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RuO_4-mediated oxidative polycyclization of linear polyenes. A new approach to the synthesis of the bis-THF diol core of antitumour cis–cis adjacent bis-THF annonaceous acetogenins

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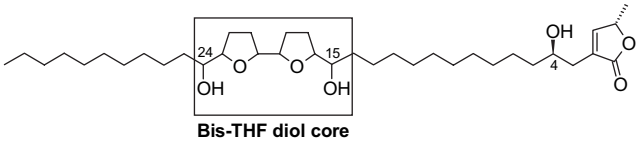
Abstract—The RuO_4-catalyzed oxidative polycyclization of some selected linear polyenes, possessing a repetitive 1,5-diene structural motif, has been investigated. The all-*trans* triene (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester gave the expected bis-tetrahydrofuranyl diol product possessing a *threo-cis-threo-cis-threo* relative configuration, along with a mixture of the corresponding bis-THF ketols. These compounds can be seen as useful intermediates in the synthesis of the bis-THF diol core of adjacent bis-THF antitumour acetogenins possessing a *threo-cis-threo-cis-erythro* relative configuration, such as rolliniastatiin-1, membranacin, rollimembrin and membrarollin. Oxidation of the related all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester stops at the second cyclization step giving a mixture of a *threo-cis-threo-cis-threo* bis-THF diol and the corresponding ketol products. Oxidation of the triene (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester stops at the monocyclization level failing to give bis-cyclized products, as previously observed for the related isoprenoid triene (*E*,*Z*)-farnesyl acetate. This result confirms the difficulty of closing a second THF ring when the central double bond of the triene possesses a cis configuration. Based on the collected results, a plausible model is proposed that both explains the observed cis/trans stereoselectivity for each ring-closing step in these processes, and rationalize the stereochemical course of the previously studied polycyclization of the isoprenoid polyenes (*E*,*E*)-farnesyl acetate, geranylgeranyl acetate and squalene.

1. Introduction

Annonaceous acetogenins (ACGs) are a group of secondary metabolites isolated from plants of the family *Annonaceae* many of which exhibit high cytotoxic and impressive antitumour activities.[1] The biological effect of these substances are attributed to the inhibition of mammalian mitochondrial NADH-ubiquinone oxidoreductase (complex I), a membrane-bound protein of the mitochondrial electron transport system,[2] and to the inhibition of an ubiquinone-linked NADH oxidase expressed in the plasma membrane of cancerous cells but only transiently expressed in the membranes of 'normal' cells.[3] These mechanisms result in ATP deprivation leading to apoptosis (programmed cell death) in the high energy demanding malignant cells.[4]

From a structural point of view, they are mostly made up of a mono- or bis-THF core flanked by two long alkyl chains, one of which ending with an α,β-unsaturated γ-lactone ring, usually carrying hydroxyl groups along their length (Fig. 1).



Bis-THF diol core

Figure 1. Structural features of some representative adjacent bis-THF ACGs with high antitumour activity. Configuration of the bis-THF diol core (from C_{24} to C_{15}): asimicin *threo–trans–threo–trans–threo*; bullatacin *erythro–trans–threo–trans–threo*; trilobacin *threo–cis–erythro–trans–threo*; rolliniastatin-1 *erythro–cis–threo–cis–threo*.

A common feature shared by the ACGs possessing the highest anticancer activity is the presence of a bis-THF diol portion: two adjacent THF rings each one flanked by a hydroxyl-bearing methine group (Fig. 1). This subgroup is very abundant amounting to more than 40% of all known metabolites of this type. Representative examples of this type of ACGs are asimicin, bullatacin, trilobacin and rolliniastatin-1, only differing in the configuration of the bis-THF diol core (Fig. 1); all these substances have shown an in vitro antitumour potency 10^8 times higher than that exhibited by adriamycin.[5]

The selectivity shown towards diverse human tumour cell lines,[1] including those that exhibit multidrug resistance

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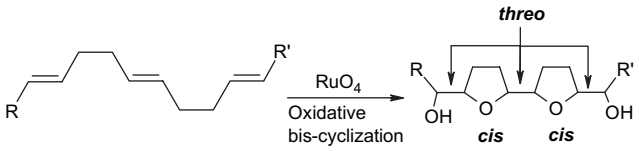
(MDR),[6] as well as their ability to only modestly affect the normal human cells growth,[6] has prompted many research groups to undertake the total synthesis of these substances or to search for suitable analogues to be tested in SAR studies.[7]

Only few adjacent bis-THF ACGs have been isolated that possess an *erythro–cis–threo–cis–threo* relative configuration, for example, rolliniastatin-1, rollimembrin, membrarollin, membranacin; however, they are among the most effective substances of this type. Compared to other annonaceous acetogenins, which are popular targets for total synthesis, there has been limited synthetic activity towards these substances possibly due to the challenges posed by the *erythro–cis–threo–cis–threo* relative configuration of their bis-THF diol portion.

Recently, we have discovered a novel oxidative polycyclization (OP) process involving catalytic amounts of RuO_4 that allows to obtain, in a single step, all-*threo* adjacently linked poly-tetrahydrofuran diol (poly-THF diol) compounds starting from isoprenoid polyenes characterized by a repetitive 1,5-diene structural motif such as (*E*,*E*)-farnesyl acetate [(*E*,*E*)-FA], geranylgeranyl acetate (GGA) and squalene (Scheme 1).[8]

We reasoned that this process could be usefully employed for the synthesis of the bis-THF diol core of the aforementioned cis–cis adjacent bis-THF ACGs provided that it could work well for the OP of linear 1,5,9-trienes as well. In particular, based on the stereochemical course of the first two ring-forming steps in the OP of the above-cited isoprenoid polyenes (a cis–cis bis-THF sequence is obtained in all cases; see Scheme 1),[8] as well as the cis-stereoselectivity of the THF-forming step in the RuO_4-mediated oxidative monocyclization of linear 1,5-dienes,[9] it was expected that a cis,cis adjacent bis-THF diol product would have been obtained from an all-*trans* 1,5,9-triene. In addition, according to the mechanistic hypothesis previously formulated for these cyclizations (*syn* addition of oxygen across each double bond), substantiated by stereochemical evidence collected for all the previously studied OP, it was also expected that this product would possess an all-*threo* arrangement (Scheme 2). In this paper we report on our studies towards this goal.

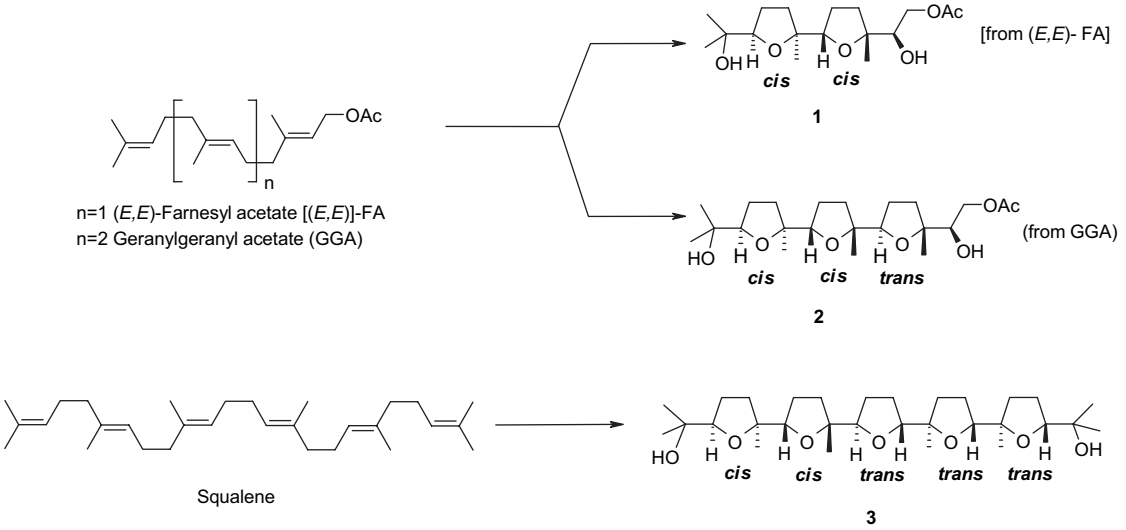


Scheme 2. Expected bis-THF diol product from the RuO_4-catalyzed bis-cyclization of an all-*trans* 1,5,9-triene.

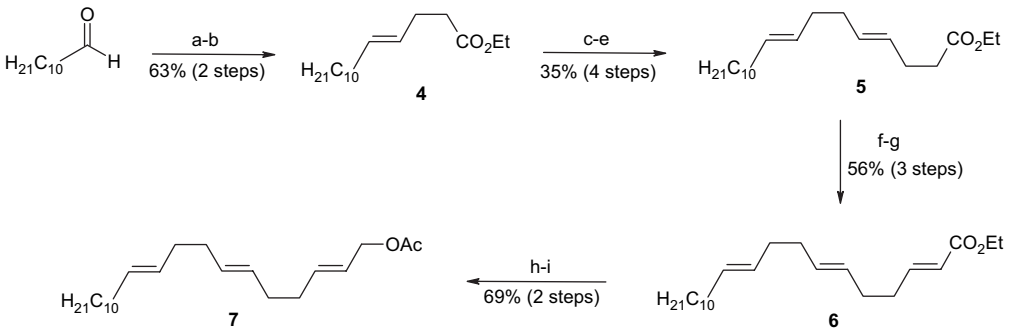
2. Results and discussion

In order to probe the above hypothesis, (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester (**7**) was synthesized as described in the literature for the C_{21} alcohol analogue,[10] starting from undecanal (Scheme 3). Cyclization of triene **7** would have allowed to access a *threo–cis–threo–cis–threo* bis-THF diol product possessing a C_{10} saturated alkyl chain (Scheme 2: R=$C_{10}H_{21}$; R′=CH_2OAc) characterizing rolliniastatin-1-type ACGs.

In particular, Grignard reaction of undecanal with vinylmagnesium bromide followed by *ortho* ester Claisen–Johnson rearrangement of the obtained allylic alcohol allowed elongation of a four-carbon fragment and concomitant stereoselective formation of the first trans double bond to give monounsaturated ester **4**. Conversion of **4** to the double unsaturated ester **5** was accomplished in four steps: transformation of **4** to the corresponding aldehyde (LAH reduction followed by PCC oxidation) followed by the two-step sequence used for the conversion of undecanal into **4**. Then, conversion of **5** into the corresponding aldehyde, as above seen for **4**, followed by Wittig–Horner olefination with triethyl phosphonoacetate gave the all-*trans* triple unsaturated ester **6**. Dibal-H reduction of this one followed by acetylation yielded the required triene **7**.



Scheme 1. Summary of the RuO_4-catalyzed polycyclization of some isoprenoid polyenes. Reagents and conditions: (*E*,*E*)-FA: $RuO_2 \cdot 2H_2O$ (20 mol %), $NaIO_4$ (4 equiv), CH_3CN–EtOAc–H_2O (3:3:1), 0 °C, 30 min. GGA and squalene: as for (*E*,*E*)-FA but $NaIO_4$ 5 equiv and 8 equiv, respectively.



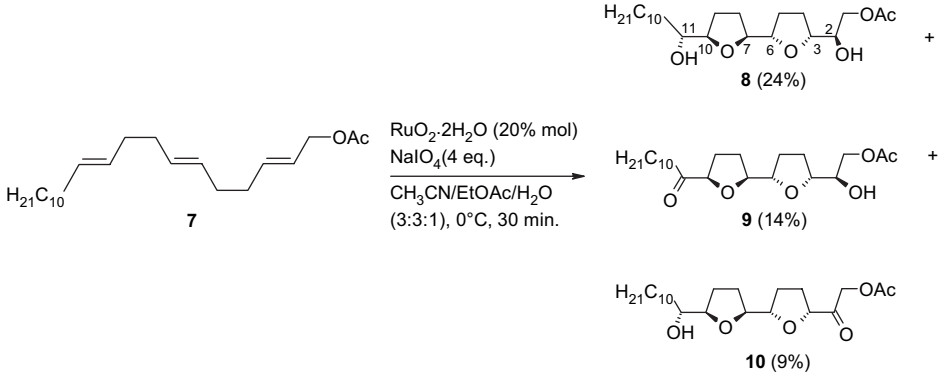
Scheme 3. Synthesis of (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester (**7**). Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C; (b) triethyl orthoacetate, propyonic acid (2%), xylene, reflux; (c) $LiAlH_4$, Et_2O, 0 °C→rt; (d) PCC, Celite, CH_2Cl_2, rt; (e) same as for sequence a–b; (f) same as for sequence c–d; (g) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C→rt; (h) DIBAL-H, THF, −78 °C; (i) Ac_2O-py, rt.

Oxidation of **7** under the standard conditions previously set up for (*E*,*E*)-FA[8a] (Scheme 4), followed by HPLC separation of the reaction mixture, gave diol **8** as the main bis-THF product (24%) along with the corresponding isomeric bis-THF ketols **9** and **10** (together 23%). The overall 47% yield is not too far from that obtained for (*E*,*E*)-FA (56%) in the same conditions;[8a] the slightly less yield probably reflects the efficiency of the first THF-closing step, in agreement with the difference in the yields previously observed for the monocyclizations of alkylsubstituted 1,5-dienes, such as geranyl acetate,[9b,9c] and linear 1,5-dienes,[11] with RuO_4. The structural relationship among the three bicyclic products **8**–**10** was proven by oxidation of **8** to a mixture of **9** and **10** with $TPAP_{(cat.)}$/NMO.

