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Studies toward the total synthesis of Cytospolide E

Paresh M. Vadhadiya, Jeetendra K. Rout, C.V. Ramana *

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411 008, India

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ABSTRACT

In this manuscript, we describe various approaches that we have examined towards the total synthesis of Cytospolide E. We initially attempted the RCM approach employing first and second generation Grubbs and Grubbs–Hoyeda catalysts resulting in the exclusive synthesis of the *Z*-isomer of Cytospolide E. With the Fürstner catalyst, the dimerization involving the less hindered olefin was the exclusive event. Alternative approach documented is a successful cross-metathesis leading to a *seco*-acid with the requisite *E*-configuration and undesired macrodiolide formation during the attempted Shiina's lactonization.

1. Introduction

Nonenolides are extremely important because of their extraordinary cytotoxic potential towards the cancerous cells. They also show a broad spectrum of bioactivities such as antifungal, antibacterial, antimicrofilament, and antimalarial activities. All the nonenolides are constructed with an even number of carbon atoms having a C-9 alkyl attachment.[1] In 2011, Zhang and co-workers reported the isolation of five new nonenolides from the fungus *Cytospora* sp. obtained from the acetone extraction of the *Ilex canariensis* shrub and named Cytospolides A–E.[2] Cyctospolides are characterized by an unprecedented 15 carbon atom skeleton having a C2 methyl group, which was rarely observed in this class of natural products. The structural interpretations and absolute configurations were determined with the help of spectroscopic techniques and single-crystal XRD together with the time dependent (TD)-DFT calculations of CD spectra. The Cytospolides A–D have a similar absolute configuration and vary mainly at the presence of acetate group(s) and its position. The Cytospolide E (**1**) is a C2 epimer of Cytospolide D. Interestingly, it exists as a mixture of conformers, which was confirmed by the soft pulse transfer NMR technique and DFT calculations. During the initial bioassay tests, these C2 epimers illustrated different cytotoxic properties against the A549 cell line, suggesting a probable stereochemical influence of the C2 methyl group in the growth inhibition of tumor cells (zero activity for Cytospolide A, B and D to IC_{50}=7.09 μg/mL for Cytospolide E). Furthermore, Zhang and co-workers reported the isolation of additional new members of this family, namely the Cytospolides F–Q and Decytospolides A and B, during their investigation on the trace compounds of the crude extract from same fungus *Cytospora* sp.[3]

In continuation of our interest in the synthesis of the nonenolide class of natural products using ring closing metathesis as a key step[4] and inspired with the cytotoxic activity of Cytospolide E, we have initiated a program to synthesize Cytospolide E. While our work was in progress, the synthesis of the *Z*-isomer of Cytospolide E was documented by the Yadav,[5] Nanda[6] and Kamal[7] groups by employing RCM-based approaches. Interestingly, even in the case of the synthesis of Cytospolide D, its unnatural *Z*-isomer was obtained when RCM was used as the key skeletal construct. However, the Kamal and Nanda groups were successful in obtaining the naturally occurring cytospolide D with the requisite *E*-configuration by employing the macrolactonization as the key reaction to construct the central nonenolide core.[7,8] Herein, we document the complete details of our efforts towards the synthesis of natural Cytospolide E culminating in various other possibilities although they were not successful in obtaining the natural *E*-configured Cytospolide E.

2. Results and discussion

The key retrosynthetic disconnections for Cytospolide E (**1**) are depicted in Fig. 1. Keeping the RCM as a key skeletal construct, the diene ester **2** was identified as the key advanced intermediate, which, in turn, could be obtained from the Yamaguchi esterification

* Corresponding author. Tel.: +91 20 2590 2577; fax: +91 20 2590 2629; e-mail address: vr.chepuri@ncl.res.in (C.V. Ramana).

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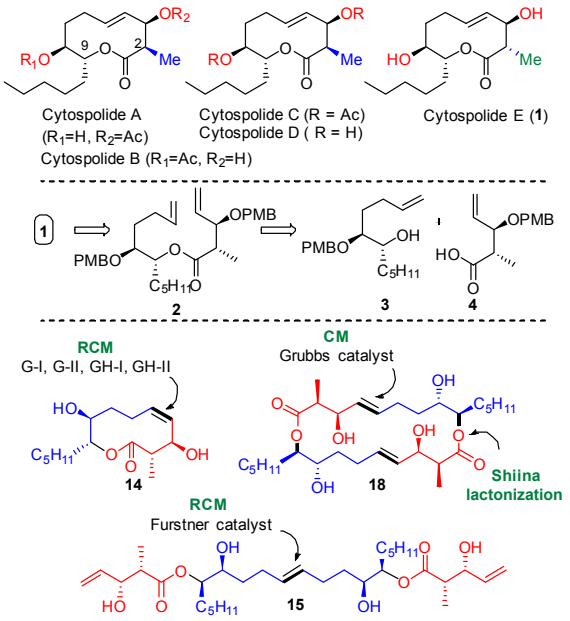
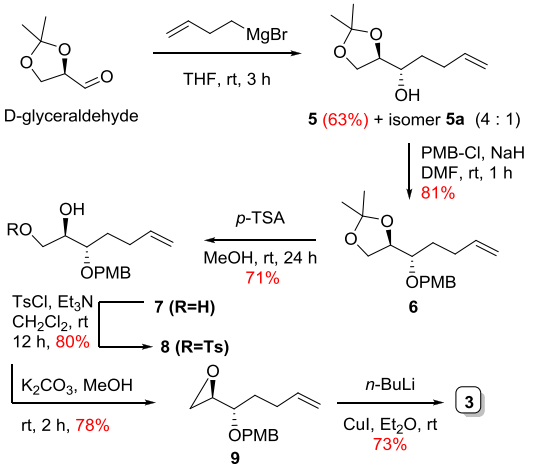


Fig. 1. Structures of Cytospolide A–E and key retrosynthetic disconnection for Cytospolide E (**1**).

