C_4–H), 5.68 (dd, J=15.0, 9.9 Hz, 2H, C_5–H), 5.60 (d, J=15.4 Hz, 2H, C_2–H), 4.97 (d, J=10.2 Hz, 2H, C_7–H), 4.72 (s, 4H, C_9–OCH_2), 3.47–3.54 (m, 6H, C_9–H, C_{11}–H), 3.42 (s, 6H, C_9–OCH_3), 2.51 (ddq, J=10.1, 9.9, 6.6 Hz, 2H, C_6–H), 1.86–2.01 (m, 4H, C_8–H, C_{10}–H), 1.05 (d, J=6.6 Hz, 6H, C_6–CH_3), 0.91 (d, J=7.0 Hz, 6H, C_8–CH_3), 0.78 (d, J=6.9 Hz, 6H, C_{10}–CH_3), OH unidentified; ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.0 (C), 145.6 (CH), 144.8 (CH), 130.8 (CH), 121.4 (CH), 100.1 (CH_2), 80.9 (CH), 76.2 (CH), 64.5 (CH_2), 56.4 (CH_3), 42.1 (CH), 36.6 (CH), 36.3 (CH), 16.0 (CH_3), 9.8

(CH_3), 9.0 (CH_3); IR (thin film): 3401 (br), 2930, 1710, 1653, 1636, 1617, 1458, 1387, 1303, 1280, 1221, 1138, 1108, 1033, 999, 878 cm^{-1}; HRMS [MNa^+] calcd: 619.3458, found: 619.3464.

*6.3.8. (2S,3R,4S)-3-Methoxymethoxy-4-[(4E,6E,12E,14E)-(2S,3S,10S,11S)-10-((1S,2R,3S)-2-methoxymethoxy-1,3-dimethyl-4-oxobutyl)-3,11-dimethyl-8,16-dioxo-1,9-dioxacyclohexadeca-4,6,12,14-tetraen-2-yl]-2-methylpentanal (**37**) and (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-bis-((1S,2S,3R)-2-methoxymethoxy-1,3-dimethylpent-4-enyl)-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**48**)*

Dess–Martin periodinane (390 mg, 0.920 mmol) was added in one portion to a stirred solution of bis-diol (110 mg, 0.184 mmol) in 5 mL CH_2Cl_2 at 0 °C. Stirring was continued for 4 h at room temperature. The reaction was quenched by the addition of 4 mL of a 1.0 M solution of $Na_2S_2O_3$ and 6 mL of a saturated solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 3:1) gave bis-aldehyde **37** (102 mg, 94%) as a white solid. The product was immediately used in the next step.

n-BuLi (2.5 M solution in hexane, 0.39 mL, 0.975 mmol) was added dropwise to a stirred solution of methyl triphenylphosphonium bromide (348 mg, 0.974 mmol) in 4.5 mL THF at −45 °C. Stirring was continued for 30 min and the temperature was allowed to warm up to −35 °C. Stirring was continued for further 5 min at 0 °C. A solution of bis-aldehyde **37** (102 mg, 0.172 mmol) in 2.5 mL THF was added dropwise and the reaction mixture was stirred at 0 °C for 60 min and at ambient temperature for 60 min. The reaction was quenched by the addition of 5 mL of a saturated solution of NH_4Cl and diluted with 5 mL Et_2O. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 5:1) gave bis-olefin **48** (93 mg, 92%) as white crystals. R_f=0.69 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +88.0 (*c* 0.46, CH_2Cl_2); mp: 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.93 (dd, *J*=15.3, 11.2 Hz, 2H, C_3–H), 5.60 (dd, *J*=14.9, 11.3 Hz, 2H, C_4–H), 5.95 (ddd, *J*=17.4, 10.3, 7.1 Hz, 2H, C_{11}–H), 5.66 (dd, *J*=15.0, 9.9 Hz, 2H, C_5–H), 5.59 (d, *J*=15.4 Hz, 2H, C_2–H), 5.07 (d, *J*=9.7 Hz, 2H, C_7–H), 5.05 (m, 2H, C_{12}–H_A), 5.01 (m, 2H, C_{12}–H_B), 4.65, 4.59 (AB system, *J*=6.5 Hz, 4H, C_9–OCH_AH_BO), 3.39 (s, 6H, C_9–OCH_3), 3.19 (dd, *J*=8.2, 3.2 Hz, 2H, C_9–H), 2.40–2.50 (m, 4H, C_6–H, C_{10}–H), 1.98 (m, 2H, C_8–H), 1.04 (d, *J*=6.6 Hz, 6H, C_6–CH_3), 1.04 (d, *J*=6.9 Hz, 6H, C_{10}–CH_3), 0.97 (d, *J*=7.1 Hz, 6H, C_8–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.6 (C), 145.4 (CH), 144.7 (CH), 142.4 (CH), 130.8 (CH), 121.3 (CH), 113.9 (CH_2), 99.0 (CH_2), 84.7 (CH), 75.9 (CH), 56.1 (CH), 42.2 (CH), 40.0 (CH), 36.2 (CH), 16.0 (CH_3), 13.4 (CH_3), 10.6 (CH_3); IR (thin film): 2970, 2930, 2881, 17.8, 1638, 1616, 1301, 1221, 1180, 1141, 1101, 1070, 1031, 994, 952, 916, 875 cm^{-1}; HRMS [M^+] calcd: 588.3662, found: 588.3674.