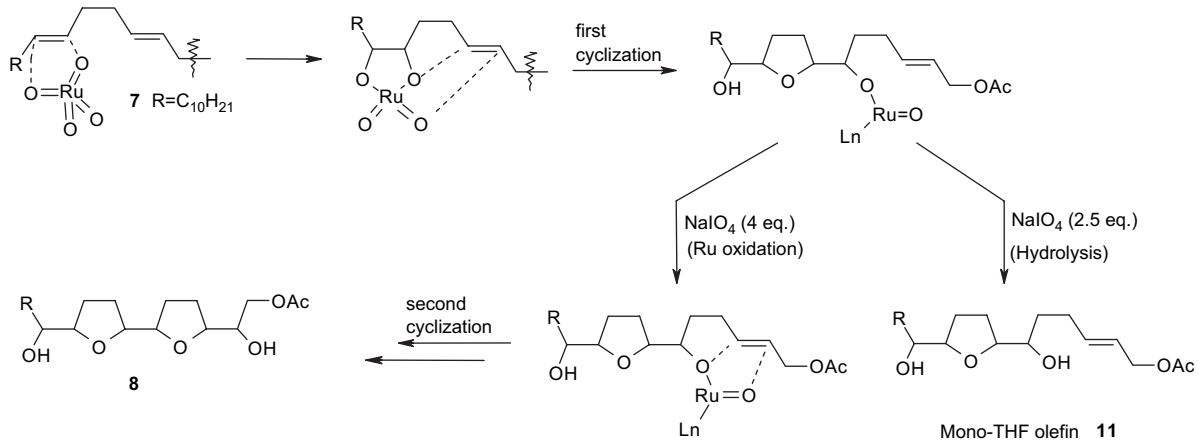
In order to establish the relative configuration of **8** a detailed 2D-NMR analysis of this compound was accomplished. In particular, a resonance specific assignment was achieved using two-dimensional COSY, TOCSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC NMR experiments. Subsequently, to assess the stereo-relationship around the bis-THF portion, 2D-ROESY experiments were carried out for **8** both in $CDCl_3$ and DMSO-d_6. In agreement with our expectations, and previous results obtained with related molecules, the experiment performed in $CDCl_3$ evidenced correlations between the resonances at δ 4.02 (H-3) and δ 3.94 (H-6), and between those at δ 3.91 (H-7) and δ 3.81 (H-10) that suggested a cis arrangement for both the proton pairs H-3/H-6 and H-7/H-10 and, therefore, a cis–cis sequence for the two contiguous THF rings. Confirmatory evidences arose from a high-quality 2D-ROESY spectrum performed in DMSO-d_6, which showed the same correlation peaks observed in the ROESY spectrum of **8** recorded in $CDCl_3$.

In an attempt to further increase the yield of the process the effect of ruthenium dioxide and periodate amounts was evaluated (Scheme 5). The increase of the amount of RuO_4, up to one equivalent, had no significant effect on the overall yield of the process and the HPLC profile of the bis-cyclization products. On the other hand, as observed for the oxidation of isoprenoid analogues,[8] reduction of the amount of the co-oxidant (from 4 to 2.5 equiv) depresses the second cyclization step, in accord with the hypothesis that oxidation at ruthenium is indispensable for the process to go ahead, as shown in Scheme 5. In fact, in these conditions mono-THF olefin **11** was obtained as the main reaction product (18%) along with the corresponding ketols (overall 9%), as an inseparable mixture while bis-THF diol **8** was only obtained in a 3% amount. Lower yields in the THF-containing material is probably to be attributed to the further RuO_4 oxidation of the mono-THF compounds at their olefin function.

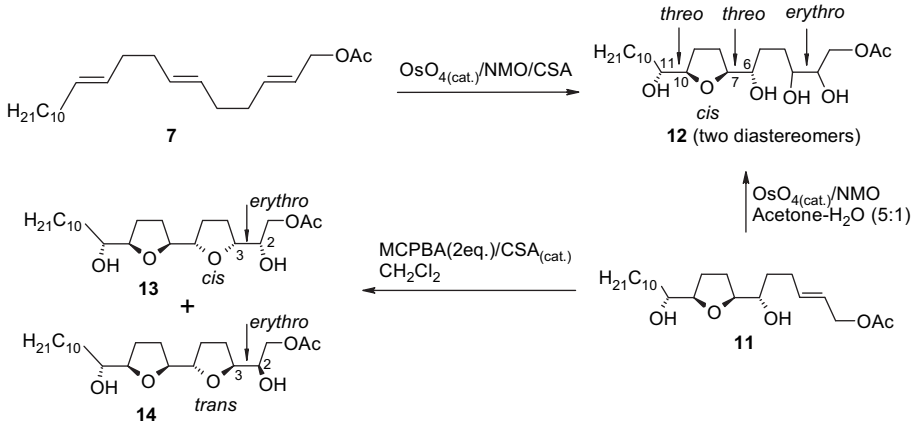
Definitive confirmation for the expected all-*threo* arrangement for compound **8** was provided by simple chemical transformations strictly similar to those previously carried out on isoprenoid analogues (Scheme 6). In particular, cis-stereoselective monocyclization of **7** with $OsO_{4(cat.)}$/NMO/CSA[12] afforded a mixture of diastereomeric mono-THF tetrols **12**, derived from THF-diol formation and further dihydroxylation of the Δ^2 double bond, that resulted identical to the dihydroxylation products of **11** with $OsO_{4(cat.)}$/NMO. This secured a *threo–cis–threo* arrangement for compound **11** and, therefore, this configuration could be inferred for the bis-THF diol **8** as well. The remaining C2/C3 *threo* relationship in **8** was secured by the different spectral and chromatographic (HPLC) properties exhibited by the two C2/C3



Scheme 4. RuO_4-mediated oxidative bis-cyclization of (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester (**7**).



Scheme 5. Proposed mechanism for the bis-cyclization and partial cyclization of triene **7**.



Scheme 6. Demonstration of the all-*threo* arrangement of compound **8**.

erythro bis-THF diol isomers of **8** (**13** and **14**, Scheme 6), synthesized by treatment of mono-THF olefin **11** with MCPBA (2 equiv)/$CSA_{(cat.)}$ in CH_2Cl_2 (one-step epoxidation/acid-catalyzed THF formation), and compound **8** itself.

In summary, our approach to a bis-THF diol fragment suitable for further synthetic elaboration along the route to cis–cis ACGs features the formation of all six chiral centres (five when ketols are formed) of the bis-THF diol portion in a single, stereoselective, step. The starting all-*trans* triene, (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester, is obtained following an easy-to-carry-out procedure based on an iterative reaction sequence that makes use of many inexpensive reagents (the starting aldehyde, PCC, Ac_2O, triethyl orthoacetate). The starting triene is achiral and formation of all chiral centres is deferred to a final single reaction, a ruthenium-catalyzed oxidative bis-cyclization where the true oxidant is sodium periodate, a product commercially available at low price. Only seven different reactions are involved into the synthesis of the starting triene and yields are overall good when considering the cost of the reagents employed. In addition, the right-hand part of our bis-THF diol fragment is functionalized in such a way to allow attachment of the remaining, γ-lactone-containing, portion following, for example, a rather short reaction sequence similar to that recently employed by Brown et al. in the synthesis of membranacin.[13] Only the inversion of configuration at C-24 (Fig. 1), a synthetic manoeuvre generally easy to carry out through well-known chemistry, needs to be accomplished to fix the C-23/C-24 *erythro* relationship that characterizes rolliniastatin-1-type ACGs.[14,15] On the other hand, adjustment of the oxidation state and generation of the proper configuration at the C-2 or C-11 centres in both ketols **9** and **10** can allow the synthetic use of these materials as well, either in the synthesis of the above-cited substances or of their C-15 unnatural epimers. In fact, production of a complete library of adjacent bis-THF acetogenins, and evaluation of their biological properties, appears an important synthetic goal towards which some research groups are currently addressing their efforts.[16]

It seems also worth mentioning that bis-THF diol **8** possesses the same relative configuration as that found in squamocin-N,[17] the sole known ACG with a *threo–cis–threo–cis–threo* configuration of the bis-THF diol portion, whose synthesis has not yet been accomplished (Fig. 2).

Having ascertained the ability of the $RuO_{2(cat.)}/NaIO_4$ oxidizing system to induce the bis-cyclization of the all-*trans* triene **7**, we were interested in probing whether the related all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester (**16**, Scheme 7) could also be tris-cyclized in the same conditions, as it happens for the isoprenoid tetraene GGA (Scheme 1). This compound was

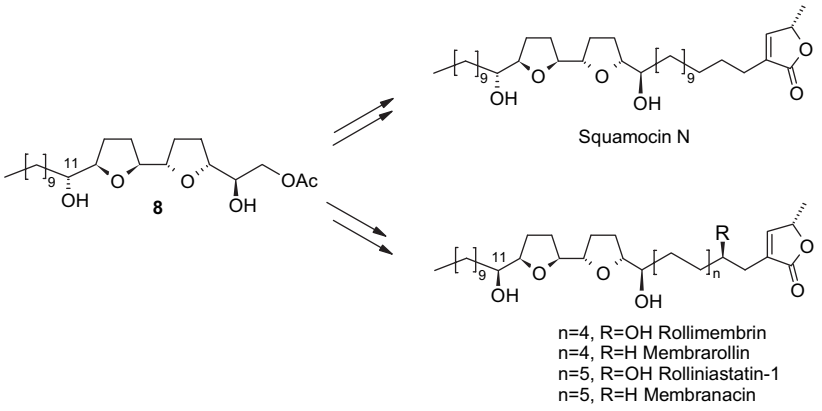
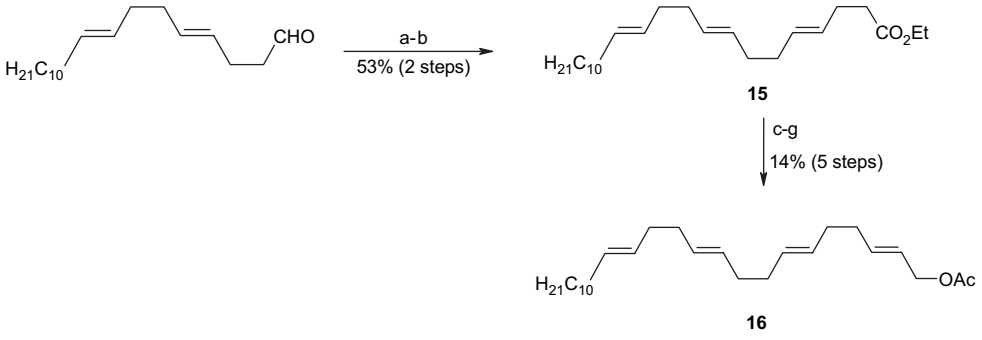


Figure 2. Bis-THF diol **8** can be further elaborated for the synthesis of some cis–cis adjacent bis-THF ACGs.

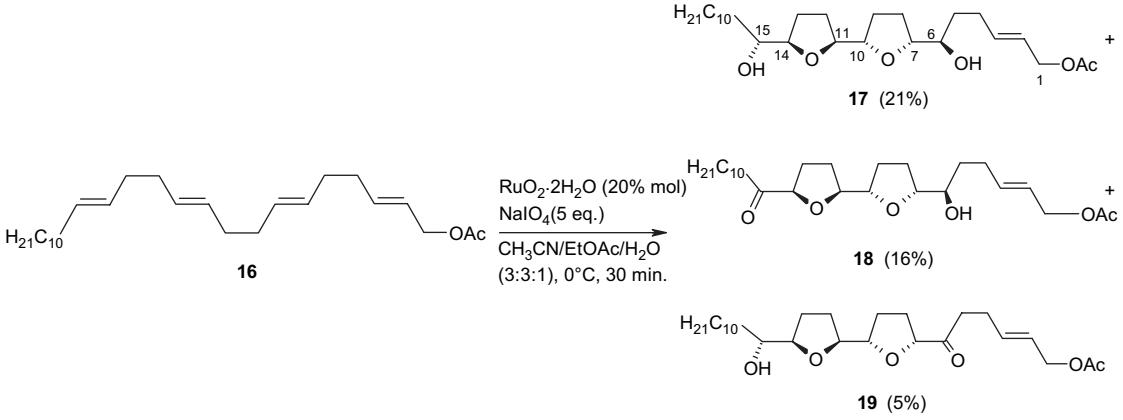
synthesized as depicted in Scheme 7 starting from (*E*,*E*)-nonadeca-4,8-dienal, an intermediate of the synthesis of triene **7**, through the same chemistry employed for the synthesis of the latter, and then subjected to RuO_4 oxidation (Scheme 8). According to the mechanism hypothesized for the process (Scheme 5) and precedents from the oxidation of GGA, the presence of one more double bond in **16**, a 5 equiv amount of co-oxidant (one more equivalent compared to **7**) was expected to be required.

Unexpectedly, contrary to what happens for GGA,[8a] no tris-THF product was obtained from the oxidation of **16**. The process stopped at the bis-cyclization level giving the three related bis-THF compounds **17–19** in an overall 42% yield (Scheme 8). The order of abundance for these products is the same observed for compounds **8–10** obtained from the oxidation of triene **7**: bis-THF diol **17** was the main oxidation product (21%) followed by ketol **18** (16%), with the keto group next to the C_{10} alkyl chain, and ketol **19** (5%). The structural relationship among compounds **17–19** was once again proven by oxidation of **17** to a mixture of **18** and **19** with TPAP/NMO.

Compounds **17–19** were subjected to the same set of 2D-NMR experiments performed for **8**. In particular, inspection of the ROESY spectrum of **17** revealed a strong correlation peak between resonances at δ 3.83 and 3.89 that, due to the pseudo-symmetry of the molecule around its bis-THF diol



Scheme 7. Synthesis of (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester **16**. Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C; (b) triethyl orthoacetate, propyonic acid (2%), xylene, reflux; (c) $LiAlH_4$, Et_2O, 0 °C→rt; (d) PCC, Celite, CH_2Cl_2, rt; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C→rt; (f) DIBAL-H, THF, −78 °C; (g) Ac_2O-py, rt.

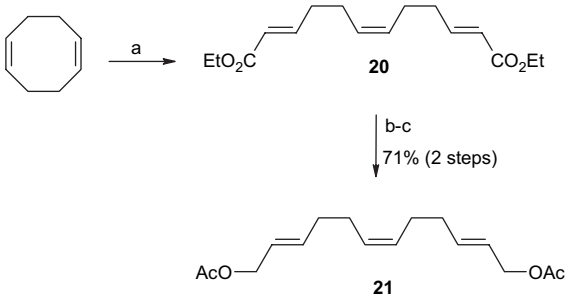


Scheme 8. RuO_4-mediated oxidative bis-cyclization of (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester **16**.

portion, accounted for the H-7/H-14 and H-10/H-11 proton pairs, respectively. This observation preliminarily suggested a cis–cis arrangement of the two adjacent rings. The unambiguous confirmation of this arrangement came from the analysis of ROESY spectra of ketols **18** and **19**. In particular, a strong ROE correlation peak between resonances at δ 4.38 (H-14) and δ 3.95 (H-11) suggested the cis relationship of this proton pair in **18**. The cis relationship between protons H-14 and H-11 was also settled in **19** due to the presence of a cross peak between resonances at δ 3.83 (H-14) and δ 3.92 (H-11). Finally, the cis arrangement of protons H-7 and H-10 in **19** was established thanks to the correlation between resonances at δ 4.37 (H-7) and δ 3.94 (H-10) observed in its ROESY spectrum. Therefore, based on all previous stereochemical evidence for bis-THF diol **8**, isoprenoid poly-THF diols **1**–**3** and the hypothesized mechanism (Scheme 5), an all-*threo* cis–cis relative configuration was assumed for compounds **17**–**19**.