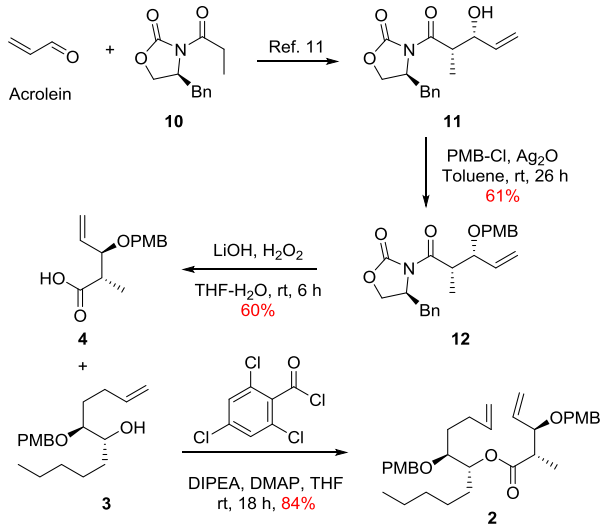
of an alcohol **3** and an acid **4**. The synthesis of alcohol **3** was planned from D-glyceraldehyde and acid **4** could be accessed by means of the asymmetric Evans aldol reaction of acrolein (Scheme 1).



Scheme 1. Synthesis of alcohol fragment **3**.

The synthesis of the key alcohol fragment **3** began with the addition of 3-butenylmagnesium bromide to D-glyceraldehyde (prepared freshly by means of the periodate cleavage of D-mannitol 1,2:5,6-diacetonide) to give a mixture of separable diastereomers **5** and **5a** in a 4:1 ratio with 78% yield.[9] The free hydroxyl group of the required anti-alcohol **5** was protected as its PMB ether using *p*-methoxy benzyl chloride (PMB-Cl) and NaH in *N*,*N*-dimethylformamide to afford compound **6** in 81% yield. Next, the deprotection of the acetonide group in compound **6** in the presence of catalytic *p*-TSA in methanol gave the diol **7** in 71% yield. The selectively tosylation of the primary hydroxyl of compound **7** was carried out using tosyl chloride and triethylamine in dichloromethane to afford the intermediate tosyl derivative **8** which was further transformed to the required epoxide **9** by treating with potassium carbonate in methanol. Finally, the regioselective opening of epoxide **9** was carried out using *n*-butyl lithium in presence of CuI and the required alcohol fragment **3** was obtained in 73% yield.[10]

The synthesis of the acid fragment **4** was started by the asymmetric aldol reaction between acrolein and Evans oxazolidinone **10** using $TiCl_4$ and diisopropylethylamine to give an allyl alcohol **11** in 73% yield.[11] The free hydroxyl group of allyl alcohol was protected as its PMB ether employing mild reaction conditions (using silver oxide and PMB-Cl in toluene for 26 h) in order to prevent epimerization at the α-position of the amide and hydrolysis of the chiral auxiliary. The reaction was sluggish and product **12** was isolated in 61% yield along with the unreacted **11**. The oxazolidinone thereafter was hydrolyzed under basic conditions to provide the requisite acid **4** (Scheme 2).



Scheme 2. Synthesis of diene ester **2**.

With both intermediates **3** and **4** in hand, our next task was their coupling. Accordingly, Yamaguchi esterification of the olefinic acid fragment **4** with the olefinic alcohol fragment **3** at ambient temperature provided the diene ester **2** in 84% yield.[12] This set the stage for the crucial ring-closing metathesis. Treatment of **2** with the Grubbs' second generation catalyst in CH_2Cl_2 at reflux temperature for 3 h gave the RCM product **13** with Z-geometry of the newly forming double bond in 73% yield. The structure of **13** was ascertained by its NMR spectrum. In the ^1H NMR spectrum of **13**, two olefinic protons were seen to resonate at δ 5.26 (t, *J*=9.9 Hz, 1H) and 5.75 (dt, *J*=3.4, 11.5 Hz) ppm as well as the terminal olefinic protons were seen to disappear. The low value of the coupling constant *J*=9.9 Hz and 11.5 Hz clearly reveals the Z-geometry of the newly formed olefin.

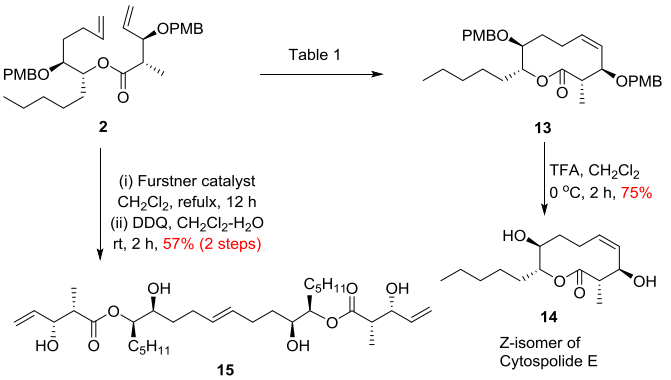
Other attempts for the ring-closing metathesis of diene ester **2** by employing CH_2Cl_2 or toluene as the solvent at different temperatures in combination with Grubbs' first generation catalyst (Ru-I) or Grubbs' second generation catalyst (Ru-II) or Hoveyda–-Grubbs' catalyst led to the formation of lactone **13** bearing a *cis*-geometry at the newly created double bond. These results are summarized in Table 1. Finally, the deprotection of PMB ethers of compound **13** using TFA in CH_2Cl_2 at 0 °C gave the *Z*-isomer of Cytospolide E **14** in 75% yield. Unexpected formation of *Z*-isomer may be attributed to the fact that the *Z*-isomer is thermodynamically more stable than the *E*-isomer. This result is in agreement with observations noticed by Gennari that less densely functionalized diene with lack of functionality at the allylic position or having functionality at only one allylic position resulted in the exclusive formation of the *Z*-isomer of the ten-membered carbocycles in the RCM reactions as a result of thermodynamic control.[13] As