*6.3.9. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-((1S,2S,3R)-2-hydroxy-1,3-dimethylpent-4-enyl)-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione and (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-bis-((1R,2S,3R)-1,3-dimethyl-2-triethylsilanyloxypent-4-enyl)-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**50**)*

TMSBr (0.06 mL, 0.450 mmol) was added dropwise to a stirred solution of bis-MOM-ether **48** (97 mg, 0.165 mmol) in 16 mL CH_2Cl_2 at −55 °C. Stirring was continued for 90 min and the reaction mixture was allowed to warm up to −15 °C. The reaction was quenched by the addition of 10 mL of a saturated solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Filtration over a short pad of silica gel (hexane/ethyl acetate, 3:1) gave the bis-diol (75 mg, 91%) as a white solid. The product was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.96 (dd, *J*=15.4, 11.2 Hz, 2H, C_3–H), 6.07 (dd, *J*=15.0, 11.2 Hz, 2H, C_4–H), 5.93 (ddd, *J*=17.3, 10.4, 7.0 Hz, 2H, C_{11}–H), 5.64 (dd, *J*=15.0, 9.6 Hz, 2H, C_5–H), 5.64 (d, *J*=15.3 Hz, 2H, C_2–H), 5.00–5.08 (6H, C_7–H, C_{12}–H), 3.28 (br d, *J*=8.8 Hz, 2H, C_9–H), 2.74 (br s, 2H, C_9–OH), 2.51 (ddq, *J*=9.8, 9.6, 6.6 Hz, 2H, C_6–H), 2.40 (m, 2H, C_{10}–H), 1.94 (m, 2H, C_8–H), 1.03 (d, *J*=6.7 Hz, 6H, C_6–CH_3), 1.00 (d, *J*=6.9 Hz, 6H, C_{10}–CH_3), 0.91 (d, *J*=7.0 Hz, 6H, C_8–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8 (C), 145.0 (CH), 144.5 (CH), 142.8 (CH), 131.5 (CH), 121.2 (CH), 114.0 (CH_2), 77.4 (CH), 74.6 (CH), 41.4 (CH), 39.1 (CH), 36.0 (CH), 15.2 (CH_3), 11.5 (CH_3), 9.3 (CH_3).

2,6-Lutidine (0.14 mL, 1.20 mmol) and TESOTf (0.11 mL, 0.487 mmol) were added dropwise to a stirred solution of the bis-diol (75 mg, 0.150 mmol) in 9 mL CH_2Cl_2 at −30 °C. The reaction mixture was stirred for 60 min and the temperature was allowed to warm up to −15 °C during that period. The reaction mixture was quenched by the addition of 5 mL of a saturated solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 30:1) gave bis-TES-ether **50** (101 mg, 93%) as colourless needles. R_f=0.20 (hexane/ethyl acetate, 15:1); $[\alpha]_D^{20}$ +96.5 (*c* 0.77, CH_2Cl_2); mp: 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.94 (dd, *J*=15.4, 11.2 Hz, 2H, C_3–H), 5.98 (dd, *J*=15.0, 11.2 Hz, 2H, C_4–H), 5.82 (ddd, *J*=17.4, 10.2, 7.3 Hz, 2H, C_{11}–H), 5.63 (dd, *J*=15.0, 9.9 Hz, 2H, C_5–H), 5.58 (d, *J*=15.3 Hz, 2H, C_2–H), 4.99–5.07 (m, 3H, C_{12}–H_AH_B, C_7–H), 3.47 (dd, *J*=6.2, 4.3 Hz, 2H, C_9–H), 2.35–2.44 (m, 4H, C_6–H, C_{10}–H), 1.89 (m, 2H, C_8–H), 1.01 (d, *J*=6.6 Hz, 6H, C_{10}–CH_3), 0.98 (d, *J*=6.8 Hz, 6H, C_6–CH_3), 0.96 (d, *J*=7.2 Hz, 6H, C_8–CH_3), 0.94 (t, *J*=7.9 Hz, 18H, CH_3CH_2), 0.62 (q, *J*=7.8 Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz,