An increasing of RuO_4 up to 50% seems not to affect this process as well, while increasing of the co-oxidant only produces the formation of some more polar products tentatively identified as the dihydroxylation products of initially formed **17**–**19** at their Δ^2 double bond. It cannot be excluded that a further increasing of yields of **17**–**19** could be obtained by employing a minor (4 equiv) amount of co-oxidant (the amount usually used for the bis-cyclization of trienes). This should prevent the residual double bond being further attacked by the oxidant with consequent yield improvement. However, for the time being these conditions were not further explored.

Finally, we probed our oxidative process on (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (**21**, Scheme 9),



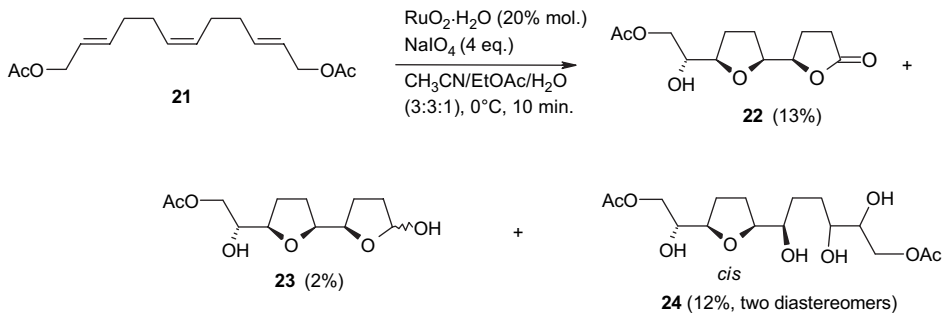
Scheme 9. Synthesis of (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (**21**). Reagents and conditions: (a) O_3, $CHCl_2$, −78 °C then PPh_3, 1 h, then Ph_3PCHCO_2Et; (b) DIBAL-H, THF, −78 °C; (c) Ac_2O–py, rt.

an easily accessible model triene with the central cis double bond. In particular, we wanted to ascertain whether the change in the configuration of the central double bond from trans (as is in triene **7**) to cis would have affected the cyclization process as had happened for the related isoprenoid triene (*E*,*Z*)-FA,[8b] for which the oxidative process stops at the monocyclization level, contrary to what happened for its isomer (*E*,*E*)-FA that gives a bis-cyclized product (Scheme 1).

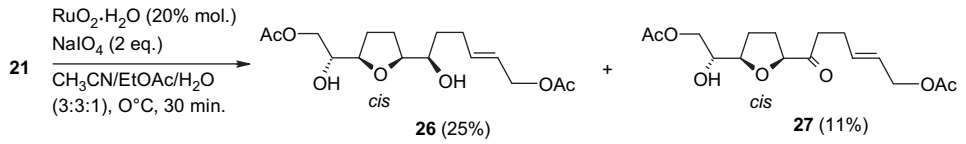
The required compound **21** was synthesized by acetylation of diester **20** in turn obtained starting from commercially available 1,5-cyclooctadiene, following a reported procedure (Scheme 9)[18] and subjected to oxidation with the usual conditions (Scheme 10). HPLC separation of the reaction mixture afforded the structurally related lactone **22** and lactol **23**, in a disappointingly overall 15% yield along with a mixture of THF tetrols **24** (12%) as the main products. All these compounds can be seen to originate from the further attack of the oxidant at the double bond of the initially formed monocyclized product (THF-olefin **26**, Scheme 11) indicating that the process stops at the first cyclization step, in line with the previously observed reactivity of (*E*,*Z*)-FA. No further detailed studies were carried out to ascertain the identity of the remaining material required for mass balance. However, ^1H NMR analysis of some partially purified (HPLC) side products indicated that they could derive from oxidation of the double bond of the initially formed mono-THF olefin **26**, followed by its further evolution.

Therefore, we could conclude that the presence of a cis double bond, immediately following a trans one in the polyenic chain (at least when the latter occupies the Δ^1 position), represents an obstacle for a further cyclization step to take place, irrespective of the fact that the substrate be isoprenoid, such as (*E*,*Z*)-FA, or linear, such as compound **21**.

In one case, the oxidation of **21** gave, besides compounds **22**–**24**, the expected bis-cyclized product **25** (Fig. 3), though in a very low yield (ca. 1%). Unfortunately, we were unable to reproduce this result. Referring to this experiment, it is important to say that careful HPLC and NMR analyses showed that compound **25** was the sole bis-THF product obtained. Accurate 2D-NMR analyses, ES-MS spectra, and symmetry considerations pointed to the bis-THF diol structure **25** for this compound. In particular, the proton spectrum recorded in $CDCl_3$ included, as expected, two acetate signals at 2.087 and 2.093 ppm and 10 distinct resonances for protons geminal to oxygen height of which spanning between



Scheme 10. RuO_4-mediated oxidative cyclization of triene **21**.



Scheme 11. Partial oxidative cyclization of triene **21**.

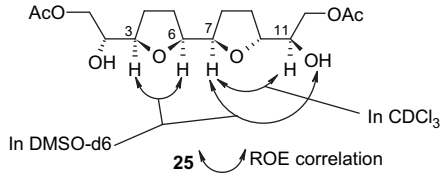


Figure 3. Significant ROE correlations for bis-THF **25**.

3.95 and 4.30 ppm (2×C*H*$_2$OAc and four THF protons) and two in the range 3.62–3.73 attributable to the two C*H*–OH protons. 2D-ROESY experiments carried out both in $CDCl_3$ and DMSO-d_6 showed strong ROE correlation peaks between resonances for the proton pairs H-3/H-6, H-7/H-11 and H-7/OH-11 as shown in Figure 3. This, in conjunction with the absence of a correlation between the H-7 and H-10 protons, were clear evidence for the cis–trans relative configuration of the THF pair. On the other hand, symmetry considerations excluded the structures with *threo–trans–erythro–trans–threo* and *threo–cis–erythro–cis–threo* configuration, incompatible with the observed NMR characteristics of **25**. The presence of a *cis*-THF is also in line with the structure of all the related compounds **22**–**24**, derived from the oxidation of **21**, where the THF ring from the first cyclization invariably possesses a cis configuration.

The above results indicate that, at the present level of optimization, the oxidation of **21**, can hardly have synthetic value; nevertheless, formation of bis-THF **25** has mechanistic relevance as will be explained in the next section.

Stopping oxidation of **21** at the first ring-closing step may have synthetic value, provided that the first-formed mono-THF product does not undergo overoxidation. We reasoned that the use of a lesser amount of periodate (2 equiv) could induce the formation of the first THF ring preventing the successive oxidation of the remaining olefin function. Under these conditions, a mixture of mono-THF olefin compounds **26** and **27** in a 36% overall yield along with a 35% of unreacted triene (Scheme 11). This process is unoptimized but further improvements appear to be feasible by suitably tuning the co-oxidant amount and reaction times.

It is interesting to note that, due to the type of functionalisation at both termini, mono-cyclized products **26** and **27** lend themselves to further synthetic manipulations. In particular, the *threo–cis–erythro* stereochemical relationship around the mono-THF portion suggests their use for the synthesis of acetogenins of the type trilobin and trilobacin (Fig. 4) by using, for example, previously reported chemistry.[5a]

Finally, the structural relationship among compounds **23**–**25** was proven as shown in Scheme 12, through simple chemical transformations involving OsO_4 chemistry.

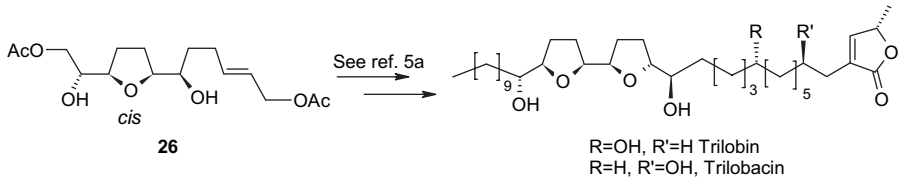
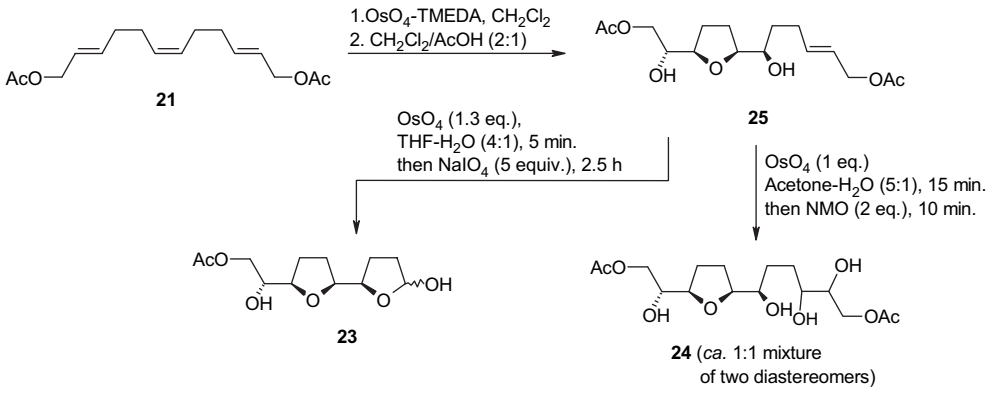


Figure 4.



Scheme 12. Chemical correlation of compounds **23**–**25**.

2.1. An explanation for the diastereoselectivity observed in the OP of polyenes with a repetitive 1,5-diene motif

The following points, emerged, both in the present and in our previous related studies on the OP of isoprenoid polyenes,[8] which need to be explained.

(a) Why in all the studied cases (isoprenoid or linear polyenes) the first two THF rings are invariably obtained with a cis selectivity;
(b) Why a cis double bond immediately following a trans one, as in (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester **21** and in (*E*,*Z*)-FA, prevents the second cyclization step to take place;
(c) Why for the all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester **16** the polycyclization stops at the bis-THF level contrary to what happens for the isoprenoid analogue GGA that gives a tris-THF product.

2.2. Model for the cis-selective first cyclization

We will now try to give a plausible explanation of the above points taking into account previously developed models for the rhenium(VII)-mediated oxidative cyclization of hydroxy-polyenes[19] as well as reported oxidative chemistry for related metal oxo-species.[9]

The cis selectivity observed for the first cyclization step could be explained as shown in Figure 5. We cannot know the oxidation state of ruthenium during each cyclization step; however, the oxidation states +6 or +8 appear to be the most plausible.[20] Assuming an octahedral geometry for ruthenium[21] in the first-formed Ru(VI) diester **28** and a chair-like conformation of the molecule in the transition state for the cyclization step,[19] a [3+2] cycloaddition,[21] the correct positioning of the double bond involved in the THF closure, close to an O═Ru–O portion, can only occur in the stereochemical arrangement **29**. Though this arrangement suffers for steric repulsions of the pseudoaxially disposed C-2 carbon (numeration relative to the isoprenoid substrate), this appears not to hamper the cyclization event also in isoprenoid polyenes (R=Me). On the other hand, arrangement **31**, similar to **29**, can also exist where the C(2)O–Ru bond underwent hydrolytic cleavage (see **30**) and the free C(2)–OH group is still coordinated to ruthenium, that also would lead to a *cis*-THF.

It is to be noted that the ruthenium ester species **30** could, in principle, also lead to a *trans*-THF via arrangement **32**. In fact, this species is strictly similar to the perrhenate ester involved into the *trans*-diastereoselective cyclization of bishomoallylic alcohols promoted by rhenium (VII) oxo-species. In this case, the steric control model formulated by McDonald[10b,19c] (Fig. 6) could be invoked, with the molecule

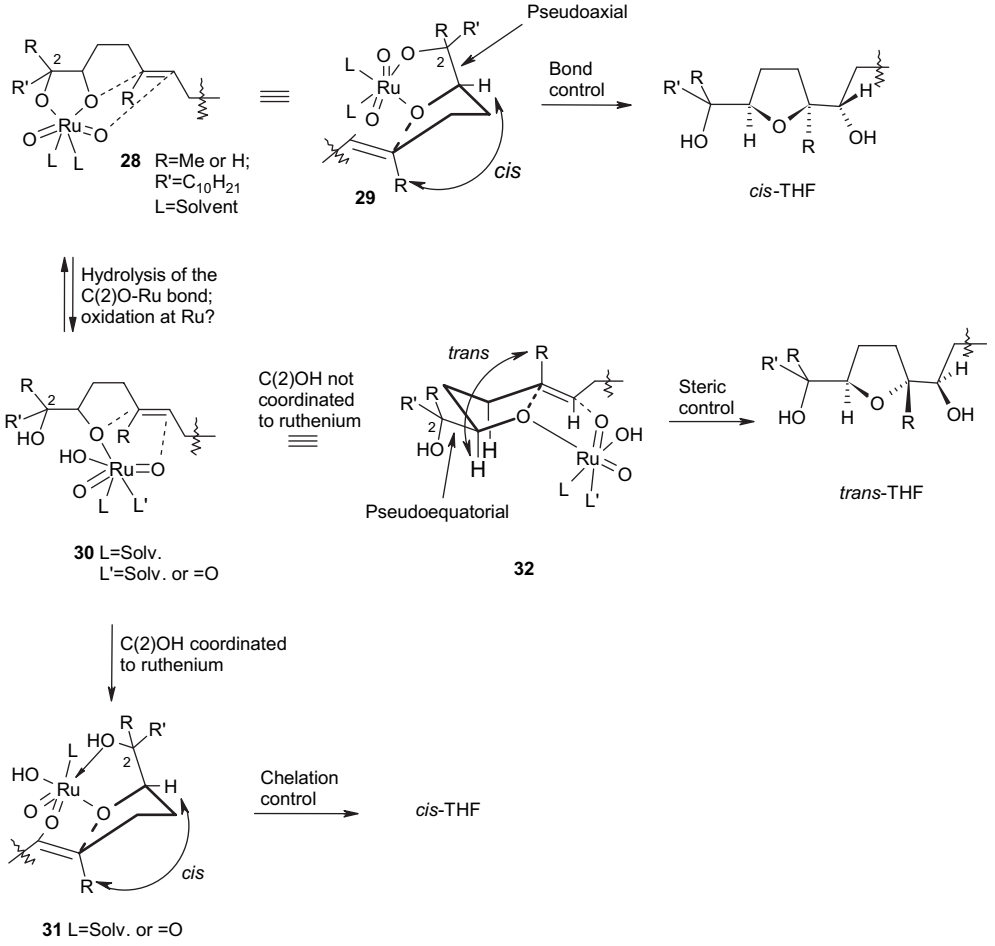


Figure 5. Chelation versus steric control in the first cyclization step of RuO_4-mediated OP process.