Table 1
Attempted RCM of diene ester **2** via Scheme 3

Entry	Catalyst	Solvent	Product/yield
1	First Generation Grubbs Catalyst	CH_2Cl_2, Toluene	**13**, 71%
2	Second Generation Grubbs Catalyst	CH_2Cl_2, Toluene	**13**, 73%
3	First Generation Hoveyda–Grubbs Catalyst	CH_2Cl_2, Toluene	**13**, 68%
4	Second Generation Hoveyda–Grubbs Catalyst	CH_2Cl_2, Toluene	**13**, 70%
5	Fürstner Catalyst	CH_2Cl_2	**15**, 57%[a]

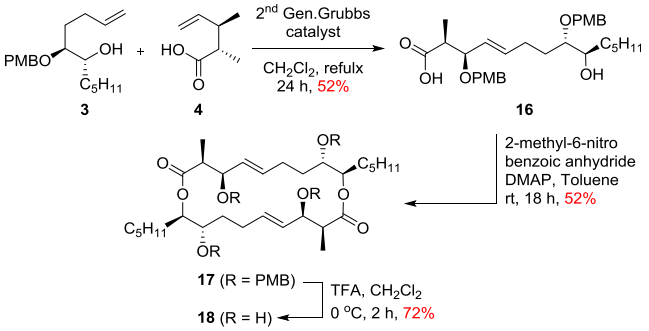
[a] Isolated yield after PMB deprotection.

suggested by Fürstner, the Grubbs catalysts, due to their higher overall activity, are able to isomerize the cycloalkenes formed during the course of the reaction and hence enrich the mixture in the thermodynamically favored product. Thus, to avoid equilibration of the products initially formed, a less reactive ruthenium indenylidene complex should be used.[14] Surprisingly, when the RCM of **2** was attempted using a catalytic amount of the ruthenium indenylidene complex with CH_2Cl_2 as solvent under reflux conditions, the purification of the metathesis product was found to be difficult, We subsequently subjected it for PMB deprotection with DDQ. Surprisingly, the homo metathesis product **15** was obtained as the major product. The structure of the homo metathesis product **15** was established with the help of spectral and mass analysis. In the ^{1}H NMR spectrum of **15**, two terminal and internal olefinic protons of the terminal olefin moiety were seen to resonate at δ 5.32 (br d, J=17.4 Hz, 2H), 5.20 (br d, J=10.4 Hz, 2H) and 5.81–5.90 ppm as a multiplet, respectively, whereas internal olefin protons were seen to resonate at δ 5.39 (t, J=5.0 Hz, 1.2H), 5.46 (t, J=3.8 Hz, 0.4H) ppm. Similarly, in the ^{13}C NMR spectrum, the terminal and internal olefinic carbons were seen to resonate at δ 116.3 (t, 2C), 137.5 (d, 2C) and 129.9 (d, 2C, Major) ppm, respectively. The structure of **15** was further supported by the presence of a peak at m/z 591.3865 ([M+Na]$^+$) in the ESI-HRMS spectrum of compound **15** (Scheme 3).



Scheme 3. RCM of diene ester **2**.

The failure in the synthesis of the natural Cytospolide E (by following Yamaguchi esterification and the RCM strategy) led us to think in the reverse direction of the ring closure. For that, we intended on a cross metathesis reaction at the beginning and an intramolecular esterification was planned at a later stage. According to the hypothesis, the cross metathesis in between the alcohol **3** and the acid **4** proceeded smoothly in the presence of Grubbs second generation catalyst under reflux conditions in CH_2Cl_2 for 24 h to give exclusively the alkene **16** having a *trans* geometry in 52% yield[15] (Scheme 4).



Scheme 4. Synthesis of macrodiolide **18**.

After having the fully characterized *seco*-acid **16** in hand, the next task was the lactonization to prepare the macrolide core. Attempted lactonization of *seco*-acid using Yamaguchi lactonization, Corey–Nicolaou lactonization methods or other coupling reagents such as DCC, EDCI resulted in a complex reaction mixture. However, the Shiina lactonization using 2-methyl-6-nitrobenzoic anhydride in the presence of DMAP proceeded smoothly to give a 20-membered macrolide **17** in 52% yield instead of the required 10-membered nonenolide.[16] The structure of **17** was confirmed by NMR as well as HRMS. The ^{1}H NMR and C NMR of compound **17** were found to be comparable to the expected 10 membered lactone. However in HRMS, the presence of a strong peak at 1043.5865 ([M+Na]$^+$, 100%) confirmed the presence of a 20-membered macrolide structure in **17**. Finally, global deprotection of the PMB groups in macrolide **17** was carried out using TFA in dichloromethane at 0 °C to give a 20-membered macrolide **18** in 72% yield. In the HRMS spectrum of compound **18**, the presence of a strong peak at 563.3550 ([M+Na]$^+$) indicated its dimeric structure. The NMR spectra of **18** was characterized by the presence of two sets of signals indicating mixture of two equilibrating conformational isomers. However, the lack of sufficient quantity, especially in its pure form, was the major hurdle in comprehensively assigning its structure.

3. Conclusion

In conclusion, we document various approaches toward the total synthesis of Cytospolide E that resulted with the synthesis of unwarranted end products. The requisite building blocks are synthesized from easily available D-glyceraldehyde and acrolein by following simple synthetic transformations. In general, the RCM based approaches resulted in the synthesis of the *Z*-isomer of Cytospolide E (with 2.02% overall yield) or when employed the Fürstner catalyst, the synthesis of an acyclic dimer. On the other hand, the attempted cross-metathesis of the requisite coupling partners and subsequent Shina's lactonization resulted in the isolation of a 20-membered macrodiolide. Overall, these investigations reveal that Cytospolide E is a unique nonenolide target that may not be accessed by metathesis approaches that are routinely employed for this family of natural products. Alternative approaches to accomplish the total synthesis of Cytospolide E are currently under progress in our laboratory.