$CDCl_3$): δ=167.4 (C), 145.1 (CH), 144.6 (CH), 142.6 (CH), 130.7 (CH), 121.4 (CH), 114.2 (CH_2), 78.4 (CH), 75.8 (CH), 42.4 (CH), 41.1 (CH), 37.4 (CH), 16.2 (CH_3), 13.9 (CH_3), 10.9 (CH_3), 7.1 (CH_3), 5.5 (CH_2); IR (thin film): 2960, 2876, 1705, 1697, 1685, 1638, 1458, 1299, 1282, 1226, 1143, 1120, 1006, 912, 740; HRMS [M^+] calcd: 728.4867, found: 728.4854.

*6.3.10. (3E,5E,11E,13E)-(7S,8S,15S,16S)-8,16-Bis-((1R,2R,3S)-1,3-dimethyl-4-oxo-2-triethylsilanyloxypentyl)-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (**13**)*

$PdCl_2$ (3.5 mg, 0.020 mmol) and CuCl (13 mg, 0.131 mmol) were added to a stirred suspension of **50** (33.7 mg, 0.046 mmol) in 1.5 mL DMF, 0.3 mL THF and 0.3 mL H_2O at room temperature. O_2 was bubbled through the reaction mixture for 15 min. Stirring was continued for 120 h at room temperature under an atmosphere of O_2. The reaction mixture was then diluted with 3 mL H_2O and 3 mL Et_2O. The organic phase was separated and the aqueous phase was extracted four times with EtOAc/Et_2O (1:1). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 7:1) gave bis-methylketone **13**[15a] (23.5 mg, 67%) as a white crystalline solid. Additionally, mono-methylketone (5 mg, 14%) was isolated. R_f=0.25 (hexane/ethyl acetate, 6.1); $[\alpha]_D^{20}$ +89.0 (*c* 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.94 (dd, *J*=15.3, 11.1 Hz, 2H, C_3–H), 5.99 (dd, *J*=15.1, 11.2 Hz, 2H, C_4–H), 5.63 (dd, *J*=15.0, 9.9 Hz, 2H, C_5–H), 5.59 (d, *J*=15.4 Hz, 2H, C_2–H), 4.94 (br d, *J*=10.1 Hz, 2H, C_7–H), 4.00 (dd, *J*=6.1, 4.3 Hz, 1H, C_9–H), 2.72 (dq, *J*=7.1, 4.3 Hz, 2H, C_{10}–H), 2.40 (m, 2H, C_6–H), 2.18 (s, 6H, C_{12}–H), 1.88 (m, 2H, C_8–H), 1.11 (d, *J*=7.1 Hz, 6H, C_{10}–CH_3), 1.01 (d, *J*=6.6 Hz, 6H, C_6–CH_3), 0.98 (d, *J*=7.1 Hz, 6H, C_8–CH_3), 0.93 (t, *J*=8.0 Hz, 18H, CH_3CH_2), 0.60 (q, *J*=8.0 Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=211.1 (C), 167.4 (C), 145.4 (CH), 144.4 (CH), 130.8 (CH), 121.3 (CH), 75.8 (CH), 74.8 (CH), 50.6 (CH), 42.4 (CH), 38.0 (CH), 29.3 (CH_3), 16.2 (CH_3), 11.5 (CH_3), 10.6 (CH_3), 7.0 (CH_3), 5.3 (CH_2); IR (thin film): 2952, 2876, 1718, 1707, 1226, 1144, 1125, 1005; HRMS [M^+] calcd: 760.4766, found: 760.4781.

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