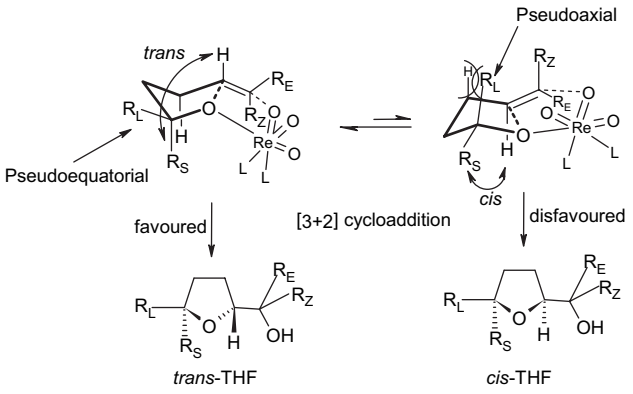


Figure 6. Steric control model for a trans-diastereoselective cyclization of bishomoallylic alcohols promoted by rhenium (VII) oxo-species.[19c]

preferably adopting an arrangement with the bulk group (RR′CHOH) at C-3 pseudoequatorially disposed in the chair-like transition state **32**. That an equilibrium **28/30/32** could exist is substantiated by the formation of minor amounts of *trans*-THF products both in the RuO_4-mediated monocyclization of 1,5-dienes[9] and the partial oxidative cyclization of (*E*,*E*)-FA with the same reagent.[8a] It is also interesting to note here that strictly related monocyclizations processes of 1,5-dienes in the presence of OsO_4,[22] MnO_4^- [23] and RuO_4^- [24] evidently proceed through an intermediate such as **28/29** since the formation of *trans*-THF products has never been observed for these processes a fact that render the involvement of the open ester form **30**, in these cases, not plausible.

The above model is also in accordance with the stereochemical course of the strictly related oxidative cyclization processes promoted by Cr(VI) oxo-species (Fig. 7, top).[25] In particular, the monocyclization of 1,2-dihydroxyalkenes to *cis*-THF's can be explained through the formation of a chromium monoester such as **33** where the coordination of the C-2 OH group to the metal forces the molecule to adopt a spatial arrangement analogous to **31**, thus ensuring the closure of a *cis*-THF ring.[10b] It is to be said, however, that the involvement of a cyclic diester species of the type **28/29** cannot be ruled out in this process as well, owing to the bidentate character of the dihydroxyalkene. Conversely, the same authors reported that the cyclization of a monodentate hydroxydiene such as **34** with PCC[25d] gives a *trans*-THF product (Fig. 7, bottom). In this case, due to the absence of a coordinating OH group, the path depicted for rhenium (VII) in Figure 6 (steric control, trans-selectivity) would be followed.

In conclusion, the first cyclization step of the RuO_4-involving process appears to be under chelation control, if species **31** is involved, or under bond control (C(2)O–Ru bond), if species **28** is involved. On the other hand, when formation of a *trans*-THF is observed, as in related RuO_4-mediated monocyclization of polyenes,[8a] a steric control should be operative via an intermediate of the type **32**.

2.3. Model for the cis-selective second cyclization

As for the second cyclization step, once again it can be speculated that the C(2)O–Ru bond could either be unbroken or already cleaved. The observed cis-selectivity for this step would be explained by either arrangements **35** (C(2)O–Ru intact) or **36** (C(2)O–Ru cleaved) (Fig. 8). As far as arrangement **35** is concerned, the C(2)O–Ru bond imposes the closure of a *cis*-THF ring, irrespective of the fact that the

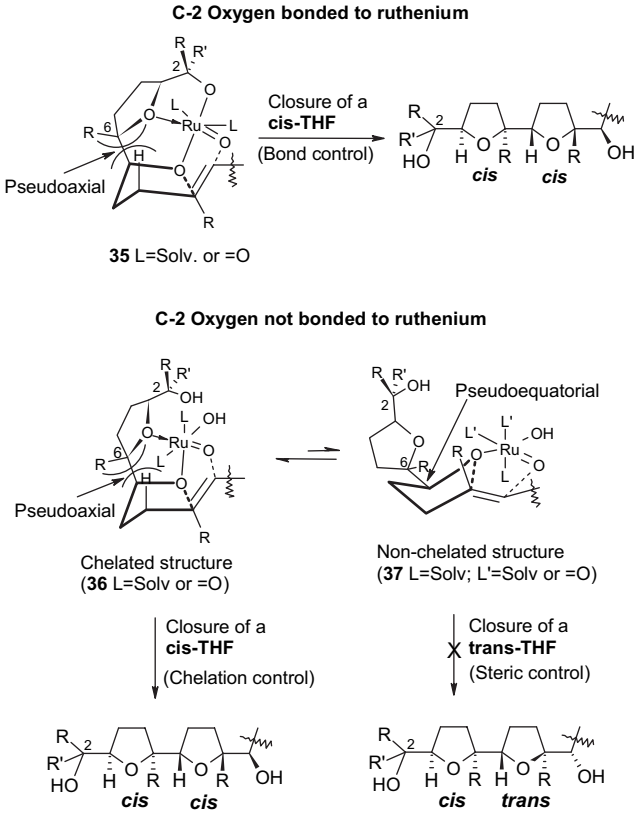


Figure 8. Chelation versus steric control in the second cyclization step of RuO_4-mediated OP process.

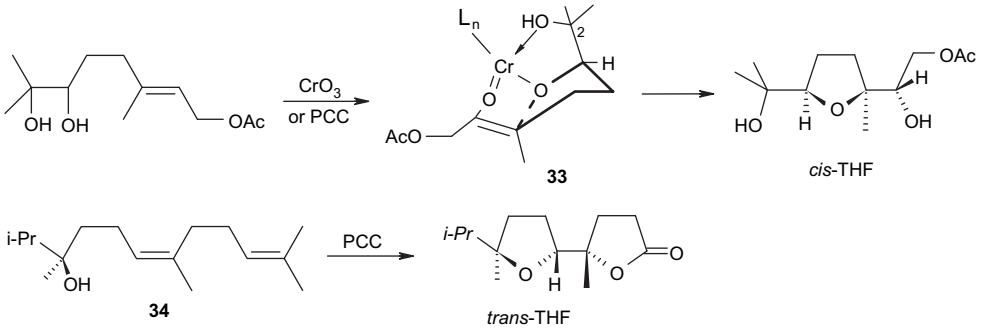


Figure 7. McDonald's model for the *cis*-selective monocyclization of the 6,7-dihydroxyalkene from geranyl acetate (top) and trans-selectivity for a monodentate hydroxydiene (bottom).

first-formed THF ring be or not coordinated to the metal, though this seems possible as molecular models of **35** show. In fact, in this case, the alignment of the alkene for the reaction to take place is incompatible with the closure of a *trans*-THF. In the case the C(2)O–Ru bond be broken, to explain the closure of the *cis*-THF, one should assume that the chelated structure **36** (THF coordinated to Ru), where the angular carbon (C-6) of the coordinated THF is positioned in a sterically demanding pseudoaxial position, should be energetically preferred over the non-chelated structure **37**, where the THF ring is pseudoequatorial, since the latter would lead to a *trans*-THF (not observed) in accord with the steric control model (Fig. 5). This is just what hypothesized by Sinha et al. to explain the observed cis selectivity in the second cyclization step of 4,8-dien-1-ols with $CF_3CO_2ReO_3$ when a *trans–threo* substructure is formed in the first cyclization step.[19b]

On the other hand, it is also to be said that arrangement **36** could be further stabilized by the coordination of the C-2 hydroxyl group to ruthenium as seen for structure **31** (Fig. 5). Therefore, the observed cis selectivity for the second cyclization step would be explained, as seen in the first cyclization step, by a chelation control or by a bond control depending on whether the species **35** or **36** is involved.

2.4. Model for the trans-selective third cyclization in GGA and squalene

Let us refer now to the third cyclization step in GGA and squalene, both proceeding with a trans-selectivity (Scheme 1). A chelated structure **38**, stabilised by coordination of both A and B THF rings, appears in principle possible, as models show, that would impose a cis-selective cyclization. However, a very disfavoured transition state, suffering severe steric repulsions, would be required for a correct alignment of the alkene to take place. In particular, the methyl-carrying carbon (C-10) of the B THF ring is pseudoaxially disposed and, in addition, the R′ group and the methyl at C-10 would be very close in the space during the cycloaddition step. On the other hand, alternative arrangements where the C(2)O is still bonded to ruthenium, or coordinated to it, and one or both the A/B rings coordinated as well (not shown), are also possible but overall these would substantially fix the reacting portions in a reciprocal position as in **38** and the THF closure would suffer similar steric repulsions. A much more favourable spatial arrangement, **39**, leading to a *trans*-THF, is shown in the right side of Figure 9,

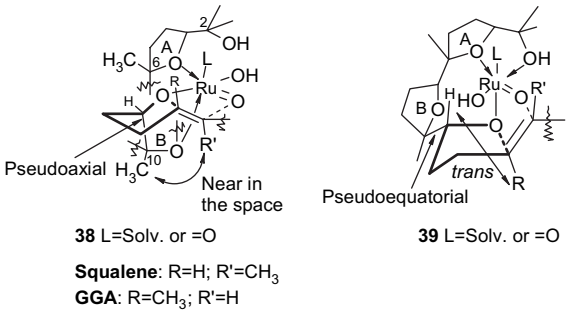


Figure 9. Left: possible chelated structure for the third cyclization step in squalene, leading to a *cis*-THF; the part of the molecule joining the two THF is omitted for sake of clarity. Right: arrangement leading to a *trans*-THF.

where the B THF is pushed away from the metal, and hence non-coordinated to it, due to its pseudoequatorial disposition. This arrangement is, however, compatible with the coordination of both the A THF and the C(2)OH group to ruthenium. Therefore, the trans-selectivity for the third cyclization step both in squalene and GGA appears to be under steric control though a chelation stabilization of the involved arrangement could also exist.

2.5. Model for the trans-selective fourth and fifth cyclizations in the OP of squalene

The trans-selectivity for the fourth ring-closing step in squalene can be explained through the steric control model (arrangement **40**, Fig. 10). In fact, the trans configuration of the third (C) THF ring pushes the metal away from both B and C rings; nor the A ring (not shown) appears to be able to reach a distance suitable for coordination. This is true for the fifth cyclization step as well. On the other hand, an arrangement with C ring chelated to the metal (not shown), that would lead to the closure of a *cis*-THF, would be possible but disfavoured by steric interactions such as those observed in the third cyclization (Fig. 9), though less severe due to the lack of the angular methyl on C THF. Therefore, the formation of *the first trans-THF (the C-THF) in the growing poly-THF chain appears to impose a trans-selectivity to all the successive cyclization steps in an all*-trans *isoprenoid polyene such as squalene*. Further experimental support to this deduction should be given by studying, for example, the oxidative cyclization of analogues of squalene with more than six isoprene units.

2.6. Explaining the failure of the second cyclization in the (*E*,*Z*)-FA and (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (21), and formation of bis-THF 25

To explain the failure of the second cyclization step in both (*E*,*Z*)-FA and (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (**21**) the same type of reasoning above seen for the second cyclization step of all-*E* polyenes can be applied; that is after the formation of the first THF, the molecule adopts a spatial arrangement of the type **35/36** (Fig. 8) where the C(2)–O oxygen is in some way linked to the metal (chelated or bonded) (Fig. 11, left). In fact, if so, the *erythro* relationship arising from the *syn* addition of two oxygens to the cis double bond during the first cyclization would impose a sterically disfavoured *endo* transition state, leading to a *cis*-THF, for the second cyclization step to take place. On the other hand, this chelated arrangement is incompatible with the closure of a *trans*-THF since the alignment of the alkene cannot take place at all. As Sinha et al.[19b] pointed out referring to the second cyclization step of the strictly related 4,8-dien-1-ols, the presence of this *erythro* relationship

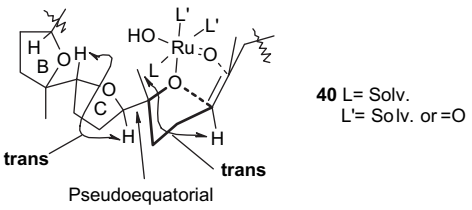


Figure 10. Arrangement explaining the trans-selective fourth cyclization in squalene; only B and C THF's and the cyclizing portion are shown.

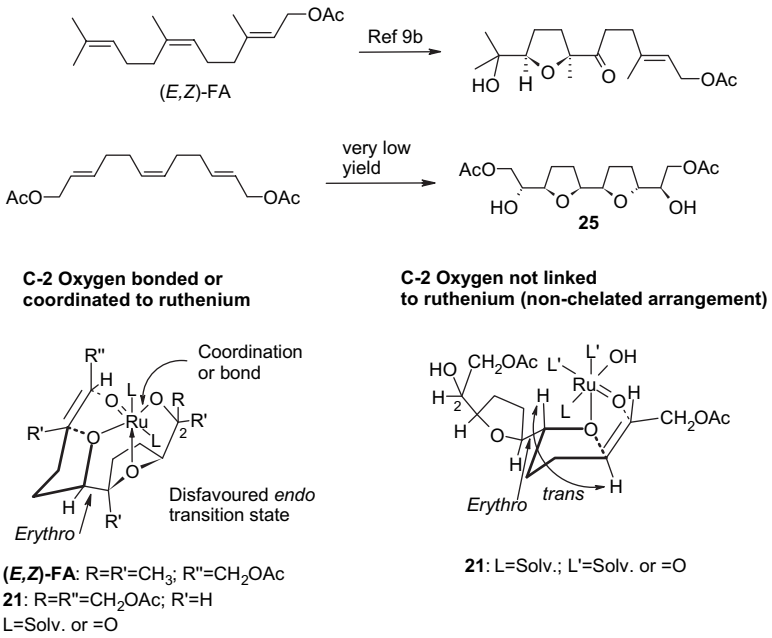


Figure 11. Model explaining the failure of the second cyclization in the (*E*,*Z*)-FA and **21**, and formation of *cis–trans* bis-THF **25**.

would render the non-chelated structure, energetically more favourable leading to a *trans*-THF through a steric control. In our case, however, this non-chelated structure cannot form at all due to the C(2)O vinculum. This explanation well agrees with, and is a further support of, the model above proposed for the cis selectivity of the second cyclization step of an all *E* polyene. On the other hand, formation of the *cis–trans* bis-THF **25** can be explained assuming that the molecule could assume, in a little extent, an arrangement (Fig. 11, right) where both the THF and C(2)–O are not linked to the metal so that a steric control is operative, that leads to a *trans*-THF in the second cyclization step, according to the Sinha's hypothesis.[19b]

2.7. Model explaining the failure of the third cyclization in the all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester (16)

Finally we have to explain why the OP of the all-*trans* tetraene **16** (Scheme 8) stops at the bis-THF level. A tentative explanation can be given by referring to the reasoning developed for the third cyclization of GGA and squalene (Fig. 9). The absence of methyl groups in **16** along the polyenic chain could render the chelated structure of the type **38** (Fig. 9, left) more stable, a fact that would preclude the further cyclization since this arrangement, only compatible with the formation of a *cis*-THF, would however require a disfavoured transition state, as pointed out above for GGA and squalene.