4. Experimental section

4.1. General

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane, 1,2-dichloroethane, DMF from CaH_2; methanol

from Mg cake; toluene from LAH; THF on Na/benzophenone; triethylamine over KOH. Commercial reagents were used without purification. Column chromatography was carried out by using spectrochem silica gel (60–120, 100–200, 230–400 mesh). ^{1}H NMR spectra were recorded on JEOL AL-400 (400 MHz), Bruker AC 200 MHz, Bruker DRX 400 MHz and Bruker DRX 500 MHz spectrometers, and TMS was used as an internal standard of spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) and for $CDCl_3$ (7.25 ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL AL-400 (100 MHz), Bruker DRX (125 MHz), Bruker DRX (100 MHz) and Bruker AC (50 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). $CDCl_3$ or Methanol-d_4 was used as an NMR solvent. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

4.2. (*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol (5)

A suspension of Mg (3.7 g, 153.7 mmol) and catalytic iodine in dry THF (150 mL) was treated with butenyl bromide (11.7 mL, 115.7 mmol) and the contents were stirred at rt for 1 h. To this, a solution of the D-glyceraldehyde (10 g, 76.8 mmol) in THF (50 mL) was added drop wise at 0 °C and the mixture was stirred for another 1 h at rt. The reaction mixture was quenched with saturated ammonium chloride (200 mL) and extracted with ethyl acetate (2×200 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (10→12% EtOAc in pet ether) afforded **5** (9 g, 63%) and **5a** (2 g, 15%) as a colorless oil. $[\alpha]_D^{25}$ 17.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.40 (s, 3H), 1.42–1.65 (m, 2H), 2.03–2.16 (m, 3H), 3.75 (dt, *J*=3.9, 7.9 Hz, 1H), 3.84–4.05 (m, 3H), 4.94–5.08 (m, 2H), 5.71–5.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2 (q), 26.4 (q), 29.8 (t), 31.8 (t), 64.7 (t), 70.2 (d), 78.6 (d), 108.9 (s), 115.0 (t), 137.9 (d) ppm; HRMS (ESI+) calcd for $C_{10}H_{18}O_3Na$ 209.1148; Found 209.1147.

4.3. (*R*)-4-((*S*)-1-((4-Methoxybenzyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxolane (6)

To a cooled solution of **5** (8 g, 42.9 mmol) in anhydrous DMF (80 mL) were added NaH (60% dispersion in mineral oil, 2.1 g, 51.5 mmol) followed by PMB-Cl (6.4 mL, 47.2 mmol) and the contents stirred at rt for 4 h. The reaction mixture was quenched with aq Na_2SO_4 (200 mL) and the aqueous layer was extracted with EtOAc (2×200 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5–8% EtOAc in petroleum ether) to procure **6** (10.7 g, 81%) as a yellow oil. $[\alpha]_D^{25}$ 3.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (s, 3H), 1.57–1.68 (m, 2H), 2.10–2.26 (m, 2H), 3.54 (q, *J*=5.2 Hz, 1H), 3.79 (s, 3H), 3.87 (t, *J*=6.4 Hz, 1H), 4.10–4.13 (m, 2H), 4.50 (d, *J*=11.2 Hz, 1H), 4.59 (d, *J*=11.1 Hz, 1H), 4.93–5.07 (m, 2H), 5.71–5.91 (m, 1H), 6.85–6.89 (m, 2H), 7.24–7.29 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1 (q), 26.4 (q), 29.0 (t), 30.3 (t), 55.0 (q), 66.0 (t), 72.3 (t), 77.7 (d), 77.8 (d), 108.8 (s), 113.6 (d, 2C), 114.6 (t), 129.2 (d, 2C), 130.4 (s), 138.2 (d), 159.0 (s) ppm; HRMS (ESI+) calcd for $C_{18}H_{26}O_4Na$ 329.1723; Found 329.1720.

4.4. (2*R*,3*S*)-3-((4-Methoxybenzyl)oxy)hept-6-ene-1,2-diol (7)

At 0 °C, *p*-TSA (500 mg, 2.94 mmol) was added to a solution of **6** (9 g, 29.4 mmol) in dry MeOH (80 mL) and the contents was stirred at same temperature for 10 h. After completion, the reaction mixture was neutralized with $NaHCO_3$ and directly concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (60–70% EtOAc in petroleum ether) to procure **7** (5.55 g, 71%) as a yellow oil. $[\alpha]_D^{25}$ 3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65–1.83 (m, 2H), 2.08–2.23 (m, 2H), 3.44–3.76 (m, 4H), 3.80 (s, 3H), 4.47 (d, *J*=11.0 Hz, 1H), 4.55 (d, *J*=10.9 Hz, 1H), 4.96–5.08 (m, 2H), 5.70–5.91 (m, 1H), 6.87 (d, *J*=8.8 Hz, 2H), 7.23–7.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.3 (t), 29.5 (t), 55.1 (q), 63.3 (t), 72.0 (t), 72.7 (d), 79.5 (d), 113.7 (d, 2C), 114.8 (t), 129.4 (d, 2C), 130.1 (s), 138.2 (d), 159.1 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{22}O_4Na$ 289.1410; Found 289.1409.

4.5. (2*R*,3*S*)-2-Hydroxy-3-((4-methoxybenzyl)oxy)hept-6-en-1-yl 4-methylbenzenesulfonate (8)

At 0 °C, a solution of **7** (5 g, 18.8 mmol), triethylamine (3.1 mL, 22.5 mmol) and DMAP (Cat.) in Dry CH_2Cl_2 (50 mL) was treated with *p*-toluenesulfonyl chloride (4 g, 20.6 mmol) and stirred at rt for 12 h. The reaction was portioned between water (100 mL) and CH_2Cl_2 (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL). Combined organic layer was dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (30→35% EtOAc in petroleum ether) gave **8** (6.3 g, 80%) as yellow oil. $[\alpha]_D^{25}$ 3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.61 (m, 1H), 1.63–1.71 (m, 1H), 2.02–2.11 (m, 1H), 2.13–2.22 (m, 1H), 2.43 (s, 3H), 3.45–3.49 (m, 1H), 3.79 (s, 3H), 3.86–3.90 (m, 1H), 4.08 (dd, *J*=6.3, 10.6 Hz, 1H), 4.15 (dd, *J*=3.6, 10.6 Hz, 1H), 4.40 (d, *J*=10.9 Hz, 1H), 4.46 (d, *J*=10.9 Hz, 1H), 4.94–5.02 (m, 2H), 5.71–5.81 (m, 1H), 6.85 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.6 Hz, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 7.78 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (q), 29.0 (t), 29.2 (t), 55.2 (q), 70.8 (d), 71.3 (t), 72.1 (t), 78.0 (d), 113.8 (d, 2C), 115.0 (t), 128.0 (d, 2C), 129.5 (d, 2C), 129.9 (d, 2C), 130.1 (s), 132.6 (s), 138.1 (d), 145.0 (s), 159.3 (s) ppm; HRMS (ESI+) calcd for $C_{22}H_{28}O_6SNa$ 443.1499; Found 443.1493.