3. Conclusion

In conclusion, the OP of some linear polyenes with the RuO_2(cat.)/$NaIO_4$ oxidizing system has been studied and its ability to induce the oxidative bis-cyclization of two all-trans linear polyenes has been established. A plausible explanation of the observed stereoselectivity of each ring-closing step, either in linear or isoprenoid polyenes, has been given based on steric or chelation control models. However, further studies need to be accomplished both to support the above models, by using suitable substrates and theoretical calculations, and to employ the chemistry developed in the present study for the synthesis of selected annonaceous acetogenin targets. In particular, the unique feature of the RuO_4-mediated OP of inducing the formation of the first two THF rings in the poly-THF product with cis selectivity renders the process useful for the synthesis of ACGs such as rollinistatin-1 and rollimembrin, two of the most active ACGs known, both possessing a *threo–cis–threo–cis–erythro* relative configuration, and/or their non-natural analogues. Further studies in this field are currently ongoing.

4. Experimental

4.1. General methods

All reagents and anhydrous solvents were purchased (Aldrich and Fluka) at the highest commercial quality and used without further purification. Where necessary, flame-dried and argon-charged glassware was used. Reactions were monitored by thin-layer chromatography carried out on precoated silica gel plates (Merck 60, F_{254}, 0.25 mm thick). Merck silica gel (Kieselgel 40, particle size 0.063–0.200 mm) was used for column chromatography. Na_2SO_4 was used as drying agent in all the extractive work-up. HPLC separations were carried out on a Varian 2510 apparatus equipped with a Waters R403 dual cell differential refractometer using phenomenex 250×10 mm and 250×4.6 mm (both 5 μm) columns. NMR experiments were performed on Bruker DRX-600, Bruker WM 400, Varian 300, and Gemini 200 spectrometers in $CDCl_3$ unless otherwise mentioned. All the 2D-NMR spectra were acquired at 600 MHz in the phase-sensitive mode with the transmitter set at the solvent resonance and TPPI (time proportional phase increment) used to achieve frequency discrimination in the ω_1 dimension.

Standard pulse sequence and phase cycling were used for DQF-COSY, 2D-TOCSY, HSQC, 2D-HSQC-TOCSY, HMBC, 2D-INEPT-INADEQUATE, 2D-INEDAQUATE and ROESY spectra. The NMR data were processed on a Silicon Graphic Indigo2 Workstation using UXNMR software. Proton chemical shifts were referenced to the residual $CHCl_3$ signal (7.26 ppm); ^{13}C NMR chemical shifts were referenced to the solvent (77.0 ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. *J* values are given in Hertz. IR spectra were collected on a Jasco FT-IR-430 spectrometer. ESI mass spectrometric analyses were recorded on a Waters Micromass ZQ mass spectrometer equipped with an electrospray source used in the positive mode. HRMS spectra were recorded on a Voyager DE-PRO mass spectrometer using MALDI-TOF ionization.

4.1.1. Synthesis of (2*E*,6*E*,10*E*)-acetic acid henicosa-2,6,10-trienyl ester (7).

4.1.1.1. (*E*)-Pentadec-4-enoic acid ethyl ester 4. To a solution of undecylic aldehyde (7.0 g, 41.1 mmol) in dry THF (5 mL), at 0 °C, was added vinylmagnesium bromide (1 M in THF, 49.3 mL, 49.3 mmol) and the mixture was stirred for 30 min. Then, a saturated NH_4Cl solution (20 mL) was added and the mixture stirred for 10 min. The phases were separated and the aqueous phase was extracted with ether (3×20 mL). The combined ether layer was dried and concentrated to yield tridec-1-en-3-ol[26] (8.0 g, 98%) as an oil that was used without further purification in the next step of the synthesis. ^1H NMR: (200 MHz) δ 5.87 (1H, ddd, *J*=17.2, 10.8, 6.6, H-2), 5.21 (1H, dt, *J*=17.2, 1.4, H_a-1), 5.09 (1H, dt, *J*=10.8, 1.4, H_b-1), 4.09 (2H, q, *J*=6.4, H-3), 1.86 (2H, m), 1.52 (2H, m), 1.25 (14H, br s), 0.87 (3H, t, *J*=7.2, Me).

A solution of the crude allyl alcohol (8.0 g, 40.3 mmol), triethyl orthoacetate (2.1 equiv, 84.6 mmol, 15.5 mL) and propionic acid (2%, 80 mmol, 82 μL) in xylene (15 mL) was refluxed for 4 h. Removal of the solvent followed by purification by column chromatography (petroleum ether→petroleum ether–ethyl ether, 9:1) afforded 6.81 g (63%) of (*E*)-pentadec-4-enoic acid ethyl ester[27] **4** as an oil.

Compound **4**: IR (neat): ν_{max} 1738 cm^{-1}. ^1H NMR: (300 MHz) δ 5.42 (2H, m, olefinic protons), 4.11 (2H, q, *J*=7.5, $CO_2CH_2CH_3$), 2.33 (4H, m), 1.95 (2H, m), 1.23 (3H, t, *J*=7.2, $CO_2CH_2CH_3$), 1.25 (16H, m), 0.87 (3H, t, *J*=7.2, Me).

4.1.1.2. Nonadeca-4,8-dienoic acid ethyl ester 5. $LiAlH_4$ (2.03 g, 53.3 mmol) was slowly added to a solution of ester **4** (6.81 g, 25.4 mmol) in dry ether (70 mL) at 0 °C. The mixture was allowed to warm to room temperature over 1 h, then wet ether was added (10 mL) followed by dropwise addition of water (10 mL). The phases were separated and the aqueous phase was extracted with ether (3×20 mL). The combined ether layer was dried and concentrated to give 5.2 g (90%) of (*E*)-pentadec-4-en-1-ol[5b] as an oil that was taken to the next step without further purification. ^1H NMR: (300 MHz) δ 5.41 (2H, m, olefinic protons), 3.65 (2H, q, *J*=5.4, H_2-1), 2.07 (2H, q, *J*=7.4), 1.96 (2H, q, *J*=6.6), 1.63 (2H, m), 1.39–1.20 (16H, m and br s), 0.87 (3H, t, *J*=7.2, Me).

Celite (9.7 g, 0.42 g/mmol) and PCC (10.4 g, 48.3 mmol) were added to a solution of the crude alcohol (5.2 g, 23.0 mmol) in CH_2Cl_2 (100 mL) and the mixture was stirred for 1.5 h. Filtration on a short pad of silica gel gave (*E*)-pentadec-4-enal (4.38 g, 85%)[5b,28] as an oil. ^1H NMR: (200 MHz) δ 9.76 (1H, t, *J*=1.6, C*H*O), 5.43 (2H, m, olefinic protons), 2.47 (2H, q, *J*=7.2), 2.33 (2H, m), 1.96 (2H, br q, 6.2), 1.38–1.17 (16H, br s), 0.88 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 201.8, 131.8, 127.5, 43.4, 32.3, 31.7, 29.5 (2C), 29.4, 29.3, 29.2, 29.0, 25.0, 22.5, 13.9.

Vinylmagnesium bromide (1 M in THF, 23.5 mL, 23.5 mmol) was added to a solution of the above crude aldehyde (4.38 g, 19.5 mmol) in dry THF (10 mL) at 0 °C. Work-up with saturated aqueous NH_4Cl and ether, as reported above for the preparation of ester **4**, gave allyl alcohol (*E*)-heptadeca-1,6-dien-3-ol[5b] (3.71 g, 76%) as an oil that was used in the next step without further purification. ^1H NMR: (200 MHz) δ 5.87 (1H, ddd, *J*=17.0, 10.8, 6.4, H-2), 5.43 (2H, m, H-6, H-7), 5.22 (1H, br d, *J*=17.2, H_a-1), 5.10 (1H, br d, *J*=10.8, H_b-1) 4.12 (1H, q, *J*=6.0, H-3), 2.08 (2H, m) 1.96 (2H, m), 1.59 (2H, m), 1.40–1.10 (16H, br s), 0.87 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 141.1, 130.8, 129.3, 114.0, 72.2, 36.6, 32.4, 31.8, 29.5 (3C), 29.4, 29.2, 29.1, 28.3, 22.5, 13.9.

A solution of the crude allyl alcohol (3.71 g, 14.7 mmol), triethyl orthoacetate (2.1 equiv, 30.9 mmol, 5.7 mL) and propionic acid (2%, 0.3 mmol, 22 μL) in xylene (10 mL) was refluxed for 2 h. Removal of the solvent followed by purification by column chromatography (petroleum ether→petroleum ether–ethyl ether, 95:5) afforded 2.84 g (60%) of (*E*,*E*)-nonadeca-4,8-dienoic acid ethyl ester **5**[5b] as an oil.

Compound **5**: IR (neat): ν_{max} 1738 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.50–5.30 (4H, m, olefinic protons), 4.12 (2H, q, *J*=7.2, $CO_2CH_2CH_3$), 2.37–2.23 (4H, m), 2.08–1.87 (6H, m), 1.38–1.18 (16H, br s), 1.22 (3H, t, *J*=7.2, $CO_2CH_2CH_3$), 0.87 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 172.5, 130.8, 130.5, 129.2, 128.1, 59.7, 34.1, 32.4, 31.7, 29.5, 29.4, 29.2, 29.0, 27.7, 22.5, 14.0, 13.8.

4.1.1.3. (*E*,*E*,*E*)-Henicosa-2,6,10-trienoic acid ethyl ester 6. Ester **5** (2.84 g, 8.8 mmol) in dry ethyl ether (20 mL) was reduced with $LiAlH_4$ (702 mg, 18.5 mmol) as reported for ester **4** to give 2.15 g (87%) of (*E*,*E*)-nonadeca-4,8-dien-1-ol as an oil that was subjected to the next step without further purification. A 200 mg amount of this material was subjected to a further HPLC purification on an RP-18 column (MeOH–H_2O, 97:3) to obtain a pure sample for spectral characterization. IR (neat): ν_{max} 3339 cm^{-1}. ^1H NMR: (200 MHz) δ 5.30–5.45 (4H, m, olefinic protons), 3.62 (2H, t, *J*=7.3, H_2-1), 2.10–1.90 (8H, m), 1.61 (2H, quintet, *J*=7.0), 1.38–1.15 (16H, br s), 0.87 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 130.7, 130.3, 129.6, 129.4, 62.1, 32.6, 32.5, 32.3, 31.8, 29.5, 29.4, 29.2, 29.1, 28.8, 22.6, 14.0.

A solution of the crude alcohol (2.15 g, 7.6 mmol) in CH_2Cl_2 was oxidized with PCC (3.45 g, 16.0 mmol) and Celite (3.2 g) as reported for the synthesis of ester **5** giving 1.79 g (85%) of (*E*,*E*)-nonadeca-4,8-dienal, as an oil, that was used in the next step. IR (neat): ν_{max} 1728 cm^{-1}. ^1H NMR: (200 MHz) δ 9.76 (1H, t, *J*=1.6, C*H*O), 5.50–5.32 (4H, m,

olefinic protons), 2.48 (2H, br t, J=7.3, H-2), 2.34 (2H, br q, J=6.4, H-3), 2.07–1.88 (6H, m), 1.37–1.17 (16H, br s), 0.88 (3H, t, J=6.7, Me). ^{13}C NMR: (50 MHz) δ 201.1, 131.0, 130.6, 129.1, 127.8, 43.2, 32.34, 32.27, 31.7, 29.46, 29.41, 29.3, 29.2, 29.0, 24.9, 22.4, 13.8. MS m/z 317 (89, M+K)$^+$, 301 (28, M+Na)$^+$. HRMS: calcd for $C_{19}H_{34}ONa$ 301.2499, found 301.2506.

To a mixture of NaH (60% in mineral oil, 113.6 mg, 2.84 mmol) in dry THF (5 mL) triethyl phosphonoacetate (563 μL, 2.84 mmol) was added dropwise at room temperature and the mixture stirred for 1 h. To the light orange solution was dropwise added a solution of the aldehyde (790 mg, 2.84 mmol), obtained as above, in dry THF (2 mL), within a 20 min period. After 1.5 h the mixture was extracted with ether (3×10 mL) and the organic phase dried and concentrated. Purification by column chromatography (gradient from 2% to 10% ethyl ether in hexanes) afforded 740 mg (75%) of pure (*E*,*E*,*E*)-henicosa-2,6,10-trienoic acid ethyl ester **6** as an oil.

Compound **6**: IR (neat): ν_{max} 1725, 1655 cm^{-1}. ^{1}H NMR: (200 MHz) δ 6.95 (1H, dt, J=15.6, 6.4, H-3), 5.81 (1H, dt, J=15.6, 1.6, H-2), 5.47–5.37 (4H, m, olefinic protons), 4.18 (2H, q, J=7.0, $CO_2CH_2CH_3$), 2.27–1.94 (10H, overlapped m's), 1.28 (3H, t, J=7.2, $CO_2CH_2CH_3$), 1.27 (16H, br s), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR: (100 MHz) δ 166.6, 148.5, 131.1, 130.8, 129.4, 128.6, 121.5, 60.0, 32.6, 32.5, 32.22, 32.18, 31.9, 30.9, 29.6, 29.5, 29.3, 29.1, 22.6, 14.2, 14.0. MS m/z 387 (56, M+K)$^+$, 371 (80, M+Na)$^+$. HRMS: calcd for $C_{23}H_{40}O_2Na$ 371.2916, found 371.2910.

4.1.1.4. (*E*,*E*,*E*)-Acetic acid henicosa-2,6,10-trienyl ester 7. To a solution of the ester **6** (740 mg, 2.1 mmol) in dry THF (3 mL) was added dropwise DIBAL-H (1 M in THF, 6.4 mL, 6.4 mmol) at −78 °C. The mixture was stirred at this temperature for 1 h and then quenched by dropwise addition of a saturated NH_4Cl solution (3 mL). The phases were separated and the aqueous phase was extracted with ether (3×5 mL). The combined ether layer was dried and concentrated to give 610 mg (94%) of crude (*E*,*E*,*E*)-henicosa-2,6,10-trien-1-ol. IR (neat): ν_{max} 3393 cm^{-1}. ^{1}H NMR: (200 MHz) δ 5.66 (2H, m, olefinic protons), 5.40 (4H, m, olefinic protons), 4.08 (2H, d, J=4.4, H_2-1), 3.65 (1H, t, J=6.8, OH), 2.18–1.90 (10H, m), 1.40–1.10 (16H, m), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR: (150 MHz) δ 132.8, 131.1, 130.8, 130.5, 129.5 (2C), 129.2, 63.8, 32.7, 32.6, 32.4, 32.3, 32.1, 29.6 (2C), 29.5, 29.3, 29.2, 28.9, 22.7, 14.1. MS m/z 345 (45, M+K)$^+$, 329 (75, M+Na)$^+$. HRMS: calcd for $C_{21}H_{38}ONa$ 329.2811, found 329.2830.

Acetic anhydride (3 mL) and pyridine (3 mL) were added to 610 mg (2.0 mmol) of the above alcohol and the solution was left at room temperature overnight. Then, the mixture was partitioned between EtOAc and HCl 0.1 M, and the organic layer was washed with a saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), filtered and concentrated. HPLC purification (hexane–EtOAc, 98:2, flow 2.5 mL/min) gave 505 mg (73%) of pure triene **7** (t_R=15.0 min) as an oil.

Compound **7**: IR (neat): ν_{max} 1738, 1229 cm^{-1}. ^{1}H NMR: (200 MHz) δ 5.78 (1H, dt, J=15.5, 6.0, olefinic proton), 5.56 (1H, dt, J=15.5, 6.6, olefinic proton), 5.45–5.34 (4H, m, olefinic protons), 4.50 (2H, d, J=6.4, CH_2OAc), 2.14–1.89 (overall 13H, m overlapped with the 3H-singlet acetate at 2.05), 1.33–1.19 (16H, m), 0.87 (3H, t, J=6.9, Me). ^{13}C NMR: (100 MHz) δ 170.8, 135.9, 130.8, 130.5, 129.5, 129.3, 124.0, 65.2, 32.6, 32.2, 31.9, 29.6, 29.3, 29.1, 22.6, 20.9, 14.1. MS m/z 387 (55, M+K)$^+$, 371 (77, M+Na)$^+$. HRMS: calcd for $C_{23}H_{40}O_2Na$ 371.2916, found 371.2923.

4.1.2. Oxidation of triene 7 with $RuO_{4(cat.)}$/$NaIO_4$. To a solution of triene **7** (50 mg, 0.14 mmol) in the biphasic mixture EtOAc–CH_3CN–H_2O (3:3:1) (17.5 mL) were added in sequence $NaIO_4$ (4 equiv, 118 mg, 0.55 mmol) and $RuO_2\cdot 2H_2O$ (20 mol %, 3.6 mg) under vigorous stirring at 0 °C. TLC monitoring (hexane–EtOAc, 3:7) indicated that the reaction to be completed after 30 min. The process was quenched by the addition of excess of a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (2 mL) until the yellowish mixture turned to black (RuO_2 precipitation). Then the mixture was filtered and extracted with EtOAc (3×10 mL), and the combined organic phase was dried and evaporated to give 60 mg of an oil. HPLC separation (hexane–EtOAc, 3:7, flow 2.5 mL/min) afforded bis-THF diol **8** (12.5 mg, 24%, t_R=15.3 min), ketol **10** (4.5 mg, 8.5%, t_R=9.2 min) and **9** (7.5 mg, 14%, t_R=11.7 min) as oils.

4.1.2.1. Acetic acid 2-hydroxy-2-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-ethyl ester 8. IR (neat): ν_{max} 3419, 1742 cm^{-1}. ^{1}H NMR (600 MHz, attributions by 2D-NMR): δ 4.17, 4.14 (1H each, AB system further coupled, J_{AB}=11.5, J_{AX}=7.0, J_{BX}=4.8, H_2-1), 4.02, 3.94, 3.91, 3.81 (1H each, m's, H-3, H-6, H-7, H-10, respectively), 3.70 (1H, dt, J=7.0, 4.8, H-2), 3.43 (1H, dt, J=7.8, 4.7, H-11), 2.09 (3H, s, acetate), 2.01, 1.97 (1H each, m's, H_2-4), 1.96 (2H, m, H_2-5) 1.96, 1.88 (1H each, m's, H_2-8), 1.96, 1.81 (1H each, m's, H_2-9), 1.45 (2H, m, H_2-12), 1.27 (16H, br s, H_2-13/H_2-20), 0.88 (3H, t, J=6.8, H_3-21).

^{1}H NMR (DMSO-d_6, 600 MHz, attributions by 2D-NMR): δ 4.88, 4.26 (1H each, d's, J=6.3 and 6.1, respectively, 2×OH), 3.99, 3.96 (1H each, AB system further coupled, J_{AB}=11.1, J_{AX}=6.9, J_{BX}=4.8, H_2-1), 3.83 (1H, m, H-3), 3.73 (2H, m, H-6 and H-7), 3.68 (1H, q, J=6.0, H-10), 3.58 (1H, ddd, J=6.9, 6.3, 4.8, H-2), 3.28 (1H, m, H-11), 2.09 (3H, s, acetate), 1.80, 1.72 (1H each, m's, H_2-4), 1.73, 1.62 (1H each, m's, H_2-9), 1.21-1.31 (2H, m, H_2-12), 1.26 (16H, br s, H_2-13/H_2-20), 0.86 (3H, t, J=6.8, H_3-21).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.1 (carbonyl), 83.2 (CH-10), 81.4 (CH-6), 81.2 (CH-7), 79.6 (CH-3), 74.1 (CH-11), 72.2 (CH-2), 66.5 (CH_2-1) 34.6 (CH_2-12), 29.9 (8×CH_2, C-13/C-20) 28.6 (CH_2-9), 28.4 (CH_2-8, CH_2-5), 28.3 (CH_2-4), 21.2 (CH_3 acetate), 14.3 (CH_3-21).

^{13}C NMR (DMSO-d_6, 150 MHz, attributions by 2D-NMR): δ 171.1 (carbonyl), 83.0 (CH-10), 81.7 (CH-6, CH-7), 79.7 (CH-3), 72.8 (CH-11), 70.7 (CH-2), 66.6 (CH_2-1) 33.5 (CH_2-12), 29.9, 29.8 (8×CH_2, C-13/C-20), 28.3 (CH_2-5, CH_2-8), 27.6 (CH_2-9), 27.4 (CH_2-4), 21.1 (CH_3 acetate), 14.6 (CH_3-21). MS m/z 453 (100, M+K)$^+$, 437 (17, M+Na)$^+$. MS m/z 453 (100, M+K)$^+$, 437 (27, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_6Na$ 437.2868, found 437.2874.

4.1.2.2. Acetic acid 2-hydroxy-2-(5′-undecanoyl-octahydro-[2,2′]bifuranyl-5-yl)-ethyl ester 9. IR (neat): ν_{max} 3444, 1734, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 4.40 (1H, dd, J=8.7, 6.0, H-10), 4.15 (2H, d, J=6.0, H_2-1), 4.07–3.89 (3H, m, H-3, H-6, H-7), 3.69 (1H, br q, J=6.0, H-2), 2.50 (2H, dt, J=7.2, 2.1, H_2-12), 2.09 (3H, s, acetate), 1.37–1.18 (16H, br s, H_2-13/H_2-20), 0.88 (3H, t, J=6.9, H_3-21). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 211.6 (C-11), 170.6 (carbonyl acetate), 82.7 (CH-7), 80.9 (CH-6), 80.8 (CH-10), 80.1 (CH-3), 71.9 (CH-2), 66.7 (CH_2-1), 33.6 (CH_2-12), 29.4 (CH_2-13/CH_2-20), 27.5, 28.3 (CH_2-4, CH_2-5, CH_2-8, CH_2-9), 20.9 (CH_3 acetate), 13.9 (CH_3-21). MS m/z 451 (100, M+K)$^+$, 435 (78, M+Na)$^+$, 413 (16, M+H)$^+$. HRMS: calcd for $C_{23}H_{40}O_6Na$ 435.2712, found 435.2719.

4.1.2.3. Acetic acid 2-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-2-oxo-ethyl ester 10. IR (neat): ν_{max} 3400, 1734, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.16, 4.91 (1H each, AB system, J_{AB}=17.7, H_2-1), 4.48 (1H, dd, J=7.6, 6.4, H-3), 3.98 (1H, br q, J=6.8, H-6), 3.92 (1H, br q, J=6.8, H-7), 3.81 (1H, br q, J=6.4, H-10), 3.43 (1H, m, H-11), 2.18 (3H, s, acetate), 2.05–1.85 (H_2-4, H_2-5, H_2-8, H_2-9), 1.45 (2H, m, H_2-12), 1.27 (16H, br s, H_2-13/H_2-20), 0.88 (3H, t, J=6.9, H_3-21). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 204.9 (C-2), 170.2 (carbonyl acetate), 83.2 (CH-3), 82.8 (CH-10), 82.7 (CH-6), 80.9 (CH-7), 74.1 (CH-11), 66.5 (CH_2-1) 33.6 (CH_2-12), 29.9 (CH_2-13/CH_2-20), 27.5, 29.0 (CH_2-4, CH_2-5, CH_2-8, CH_2-9), 20.2 (CH_3 acetate), 14.0 (CH_3-21). MS m/z 451 (83, M+K)$^+$, 435 (63, M+Na)$^+$, 413 (18, M+H)$^+$. HRMS: calcd for $C_{23}H_{40}O_6Na$ 435.2712, found 435.2705.

4.1.2.4. Acetic acid 6-hydroxy-6-[5-(1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-hex-2-enyl ester 11. IR (neat): ν_{max} 3412, 1741, 1235 cm^{-1}. ^1H NMR (200 MHz): δ 5.80 (1H, dt, J=15.7, 6.6, olefinic proton), 5.59 (1H, dt, J=15.7, 5.9, olefinic proton), 4.51 (2H, d, J=6.4, H_2-1), 3.82 (2H, m, H-7, H-10), 3.42 (2H, m, H-6, H-11), 2.05 (3H, s, acetate), 1.42–1.18 (br s, H_2-13/H_2-20), 0.87 (3H, t, J=6.3, H_3-21). MS m/z 437 (65, M+K)$^+$, 421 (87, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_5Na$ 421.2919, found 421.2926.

4.1.3. Oxidation of bis-THF diol 9 with TPAP/NMO. To a solution of **8** (4.0 mg, 0.01 mmol) in CH_2Cl_2 (400 μL) were sequentially added *N*-methylmorpholine *N*-oxide monohydrate (NMO) (2.0 mg, 1.5 equiv), powdered 4 Å molecular sieves (5 mg) and TPAP (10 mol %, 0.4 mg) under stirring at room temperature. After 1 h the mixture was concentrated, filtered on silica gel ($CHCl_3$–CH_3OH, 9:1) to give 3.5 mg of a crude material. ^1H NMR analysis revealed the presence of a mixture of ketols **9** and **10** (together ca. 50%) in a ca. 2:1 ratio along with a 20–25% amount of a product tentatively identified as the corresponding diketone (δ 5.10, 4.90, AB system, J=17.7).

4.1.4. Synthesis of acetic acid 2,3,6-trihydroxy-6-[5-(1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-hexyl esters 12. A solution of triene **7** (15.6 mg, 0.046 mmol) in CH_2Cl_2 (4 mL) was treated with NMO (50 mg, 0.37 mmol) and CSA (127.2 mg, 0.55 mmol) followed by osmium tetroxide (1.2 mg, 0.0046 mmol, 10%) and the solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous sodium thiosulfate (1 mL) and $NaHCO_3$ (1 mL) solutions and the biphasic solution was extracted with $CHCl_3$ (3×10 mL), then the organic phase was dried and evaporated. The oily residue was purified by column chromatography (gradient from $CHCl_3$ to $CHCl_3$–MeOH, 98:2) to give in the first-eluted fractions (eluent $CHCl_3$) a brown oil (10 mg) tentatively identified as the osmate ester corresponding to tetrols **12** and then tetrols **12** (2 mg, 10%) as an oil. Compound **12**: ^1H NMR (200 MHz): δ 4.30–4.05 (2H, m), 3.93–3.77 (2H, m), 3.77–3.56 (2H, m), 3.56–3.35 (2H, m), 2.10 (3H, s, acetate), 1.25 (16H, br s), 0.87 (t, J=6.6, Me). MS m/z 471 (62, M+K)$^+$, 455 (100, M+Na)$^+$. HRMS: calcd for $C_{23}H_{44}O_7Na$ 455.2973, found 455.2966.

4.1.4.1. Dihydroxylation of 11 to 12. To a solution of **11** (5 mg, 0.012 mmol) in acetone–water (5:1, 600 μL) was added OsO_4 (0.3 mg, 10%) and NMO (32 mg, 0.24 mmol) and the mixture stirred at room temperature for 1 h. The reaction was quenched by the addition of a saturated solution of sodium thiosulfate (0.5 mL) and $NaHCO_3$ (0.5 mL) and the whole was extracted with $CHCl_3$ (3×3 mL). The organic phase was dried and evaporated and the residue purified by preparative TLC ($CHCl_3$–CH_3OH, 9:1, R_f=0.31) to give 4.3 mg (80%) of tetrols **12**.

4.1.5. Synthesis of acetic acid 2-hydroxy-2-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-ethyl esters 13 and 14. To a solution of **11** (5.0 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) was added MCPBA (4.4 mg, 0.026 mmol) at 0 °C and the mixture was stirred at the same temperature for 1.5 h. Then, CSA (0.6 mg, 0.0026 mmol) was added and the solution was stirred for further 45 min. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3×5 mL). The organic phase was dried and evaporated. The residue was purified by HPLC (hexane–EtOAc, 1:1) to give the two diastereomeric bis-THF diols **13** and **14** as oils. Major isomer (t_R=23 min, 1.6 mg, 30%); minor isomer (t_R=24.5 min, 1.4 mg, 26%).

Major isomer. IR (neat): ν_{max} 3440, 1742, 1240 cm^{-1}. ^1H NMR (500 MHz): δ 4.22, 4.05 (1H each, AB system further coupled, J=11.5, 3.0 and 11.5, 7.2, respectively, CH_2OAc), 4.02–3.92 (3H, m, 3×C*H*–O), 3.88 (2H, m, C*H*–O), 3.37 (1H, dt, J=7.5, 4.9, H-11), 2.10 (3H, s, acetate), 1.25 (br s, overlapped with other signals), 0.88 (3H, t, J=6.7, H_3-21). MS m/z 453 (90, M+K)$^+$, 437 (53, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_6Na$ 437.2868, found 437.2875.