4.6. (*R*)-2-((*S*)-1-((4-Methoxybenzyl)oxy)pent-4-en-1-yl)oxirane (9)

To a solution of **8** (3 g, 7.13 mmol), in methanol (20 mL) was added K_2CO_3 (2.96 g, 21.4 mmol) at rt and stirred for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to afford **9** (1.39 g, 78%) as colorless oil. $[\alpha]_D^{25}$ −2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65–1.76 (m, 2H), 2.04–2.37 (m, 2H), 2.71 (dd, *J*=2.7, 5.3 Hz, 1H), 2.78 (dd, *J*=4.0, 5.2 Hz, 1H), 2.89–2.95 (m, 1H), 3.25 (q, *J*=5.6 Hz, 1H), 3.79 (s, 3H), 4.41 (d, *J*=11.2 Hz, 1H), 4.59 (d, *J*=11.2 Hz, 1H), 4.94–5.06 (m, 2H), 5.70–5.90 (m, 1H), 6.87 (d, *J*=8.8 Hz, 2H), 7.25 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.3 (t), 31.9 (t), 45.5 (t), 53.3 (d), 55.1 (q), 71.9 (t), 77.0 (d), 113.6 (d, 2C), 114.8 (t), 129.2 (d, 2C), 130.5 (s), 138.1 (d), 159.1 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{20}O_3Na$ 271.1305; Found 271.1320.

4.7. (5*S*,6*R*)-5-((4-Methoxybenzyl)oxy)undec-1-en-6-ol (3)

At 0 °C, a suspension of CuI (1.15 g, 6.0 mmol) in dry ether (20 mL) was treated with a solution of *n*-butyl lithium (7.5 mL, 12.08 mmol, 1.6 M solution in Hexane) and the contents were stirred at 0 °C for 20 min. To this, a solution of the epoxide **9** (1 g, 4.03 mmol) in dry ether (5 mL) was introduced and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with cold water (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude product was purified by silica gel column chromatography (12→15% EtOAc in petroleum ether) to

afford **3** (900 mg, 73%) as yellow oil. $[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.7 Hz, 3H), 1.30–1.80 (m, 9H), 1.98–2.36 (m, 3H), 3.35 (td, *J*=3.5, 9.0 Hz, 1H), 3.81 (s, 3H), 3.81–2.84 (m, 1H), 4.45 (d, *J*=11.0 Hz, 1H), 4.55 (d, *J*=11.0 Hz, 1H), 4.94–5.06 (m, 2H), 5.70–5.90 (m, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 7.27 (d, *J*=6.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 22.5 (t), 25.7 (t), 27.7 (t), 29.8 (t), 31.8 (t), 32.0 (t), 55.1 (q), 71.3 (t), 71.4 (d), 81.0 (d), 113.7 (d, 2C), 114.6 (t), 129.3 (d, 2C), 130.4 (s), 138.5 (d), 159.1 (s) ppm; HRMS (ESI+) calcd for $C_{19}H_{30}O_3Na$ 329.2087; Found 329.2081.

4.8. (*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enoyl)oxazolidin-2-one (12)

To a solution of alcohol **11** (2 g, 6.91 mmol) in toluene (20 mL) was added PMB-Cl (1.9 mL, 13.82 mmol) followed by Ag_2O (3.2 g, 13.82 mmol) at rt. Then the reaction mixture was stirred at room temperature for 26 h and reaction mixture was filtered over Celite, concentrated under reduced pressure. The resulting crude product was purified by the column chromatography (230–400 silica gel, 10% EtOAc in pet ether) to give **12** (600 mg, 61%) as a colorless oil along with recovered starting material 700 mg $[\alpha]_D^{25}$ −25.7 (*c* 2.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (d, *J*=6.8 Hz, 3H), 2.71 (dd, *J*=13.3, 9.7 Hz, 1H), 3.25 (dd, *J*=13.3, 3.2 Hz, 1H), 3.77 (s, 3H), 3.88–4.12 (m, 4H), 4.25 (d, *J*=11.7 Hz, 1H), 4.37–4.51 (m, 1H), 4.55 (d, *J*=11.7 Hz, 1H), 5.24–5.33 (m, 2H), 5.83 (ddd, *J*=16.1, 9.0, 7.3 Hz, 1H), 6.84 (d, *J*=8.7 Hz, 2H), 7.16–7.37 (m, 7H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5 (q), 37.7 (t), 42.2 (d), 55.2 (q), 55.5 (d), 65.8 (t), 69.8 (t), 80.2 (d), 113.6 (d, 2C), 118.8 (t), 127.2 (d), 128.9 (d, 2C), 129.4 (d, 2C), 129.5 (d, 2C), 130.3 (s), 135.3 (s), 136.0 (d), 153.1 (s), 159.0 (s), 174.3 (s) ppm; HRMS (ESI+) calcd for $C_{24}H_{27}O_5NNa$ 432.1781; Found 432.1777.

4.9. (2*S*,3*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpent-4-enoic acid (4)

To a solution oxazolidinone **12** (450 mg, 1.1 mmol) in THF:H_2O (4:1 mL) was added LiOH.H_2O (92 mg, 2.2 mmol) followed by 30% H_2O_2 in water (149 mg, 0.5 mL, 4.4 mmol) at 0 °C. The reaction mixture was stirred at rt for 3 h. After completion of reaction, the reaction mixture was neutralized with 2N HCl and the aqueous layer was washed with CH_2Cl_2 (3×20 mL), concentrated, and purified by column chromatography (100–200 silica gel, 4% MeOH in CH_2Cl_2) to give acid **4** (165 mg, 60%). $[\alpha]_D^{25}$ −43.2 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J*=7.1 Hz, 3H), 2.69 (quin, *J*=6.9 Hz, 1H), 3.80 (s, 3H), 4.01 (dd, *J*=7.6, 5.9 Hz, 1H), 4.32 (d, *J*=11.4 Hz, 1H), 4.58 (d, *J*=11.4, 1H), 5.27–5.37 (m, 2H), 5.79 (ddd, *J*=16.9, 10.6, 7.8 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.23 (d, *J*=8.7 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.1 (q), 44.5 (d), 55.2 (q), 70.2 (t), 80.5 (d), 113.8 (d, 2C), 119.7 (t), 129.4 (d, 2C), 129.8 (s), 135.1 (d), 159.2 (s), 178.6 (s) ppm; HRMS (ESI+) calcd for $C_{14}H_{18}O_4$ Na 273.1097; Found 273.1094.

4.10. (5*S*,6*R*)-5-((4-Methoxybenzyl)oxy)undec-1-en-6-yl (2*S*,3*R*)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enoate (2)

To a solution of acid **4** (500 mg, 2.0 mmol) in dry THF (10 mL), 2,4,6-trichlorobenzyl chloride (0.37 mL, 2.40 mmol) followed by *N,N*-diisopropylethylamine (2 mL, 11.49 mmol) were added and the mixture was stirred for 2 h at ambient temperature. After completion of mixed anhydride formation as indicated by TLC, DMAP (488 mg, 4.0 mmol) and a solution of alcohol **3** (612 mg, 2.0 mmol) in THF (5 mL) was introduced and the contents were stirred for 16 h at rt. The reaction mixture was quenched with cold water (20 mL) and extracted with ethyl acetate (2×30 mL). The combined organic phase was washed with aq $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to procure diene ester **2** (900 mg, 84%) as a light yellow oil. $[\alpha]_D^{25}$ −8.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J*=6.6 Hz, 3H), 1.20 (d, *J*=7.0 Hz, 3H), 1.22–1.25 (m, 2H), 1.47–1.79 (m, 8H), 2.01–2.08 (m, 1H), 2.17–2.25 (m, 1H), 2.63 (quin, *J*=7.0 Hz, 1H), 3.41 (td, *J*=3.2, 8.9 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.97 (t, *J*=7.2 Hz, 1H), 4.27 (d, *J*=11.2 Hz, 1H), 4.31 (d, *J*=10.8 Hz, 1H), 4.50 (d, *J*=11.3 Hz, 1H), 4.58 (d, *J*=11.0 Hz, 1H), 4.93–5.00 (m, 2H), 5.06 (td, *J*=3.3, 9.3 Hz, 1H), 5.24–5.28 (m, 2H), 5.72–5.83 (m, 2H), 6.83–6.85 (m, 4H), 7.20–7.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0 (q), 14.0 (q), 22.5 (t), 25.4 (t), 29.5 (t), 29.8 (t), 30.0 (t), 31.6 (t), 45.4 (d), 55.2 (q), 55.2 (q), 70.2 (t), 71.8 (t), 74.8 (d), 79.3 (d), 81.2 (d), 113.7 (d, 2C), 113.7 (d, 2C), 114.8 (t), 118.7 (t), 129.2 (d, 2C), 129.5 (d, 2C), 130.5 (s), 130.7 (s), 136.4 (d), 138.4 (d), 159.0 (s), 159.1 (s), 173.9 (s) ppm; HRMS (ESI+) calcd for $C_{33}H_{47}O_6$ 539.3367; Found 539.3378.

4.11. (3*S*,4*R*,9*S*,10*R*,*Z*)-4,9-Bis((4-methoxybenzyl)oxy)-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one (13)

To a solution of diene ester **2** (100 mg, 0.18 mmol) in dry CH_2Cl_2 (30 mL), second gen. Grubbs' catalyst (31 mg, 0.04 mmol) was added and the mixture was degassed under an argon atmosphere thoroughly. The reaction mixture was heated at 40 °C for 3 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography (10→12% EtOAc in petroleum ether) giving macrolide **13** (69 mg, 73%) as a colorless liquid. $[\alpha]_D^{25}$ 7.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J*=6.9 Hz, 3H), 1.25–1.28 (m, 5H), 1.30 (d, *J*=6.9 Hz, 3H), 1.45–1.55 (m, 4H), 2.01–2.08 (m, 2H), 2.34–2.39 (m, 1H), 2.53–2.60 (m, 1H), 3.30 (dt, *J*=2.2, 7.2 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.20–4.27 (m, 2H), 4.44 (s, 2H), 4.52 (d, *J*=11.8 Hz, 1H), 4.99–5.02 (m, 1H), 5.25 (t, *J*=10.1 Hz, 1H), 5.73 (dt, *J*=3.6, 11.8 Hz, 1H), 6.85–6.88 (m, 4H), 7.20–7.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (q), 15.3 (q), 22.5 (t), 24.6 (t), 24.7 (t), 30.2 (t), 31.5 (t), 31.6 (t), 47.7 (d), 55.3 (q), 55.3 (q), 70.1 (t), 70.5 (t), 75.0 (d, 2C), 79.9 (d), 113.7 (d, 2C), 113.7 (d, 2C), 128.2 (d), 129.1 (d, 2C), 129.5 (d, 2C), 130.6 (s, 2C), 135.6 (d), 159.1 (s), 159.1 (s), 172.8 (s) ppm; HRMS (ESI+) calcd for $C_{31}H_{42}O_6Na$ 533.2874; Found 533.2866.