Minor isomer. IR (neat): ν_{max} 3450, 1742, 1240 cm^{-1}. ^1H NMR (500 MHz): δ 4.15 (1H, m), 4.05 (2H, m), 3.97 (1H, br ddd, J=7.2, 7.2, 3.3), 3.89 (2H, m), 3.83 (1H, q, J=6.2), 3.41 (1H, ddd, J=7.4, 5.1, 5.1), 2.09 (3H, s, acetate), 1.25 (br s, overlapped with other signals), 0.88 (3H, t, J=7.0, H_3-21). MS m/z 453 (88, M+K)$^+$, 437 (64, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_6Na$ 437.2868, found 437.2861.

4.1.6. Synthesis of (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester (16).

4.1.6.1. (*E*,*E*,*E*)-Tricosa-4,8,12-trienoic acid ethyl ester 15. (*E*,*E*)-Nonadeca-4,8-dienal (2.8 g, 10.07 mmol) in dry THF (5 mL), at 0 °C, was reacted with vinylmagnesium bromide (1 M in THF, 11 mL, 11 mmol) as reported above

for undecylic aldehyde (see synthesis of **4**) and worked-up in the same manner to give (*E*,*E*,*E*)-heneicosa-1,6,10-trien-3-ol (2.8 g, 91%) as an oil that was used without further purification in the next step of the synthesis. IR (neat): ν_{max} 3361 cm^{-1}. ^1H NMR (200 MHz): δ 5.81 (1H, ddd, J=17.2, 10.5, 6.4, H-2), 5.54–5.25 (4H, m, H-6, H-7, H-10, H-11), 5.17 (1H, br d, J=17.2, H_a-1), 5.04 (1H, br d, J=10.5, H_b-1), 4.06 (1H, q, J=6.2, H-3), 2.17–1.84 (8H, m), 1.70–1.45 (2H, m), 1.40–1.13 (16H, m), 0.86 (3H, t, J=6.7, Me). ^{13}C NMR (50 MHz): δ 141.1, 130.6, 130.4, 129.7, 129.4, 114.3, 72.4, 36.6, 32.63, 32.60, 32.5, 31.8, 29.6, 29.5, 29.3, 29.1, 28.4, 22.6, 14.0. MS *m*/*z* 345 (40, M+K)$^+$, 329 (83, M+Na)$^+$. HRMS: calcd for $C_{21}H_{38}ONa$ 329.2811, found 399.2800.

A solution of crude allyl alcohol (2.8 g, 9.1 mmol), triethyl orthoacetate (2.1 equiv, 19.2 mmol, 3.5 mL) and propionic acid (2%, 0.18 mmol, 19 μL) in xylene (3.5 mL) was refluxed for 4 h. Removal of the solvent followed by purification by column chromatography (petroleum ether → petroleum ether–ethyl ether, 9:1) afforded 1.77 g (53%) of (*E*,*E*,*E*)-tricosa-4,8,12-trienoic acid ethyl ester **15** as an oil.

Compound **15**: IR (neat): ν_{max} 1738 cm^{-1}. ^1H NMR (200 MHz): δ 5.49–5.26 (6H, m, olefinic protons), 4.12 (2H, q, J=6.7, $CO_2CH_2CH_3$), 2.42–2.21 (2H, m), 2.15–1.86 (12H, m), 1.41–1.15 (19H, br s including the $CO_2CH_2CH_3$ signal), 0.88 (3H, t, J=6.5, Me). ^{13}C NMR (50 MHz): δ 172.7, 130.9, 130.5, 130.0, 129.6, 129.4, 128.2, 59.9, 34.2, 32.5, 32.43, 32.38, 31.8, 29.5, 29.4, 29.2, 29.0, 27.8, 22.5, 14.0, 13.9. MS *m*/*z* 415 (54, M+K)$^+$, 399 (85, M+Na)$^+$. HRMS: calcd for $C_{25}H_{44}O_2Na$ 399.3228, found 399.3223.

4.1.6.2. (*E*,*E*,*E*,*E*)-Acetic acid pentacosa-2,6,10,14-tetraenyl ester 16. Ester **15** (1.77 g, 4.7 mmol) was reduced with $LiAlH_4$ (178 mg, 4.7 mmol) in dry ethyl ether (15 mL) following the same procedure employed for the synthesis of ester **5** to give 1.74 g of crude (*E*,*E*,*E*)-tricosa-4,8,12-trien-1-ol as an oil that was used without further purification in the next step of the synthesis. IR (neat): ν_{max} 3347 cm^{-1}. ^1H NMR (200 MHz): δ 5.50–5.24 (6H, m, olefinic protons), 3.57 (2H, t, J=7.0, H_2-1), 2.13–1.87 (12H, m), 1.57 (2H, quintet, J=7.0), 1.30 1.17 (16H, br s), 0.85 (3H, t, J=6.7, Me). ^{13}C NMR (50 MHz): δ 130.6, 130.4, 130.1, 129.8, 129.6, 129.5, 62.1, 32.64, 32.61, 32.56, 32.5, 32.3, 31.8, 29.6, 29.4, 29.3, 29.1, 28.8, 22.6, 14.0. MS *m*/*z* 373 (70, M+K)$^+$, 399 (45, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}ONa$ 357.3123, found 357.3140.

A solution of the crude alcohol (1.74 g, 5.2 mmol) in CH_2Cl_2 (23 mL) was oxidised with PCC (2.25 g, 10.4 mmol) and Celite (2.2 g) as reported for the synthesis of ester **5** to give 1.8 g of (*E*,*E*,*E*)-tricosa-4,8,12-trienal, as an oil, that was used in the next step. IR (neat): ν_{max} 1729 cm^{-1}. ^1H NMR (200 MHz): δ 9.76 (1H, t, J=1.6, C*H*O), 5.53–5.22 (6H, m, olefinic protons), 2.52–2.32 (2H, m), 2.39–2.24 (2H, m), 2.09–1.88 (10H, overlapped m's), 1.42–1.15 (16H, br s), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR (50 MHz): δ 201.9, 131.2, 130.6, 130.1, 129.55, 129.47, 127.9, 43.4, 32.6, 32.5, 32.3, 31.8, 29.5, 29.4, 29.2, 29.0, 25.1, 22.6, 14.0. MS *m*/*z* −371 (45, M+K)$^+$, 355 (90, M+Na)$^+$. HRMS: calcd for $C_{23}H_{40}ONa$ 355.2967, found 355.2961.

The crude aldehyde obtained as above (1.80 g, 5.42 mmol) dissolved in dry THF (2 mL) was added to a solution of triethyl phosphonoacetate (1.07 mL, 5.42 mmol) in dry THF (3 mL), previously mixed with NaH (60% in mineral oil, 216 mg, 5.42 mmol), as described for the synthesis of ester **6**, to give 1.66 g of crude (*E*,*E*,*E*,*E*)-pentacosa-2,6,10,14-tetraenoic acid ethyl ester as an oil. Purification of a 50 mg amount of this material by HPLC (hexane–EtOAc, 98:2, flow: 2.5 mL/min) afforded a pure sample (25 mg, 38%, t_R=14.6 min) for spectral characterization. IR (neat): ν_{max} 1724 cm^{-1}. UV λ_{max} (MeOH)=208 nm (ε=25,300). ^1H NMR (300 MHz): δ 6.95 (1H, dt, J=15.8, 6.7, H-3), 5.81 (1H, dt, J=15.8, 1.2, H-2), 5.50–5.30 (6H, m, olefinic protons), 4.18 (2H, q, J=7.4, $CO_2CH_2CH_3$), 2.31–2.19 (2H, m), 2.19–2.09 (2H, m), 2.09–1.90 (10H, overlapped m's), 1.38–116 (19H, br s partly overlapped with a triplet (J=7.6) attributable to $CO_2CH_2CH_3$), 0.88 (3H, t, J=7.0, Me). ^{13}C NMR (50 MHz): δ 166.6, 148.5, 131.1, 130.7, 130.2, 129.7, 129.6, 128.6, 121.5, 60.0, 32.7, 32.57, 32.55, 32.52, 32.2, 31.9, 30.9, 29.6, 29.5, 29.3, 29.1, 22.6, 14.0. MS *m*/*z* 441 (90, M+K)$^+$, 425 (65, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_2Na$ 425.3384, found 425.3378.

The remaining crude ester (1.60 g, 4.23 mmol) dissolved in dry THF (12 mL) was reduced with DIBAL-H (1 M in THF, 12.7 mL, 12.7 mmol) at −78 °C as described for triene **7** to give 1.26 g of an oily product. HPLC purification (hexane–ethyl acetate, 7:3) gave 410 mg (24% respect to ester **15**; four steps) of (*E*,*E*,*E*,*E*)-pentacosa-2,6,10,14-tetraen-1-ol as an oil. IR (neat): ν_{max} 3348 cm^{-1}. ^1H NMR (200 MHz): δ 5.67 (2H, m, olefinic protons), 5.40 (6H, m, olefinic protons), 4.08 (2H, d, J=4.4, H_2-1), 2.15–1.87 (14H, overlapped m's), 1.35–1.5 (16H, br s), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR (100 MHz): δ 132.7, 130.7, 130.4, 130.1, 129.9, 129.6, 129.5, 129.2, 63.8, 32.65, 32.62, 32.5, 32.2, 32.1, 31.9, 29.6, 29.5, 29.3, 29.1, 22.6, 14.0. MS *m*/*z* 399 (80, M+K)$^+$, 383 (43, M+Na)$^+$. HRMS: calcd for $C_{25}H_{44}ONa$ 383.3279, found 383.3277.

Acetylation of the above alcohol (410 mg, 1.14 mmol) with Ac_2O–pyridine (1:1, 1 mL), as described for the synthesis of triene **7**, gave 495 mg of tetraene **16**. Accurate ^1H NMR analysis revealed it to be still contaminated by other minor products exhibiting very similar chromatographic (HPLC direct-phase) mobility. Pure **16**, an oil, could be obtained after reverse-phase (MeOH) HPLC (250 mg, 55%).

Compound **16**: IR (neat): ν_{max} 1738, 1229 cm^{-1}. ^1H NMR (400 MHz): δ 5.78 (1H, dt, J=15.4, 6.2, olefinic proton), 5.58 (1H, dt, J=15.4, 6.4, olefinic proton), 5.35–5.45 (6H, m, olefinic protons), 4.51 (2H, d, J=6.4, H_2-1), 2.13–1.95 (17H, overlapped m's including a 3H singlet at 2.06 ppm due to the acetate methyl), 1.40–1.20 (16H, br s), 0.90 (3H, t, J=7.2, Me). ^{13}C NMR (100 MHz): δ 170.7, 135.8, 130.7, 130.5, 130.1, 129.8, 129.6, 129.3, 124.1, 65.1, 32.67, 32.65, 32.61, 32.5, 32.2, 31.9, 29.6, 29.5, 29.3, 29.1, 22.6, 20.9, 14.0. MS *m*/*z* 441 (33, M+K)$^+$, 425 (62, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_2Na$ 425.3384, found 425.3377.

4.1.7. Oxidation of tetraene 16 with $RuO_{4(cat.)}$/$NaIO_4$. Tetraene **16** was oxidised as reported above for triene **7**. In particular, to a solution of tetraene **16** (27.3 mg,

0.068 mmol) in the biphasic mixture EtOAc–CH_3CN–H_2O (3:3:1) (10.5 mL) were added in sequence $NaIO_4$ (5 equiv, 75 mg) and $RuO_2\cdot 2H_2O$ (20 mol %, 1.7 mg) under vigorous stirring at 0 °C. After 20 min a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (2 mL) was added and, after a further 10 min stirring, the mixture was filtered and extracted with EtOAc (3×10 mL). The combined organic phase was dried and evaporated to give 35 mg of an oily product. HPLC separation (hexane–EtOAc, 3:7, flow 2.5 mL/min) afforded bis-THF diol **17** (6.2 mg, 21%, t_R=13 min), bis-THF ketol **18** (4.8 mg, 16%, t_R=9.6 min) and bis-THF ketol **19** (1.1 mg, 5%, t_R=9.2 min) as oils.

4.1.7.1. Acetic acid 6-hydroxy-6-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-hex-2-enyl ester 17. IR (neat): ν_{max} 3414, 1737 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.73 (1H, dt, J=15.2, 6.5, H-3), 5.59 (1H, dt, J=15.2, 6.5, H-2), 4.50 (2H, d, J=6.5, H_2-1), 3.89 (2H, m, H-10 and H-11), 3.83 (2H, m, H-7 and H-14), 3.40 (1H, m, H-6), 3.39 (1H, m, H-15), 2.28, 2.15 (1H each, m's, H_2-4), 2.06 (3H, s, acetate), 1.94, 1.81 (4H each, m's, H_2-8, H_2-9, H_2-12, H_2-13), 1.55, 1.53 (1H each, m's, H_2-5), 1.45 (2H, m, H_2-16), 1.26 (16H, br s, H_2-17/H_2-24), 0.87 (3H, t, J=6.8, H_3-25).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.4 (carbonyl), 136.2 (CH-3), 124.1 (CH-2), 83.1 (CH-7, CH-14), 81.3 (CH-10, CH-11); 74.1 (CH-15), 73.4 (CH-6), 65.3 (CH_2-1), 34.5 (CH_2-16), 33.9 (CH_2-5), 29.7 (CH_2-17/CH_2-24), 28.5 (CH_2-4, CH_2-8, CH_2-9, CH_2-12, CH_2-13), 21.1 (acetate), 14.0 (CH_3-25). MS m/z 507 (47, M+K)$^+$, 491 (75, M+Na)$^+$. HRMS: calcd for $C_{27}H_{48}O_6Na$ 491.3336, found 491.3343.