4.12. (3*S*,4*R*,9*S*,10*R*,*Z*)-4,9-Dihydroxy-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one (14)

To an ice cooed solution of **13** (50 mg, 97.91 μmol) in dry CH_2Cl_2 (2 mL) was added TFA (15 μL) and stirred for 2 h at 0 °C. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column (30→35% EtOAc in petroleum ether) to furnish **14** (20.0 mg, 75%) as a white solid. mp: 157–160 °C; $[\alpha]_D^{25}$ 15.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J*=6.5 Hz, 3H), 1.29–1.36 (m, 6H), 1.38 (d, *J*=6.7 Hz, 3H), 1.55–1.62 (m, 2H), 1.76–1.85 (m, 1H), 1.92–2.03 (m, 2H), 2.47–2.55 (m, 1H), 2.73 (dq, *J*=3.7, 12.2 Hz, 1H), 3.79 (br s, 1H), 4.62 (t, *J*=9.5 Hz, 1H), 5.11 (td, *J*=3.7, 8.3 Hz, 1H), 5.35 (dt, *J*=1.5, 10.9 Hz, 1H), 5.73 (dt, *J*=3.5, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (q), 14.9 (q), 22.4 (t), 25.2 (t), 25.3 (t), 30.9 (t), 31.3 (t), 31.4 (t), 49.1 (d), 69.5 (d), 74.3 (d), 77.7 (d), 129.9 (d), 133.9 (d), 174.7 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{26}O_4Na$ 293.1723; Found 293.1722.

4.13. (6*R*,7*S*,14*S*,15*R*,*E*)-7,14-Dihydroxyicos-10-ene-6,15-diyl (2*S*,2′*S*,3*R*,3′*R*)-bis(3-hydroxy-2-methylpent-4-enoate) (15)

To a solution of diene ester **2** (100 mg, 0.18 mmol) in dry CH_2Cl_2 (30 mL), furstner' catalyst (18 mg, 0.02 mmol) was added and the mixture was degassed under an argon atmosphere thoroughly. The reaction mixture was heated at 40 °C for 12 h and the solvent was

removed under reduced pressure. A solution of resulting crude CM product (70 mg, 0.07 mmol) and DDQ (76 mg, 0.33 mmol) in CH_2Cl_2-water (3 mL, 18:1) was stirred for 3 h at room temperature. To this was added aqueous sodium bicarbonate solution (5 mL), and the contents were partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (5 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (60→70% EtOAc in petroleum ether) to give **15** (30 mg, 57%) as yellow syrup. $[\alpha]_D^{25}$ 28.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J*=6.7 Hz, 6H), 1.15 (d, *J*=7.1 Hz, 6H), 1.24–1.26 (m, 14H), 1.44–1.52 (m, 6H), 2.16–2.34 (m, 4H), 2.62–2.68 (m, 2H), 3.64–3.72 (m, 2H), 4.47 (s, 2H), 4.88–4.93 (m, 2H), 5.20 (d, *J*=10.5 Hz, 2H), 5.32 (d, *J*=17.2 Hz 2H), 5.39 (t, *J*=5.0 Hz, 1.2H), 5.46 (t, *J*=3.8 Hz, 0.4H), 5.81–5.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (q, 2C), 14.0 (q, 2C), 22.5 (t, 4C, Major), 22.6 (t, 2C, Minor), 23.4 (t, 2C, Minor), 25.4 (t, 2C), 28.9 (t, 2C, Minor), 29.7 (t, 2C, Major), 31.3 (t, 4C, Minor), 31.6 (t, 4C, Major), 45.2 (d, 2C, Minor), 45.3 (d, 2C, Major), 71.9 (d, 2C, Major), 72.5 (d, 2C, Minor), 73.2 (d, 2C, Minor), 73.3 (d, 2C, Major), 77.9 (d, 2C), 116.3 (t, 2C, Major), 116.4 (t, 2C, Minor), 129.9 (d, 2C, Major), 130.0 (d, 2C, Minor), 137.5 (d, 2C, Major), 138.5 (d, 2C, Minor), 175.2 (s, 2C) ppm; HRMS (ESI+) calcd for $C_{32}H_{56}O_8Na$ 591.3867; Found 591.3865.

4.14. (2*S*,3*R*,8*S*,9*R*,*E*)-9-Hydroxy-3,8-bis((4-methoxy-benzyl) oxy)-2-methyltetradec-4-enoic acid (16)

A degassed solution of acid **4** (50 mg, 0.2 mmol), alcohol **3** (122 mg, 0.4 mmol) and Grubbs' second gen. catalyst (33 mg, 0.04 mmol) in dichloromethane (30 mL) was heated under reflux under argon for 96 h and concentrated. The residue was purified by column chromatography (4–5% MeOH in CH_2Cl_2) to afford **16** (55 mg, 52%) as yellow oil along with self-dimerization products of alcohol **3** (55 mg, 47%) and **4** (18 mg, 38%). $[\alpha]_D^{25}$ −20.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.9 Hz, 3H), 1.16 (d, *J*=7.2 Hz, 3H), 1.29–1.35 (m, 5H), 1.36–1.55 (m, 4H), 1.63–1.75 (m, 1H), 2.04–2.17 (m, 1H), 2.21–2.29 (m, 1H), 2.67 (quin, *J*=6.3 Hz, 1H), 3.34 (td, *J*=3.7, 8.6 Hz, 1H), 3.73–3.79 (m, 1H), 3.79 (s, 6H), 3.89 (dd, *J*=6.1, 8.3 Hz, 1H), 4.29 (d, *J*=11.4 Hz, 1H), 4.44 (d, *J*=11.2 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 2H), 5.36 (dd, *J*=8.8, 15.4 Hz, 1H), 5.67 (td, *J*=6.8, 15.4 Hz, 1H), 6.85–6.89 (m, 4H), 7.21 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5 (q), 14.0 (q), 22.6 (t), 25.9 (t), 28.0 (t), 28.4 (t), 31.8 (t, 2C), 44.6 (d), 55.2 (q, 2C), 69.8 (t), 71.4 (d), 71.5 (t), 80.5 (d), 81.0 (d), 113.8 (d, 2C), 113.8 (d, 2C), 126.9 (d), 129.4 (d, 2C), 129.5 (d, 2C), 129.7 (s), 130.3 (s), 136.7 (d), 159.2 (s), 159.3 (s), 176.9 (s) ppm; HRMS (ESI+) calcd for $C_{31}H_{44}O_7Na$ 551.2979; Found 551.2972.

4.15. (3*S*,4*R*,5*E*,9*S*,10*R*,13*S*,14*R*,15*E*,19*S*,20*R*)-4,9,14,19-Tetrakis((4-methoxybenzyl)oxy)-3,13-dimethyl-10,20-dipentyl-1,11-dioxacycloicosa-5,15-diene-2,12-dione (17)

A solution of *seco*-acid **16** (40 mg, 75.6 μmol) in dry toluene (20 mL), was added to the stirred solution of molecular sieves (4Å, 1g), DMAP (27 mg, 0.22 mmol) and 2-Methyl-6-Nitrobenzoic anhydride (20 mg, 0.06 mmol) in dry toluene (20 mL) using syringe pump (0.8 mL/h). After the addition was complete it was stirred for another 6 h at rt. The reaction mix was diluted with ethyl acetate and was filtered. The organic phase was washed with satd $NaHCO_3$, brine, dried and concentrated. The residue was purified by column chromatography (20→25% EtOAc in petroleum ether) giving macrolide **17** (20 mg, 52%) as a yellow liquid. $[\alpha]_D^{25}$ 13.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J*=7.3 Hz, 6H), 1.19 (d, *J*=6.7 Hz, 6H), 1.25–1.32 (m, 16H), 1.40–1.46 (m, 2H), 1.65–1.72 (m, 2H), 1.95–2.02 (m, 2H), 2.24–2.31 (m, 2H), 2.71 (quin, *J*=7.4 Hz, 2H), 3.36–3.38 (m, 2H), 3.71 (t, *J*=7.8 Hz, 2H), 3.77 (s, 6H), 3.77 (s, 6H), 4.21 (d, *J*=11.3 Hz, 2H), 4.34 (d, *J*=10.8 Hz, 2H), 4.48 (d, *J*=11.1 Hz, 2H), 4.54 (d, *J*=10.9 Hz, 2H), 4.99–5.00 (m, 2H), 5.50 (dd, *J*=8.7, 15.7 Hz, 2H), 5.62 (td, *J*=5.6, 15.2 Hz, 2H), 6.82–6.85 (m, 8H), 7.21 (d, *J*=8.1 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q, 2C), 14.1 (q, 2C), 22.5 (t, 2C), 25.3 (t, 2C), 28.0 (t, 2C), 29.3 (t, 2C), 30.3 (t, 2C), 31.7 (t, 2C), 46.0 (d, 2C), 55.2 (q, 4C), 69.3 (t, 2C), 71.3 (t, 2C), 74.2 (d, 2C), 78.7 (d, 2C), 81.2 (d, 2C), 113.7 (d, 4C), 113.7 (d, 4C), 128.2 (d, 2C), 129.2 (d, 4C), 129.4 (d, 4C), 130.4 (s, 2C), 130.6 (s, 2C), 135.5 (d, 2C), 159.0 (s, 2C), 159.2 (s, 2C), 173.3 (s, 2C) ppm; HRMS (ESI+) calcd for $C_{62}H_{84}O_{12}Na$ 1043.5855; Found 1043.5865.

4.16. (3*S*,4*R*,5*E*,9*S*,10*R*,13*S*,14*R*,15*E*,19*S*,20*R*)-4,9,14,19-Tetrahydroxy-3,13-dimethyl-10,20-dipentyl-1,11-dioxacycloicosa-5,15-diene-2,12-dione (18)

To an ice cooed solution of **17** (20 mg, 19.58 μmol) in dry CH_2Cl_2 (2 mL) was added TFA (10 μL) and stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column (3→4% MeOH in CH_2Cl_2) to furnish macrolide **18** (7.6 mg, 72%) as a white-cream solid. mp: 68–71 °C; $[\alpha]_D^{25}$ 26.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J*=7.3 Hz, 6H), 1.18–1.32 (m, 22H), 1.57–1.69 (m, 4H), 2.00–2.03 (m, 4H), 2.76–2.92 (m, 2H), 3.40–3.45 (m, 1H, Minor), 3.62–3.67 (m, 2H, Major), 4.08–4.13 (m, 2H), 4.87–4.96 (m, 2H), 4.96–5.0 (m, 1H, Minor), 5.59–5.66 (m, 2H), 5.77–5.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (q, 2C, Minor), 13.8 (q, 2C, Major), 14.0 (q, 2C, Minor), 14.1 (q, 2C, Major), 22.4 (t, 2C, Minor), 22.7 (t, 2C, Major), 25.3 (t, 2C, Minor), 25.6 (t, 2C, Major), 28.1 (t, 2C, Minor), 28.5 (t, 2C, Major), 28.9 (t, 2C, Minor), 29.4 (t, 2C, Major), 30.1 (t, 2C, Minor), 30.4 (t, 2C, Major), 31.4 (t, 2C, Minor), 31.5 (t, 2C, Major), 45.6 (d, 2C, Minor), 46.7 (d, 2C, Major), 72.5 (d, 2C, Minor), 73.1 (d, 2C, Major), 73.9 (d, 2C, Minor), 74.4 (d, 2C, Major), 75.8 (d, 2C, Minor), 77.9 (d, 2C, Major), 129.2 (d, 2C, Major), 130.5 (d, 2C, Minor), 130.8 (d, 2C, Major), 131.6 (d, 2C, Minor), 174.5 (s, 2C, Major), 174.7 (s, 2C, Minor) ppm; HRMS (ESI+) calcd for $C_{30}H_{52}O_8Na$ 563.3554; Found 563.3550.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.10.018.

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