4.1.7.2. Acetic acid 6-hydroxy-6-(5′-undecanoyl-octahydro-[2,2′]bifuranyl-5-yl)-hex-2-enyl ester 18. IR (neat): ν_{max} 3414, 1734, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.77 (1H, dt, J=15.4, 6.5, H-3), 5.62 (1H, dt, J=15.4, 6.7, H-2), 4.50 (2H, d, J=6.7, H_2-1), 4.38 (1H, dd, J=8.3, 5.8, H-14), 3.95 (2H, m, H-10 and H-11), 3.83 (1H, dt, J=7.5, 5.6, H-7), 3.40 (1H, m, H-6), 2.57 (2H, dt, J=7.2, 2.6, H_2-16), 2.30, 2.19 (1H each, m's, H_2-4), 2.16, 1.96 (1H each, m's, H_2-13), 2.07 (3H, s, acetate), 2.03, 1.71 (1H each, m's, H_2-12), 1.96, 1.81 (1H each, m's, H_2-9), 1.95, 1.77 (1H each, m's, H_2-8), 1.56, 1.54 (1H each, m's, H_2-5), 1.27 (16H, br s, H_2-17/H_2-24), 0.88 (3H, t, J=6.8, H_3-25).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 211.0 (C-15), 171.6 (carbonyl acetate), 136.3 (CH-3), 124.1 (CH-2), 83.4 (CH-14), 82.9 (CH-7), 82.7 (CH-11), 81.1 (CH-10), 73.4 (CH-6), 65.3 (CH_2-1), 39.2 (CH_2-16), 33.5 (CH_2-5), 29.8 (CH_2-17/CH_2-24), 29.1 (CH_2-13), 28.8 (CH_2-4), 28.2 (CH_2-8), 28.1 (CH_2-9), 27.9 (CH_2-12), 21.1 (CH_3 acetate), 14.2 (CH_3-25). MS m/z 505 (45, M+K)$^+$, 489 (71, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_6Na$ 489.3180, found 489.3172.

4.1.7.3. Acetic acid 6-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-6-oxo-hex-2-enyl ester 19. IR (neat): ν_{max} 3444, 1739, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.76 (1H, dt, J=15.3, 6.8, H-3), 5.59 (1H, dt, J=15.3, 6.5, H-2), 4.48 (2H, d, J=6.5, H_2-1), 4.37 (1H, dd, J=8.5, 6.0, H-7), 3.94 (1H, m, H-10), 3.92 (1H, m, H-11), 3.83 (1H, m, H-14), 3.37 (1H, br q, J=7.2, H-15), 2.69 (1H, dt, J=7.2, 2.0, H_2-5), 2.33 (2H, br q, J=7.4, H_2-4), 2.15, 1.98 (1H each, m's, H_2-8), 2.05 (3H, s, acetate), 1.92, 1.76 (3H each, m's, H_2-9, H_2-12, H_2-13), 1.26 (16H, br s, H_2-17/H_2-24), 0.87 (3H, t, J=6.8, H_3-25).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 213.0 (C-6), 171.6 (carbonyl acetate), 134.5 (CH-3), 124.1 (CH-2), 84.2 (CH-7), 83.1 (CH-10, CH-14), 81.6 (CH-11), 74.2 (CH-15), 65.2 (CH_2-1), 38.1 (CH_2-5), 29.8 (CH_2-17/CH_2-24), 28.8 (CH_2-8), 28.5 (CH_2-9, CH_2-12, CH_2-13), 25.7 (CH_2-4), 21.0 (CH_3 acetate), 14.2 (CH_3-25). MS m/z 505 (60, M+K)$^+$, 489 (82, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_6Na$ 489.3180, found 489.3187.

4.1.8. Oxidation of bis-THF diol 17 with TPAP/NMO. To a solution of **17** (5.0 mg, 0.01 mmol) in CH_2Cl_2 (400 μL) were sequentially added NMO (2.0 mg, 1.5 equiv), powdered 4 Å molecular sieves (5 mg) and TPAP (10 mol %, 0.4 mg) under stirring at room temperature. After 1 h, the mixture was concentrated, filtered on silica gel ($CHCl_3$–CH_3OH, 9:1) to give 4.5 mg of a crude material whose ^1H NMR analysis revealed the presence of a mixture of ketols **18** and **19** in a ca. 1:1 ratio.

4.1.9. Synthesis of (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (21). Ozone was bubbled through a solution of 12 g (110 mmol) of 1,5-cyclooctadiene (COD) in 120 mL of CH_2Cl_2 at −78 °C as reported in Ref. 18. Then PPh_3 (5.82 g, 22 mmol) was added and the bath removed. After 1 h $Ph_3P{=}CHCO_2Et$ (25 g, 71.8 mmol) was added and the mixture kept at room temperature for 16 h. Then the solvent was evaporated to give a white solid to which was added petroleum ether (40–70). Filtration under vacuum afforded a yellowish oil that was chromatographed on silica gel. The fraction eluted with petroleum ether–ethyl ether (85:15) gave 4.42 g (14.3%) of pure (*E*,*Z*,*E*)-dodeca-2,6,10-trienedioic acid diethyl ester **20** as an oil.[18]

Compound **20**: IR (neat): ν_{max} 1720, 1655 cm^{-1}. ^1H NMR (300 MHz): δ 6.94 (1H, dt, J=15.6, 6.6, H-3), 5.83 (1H, d, J=15.6, H-2), 5.40 (1H, br t, J=4.2, H-6), 4.18 (2H, q, J=6.9, $CO_2CH_2CH_3$), 2.30–2.10 (4H, m, 2×CH_2), 1.28 (3H, t, J=7.2, Me). ^{13}C NMR (75 MHz): δ 165.9, 147.7, 128.8, 121.4, 59.6, 31.5, 25.4, 13.8. MS m/z 319 (55, M+K)$^+$, 303 (90, M+Na)$^+$.

To a solution of diester **20** (1.64 g, 5.86 mmol) in dry THF (10 mL) was dropwise added DIBAL-H (1 M in toluene, 25.8 mL, 25.8 mmol) at −78 °C. The mixture was stirred at this temperature for 1 h and then a saturated NH_4Cl solution (5 mL) was dropwise added. The mixture was extracted with EtOAc (4×20 mL). The combined organic layer was dried and concentrated to give 1.12 g (98%) of (*E*,*Z*,*E*)-dodeca-2,6,10-triene-1,12 diol as an oil. IR (neat): ν_{max} 3330 cm^{-1}. ^1H NMR (200 MHz): δ 5.63 (2H, m, olefinic protons), 5.35 (1H, br t, J=3.8, olefinic proton), 4.03 (2H, d, J=3.8, olefinic proton, H_2-1), 2.20–2.00 (4H, br s, 2×CH_2).[18] ^{13}C NMR (50 MHz): δ 132.0, 129.3, 63.2, 32.0, 26.7. MS m/z 235 (70, M+K)$^+$, 219 (86, M+Na)$^+$.

To 1.12 g (5.7 mmol) of the above diol were added Ac_2O and pyridine (1:1, 5 mL) and the mixture was kept overnight at room temperature. Usual work-up followed by HPLC purification (4:6 hexane–EtOAc) afforded 1.16 g (73%) of pure triene diacetate **21** as an oil.

4.1.9.1. (*E*,*Z*,*E*)-Acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester 21. IR (neat): ν_{max} 1738, 1234 cm^{-1}. ^1H NMR (300 MHz): δ 5.84–5.65 (1H, m, olefinic proton), 5.57 (1H, dt, J=15.3, 6.0, olefinic proton), 5.42–5.28 (1H, br s, olefinic proton), 4.48 (2H, d, J=6.3, H_2-1), 2.10, 2.03 (overall 7H, br s and s, 2×CH_2 and methyl acetate). ^{13}C NMR (75 MHz): δ 170.8, 135.7, 129.3, 124.2, 65.1, 32.2, 26.6, 21.00. MS *m*/*z* 319 (43, M+K)$^+$, 303 (91, M+Na)$^+$. HRMS: calcd for $C_{16}H_{24}O_4Na$ 303.1566, found 303.1573.

4.1.10. Oxidation of triene 21 with $RuO_{4(cat.)}$/$NaIO_4$. Triene **21** was oxidised as reported above for triene **7**. In particular, to a solution of **21** (45 mg, 0.16 mmol) in the biphasic mixture EtOAc–CH_3CN–H_2O (3:3:1) (21 mL) were added in sequence $NaIO_4$ (4 equiv, 137.5 mg) and $RuO_2\cdot 2H_2O$ (20%, 4.2 mg) under vigorous stirring at 0 °C. After 30 min, the process was complete (disappearance of the starting product). A saturated $Na_2S_2O_3\cdot 5H_2O$ solution (2 mL) was added and stirring continued for further 10 min. Then the mixture was filtered and extracted with EtOAc (3×10 mL) and the combined organic phase was dried and evaporated to give 30 mg of an oily product. HPLC separation (hexane–EtOAc, 2:8, flow 2.5 mL/min) afforded mono-THF lactone **22** (5.4 mg, 13%), the corresponding lactol (ca. 1:1 mixture of epimers) **23** (0.8 mg, 2%) and a mixture of diastereomeric tetrols **24** (6.9 mg, 12%).

When the reaction was conducted in the same conditions using a 2.0 equiv amount of $NaIO_4$ (**21**: 30 mg; $NaIO_4$: 45.8 mg; solvent amount 12 mL) a partial cyclization was observed as previously seen for triene **7**. In particular, the starting triene was recovered in a 35% yield while mono-THF diol **26** and mono-THF ketone **27** were obtained in 25% and 11% yields, respectively, after HPLC (EtOAc–hexane, 75:25, flow 2.5 mL/min; **26**: t_R=17.0 min; **27**: t_R=12.5 min).

4.1.10.1. Acetic acid 2-hydroxy-2-(5′-oxo-octahydro-[2,2′]bifuranyl-5-yl)-ethyl ester 22. IR (neat): ν_{max} 3430, 1772, 1733 cm^{-1}; ^1H NMR (300 MHz): δ 4.49 (1H, br q, J=−5.5, H-7), 4.15 (2H, d, J=6.0, H_2-1), 4.02 (1H, br q, J=5.5, H-3 or H-6), 3.97 (1H, br q, J=6.0, H-6 or H-3), 3.74 (1H, br q, J=5.5, H-2), 2.54 (2H, m), 2.32 (2H, m), 2.13–1.95 (overall 5H, multiplet overlapped to a 3H singlet at 2.10 ppm for the acetate methyl), 1.95–1.82 (2H, m). ^{13}C NMR (75 MHz): δ 176.7, 171.1, 80.9, 80.4, 79.8, 71.8, 66.1, 28.1, 27.3, 27.2, 24.0, 20.9. MS *m*/*z* 297 (60, M+K)$^+$, 281 (100, M+Na)$^+$. MS *m*/*z* 297 (36, M+K)$^+$, 281 (77, M+Na)$^+$. HRMS: calcd for $C_{12}H_{18}O_6Na$ 281.0996, found 281.0989.

4.1.10.2. Acetic acid 2-hydroxy-2-(5′-hydroxy-octahydro-[2,2′]bifuranyl-5-yl)-ethyl esters 23. IR (neat): ν_{max} 3396, 1733 cm^{-1}; ^1H NMR (300 MHz): δ 5.50, 5.59 (1H each, br s's, 2×H-10), 4.41, 4.25 (1H each, m's, 2×H-7), 4.20–4.08 (5H, overlapped m's, 2×H_2-1 and 1×C*H*O-THF), 4.08–3.96 (3H, m, 3×C*H*O-THF), 3.66 (2H, m, 2×H-2), 2.22–1.78 (overall 11H, multiplet overlapped with a 3H singlet at 2.09 ppm for the acetate methyl). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 170.8 (carbonyl), 81.5, 81.0 (CH-1, CH-4, CH-5), 78.9 (CH-8), 72.0 (CH-9), 66.1 (CH-10), 29.0, 27.5 (CH_2-2, CH_2-3, CH_2-6, CH_2-7), 20.9 (CH_3 acetate). MS *m*/*z* 299 (56, M+K)$^+$, 283 (78, M+Na)$^+$. HRMS: calcd for $C_{12}H_{20}O_6Na$ 283.1152, found 283.1160.

4.1.10.3. Acetic acid 6-[5-(2-acetoxy-1-hydroxy-ethyl)-tetrahydro-furan-2-yl]-2,3,6-trihydroxy-hexyl ester 24. IR (neat): ν_{max} 3390, 1733 cm^{-1}; ^1H NMR (selected values, 200 MHz): δ 4.30–4.10 (4H, m, 2×C*H*$_2$OAc), 4.10–3.84 (2H, br m, 2×H-THF), 3.84–3.55 (4H, br m, H-2, H-3, H-6, H-11), 2.10, 2.09 (3H each, s's, 2×OAc), 2.10–1.40 (8H, m, 4×CH_2). MS *m*/*z* 403 (100, M+K)$^+$, 387 (78, M+Na)$^+$, 365 (30, M+H)$^+$. MS *m*/*z* 403 (88, M+K)$^+$, 387 (43, M+Na)$^+$. HRMS: calcd for $C_{16}H_{28}O_9Na$ 387.1623, found 387.1617.

4.1.10.4. Acetic acid 2-[5′-(2-acetoxy-1-hydroxy-ethyl)-octahydro-[2,2′]bifuranyl-5-yl]-2-hydroxy-ethyl ester 25. IR (neat): ν_{max} 3422, 1739 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 4.28 (1H, A part of an AB system further coupled, J=11.3, 7.7, C(1)H_aHOAc), 4.23 (1H, ddd, J=9.3, 6.0, 4.0, H-7), 4.17, 4.12 (1H each, AB system further coupled, J=11.7, 4.1 and 11.7, 6.8, respectively, C(12)H_2OAc), 4.09, 4.07, 4.05 (overall 3H, overlapped m's, C(1) HH_bOAc, H-3, H-6, respectively), 4.00 (1H, dt, J=8.5, 5.6, H-10), 3.73 (1H, q, J=5.0, H-11), 3.67 (1H, q, J=4.1, H-2), 2.093 (3H, s, acetate), 2.087 (3H, s, acetate), 1.85–2.05 (8H, overlapped m's, H_2-4, H_2-5, H_2-8, H_2-9). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.1 (acetate carbonyl linked to C-12), 170.8 (acetate carbonyl linked to C-1), 82.0 (CH-6), 81.3 (CH-7), 80.4 (CH-10), 79.2 (CH-3), 72.6 (CH-2), 72.0 (CH-11), 65.9 (CH_2-1), 65.7 (CH_2-12), 28.3, 27.5 (CH_2-4, CH_2-5, CH_2-8, CH_2-9), 21.3 (acetate methyl linked to C-1), 21.2 (acetate methyl linked to C-12). MS *m*/*z* 385 (89, M+K)$^+$, 369 (71, M+Na)$^+$. HRMS: calcd for $C_{16}H_{26}O_8Na$ 369.1518, found 369.1526.

4.1.10.5. Acetic acid 6-[5-(2-acetoxy-1-hydroxy-ethyl)-tetrahydro-furan-2-yl]-6-hydroxy-hex-2-enyl ester 26. IR (neat): ν_{max} 3419, 1739 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.78 (1H, dt, J=15.6, 6.8, H-3), 5.61 (1H, dt, J=15.6, 6.5, H-2), 4.52 (2H, d, J=6.5, C(1)H_2OAc), 4.19, 4.16 (1H each, AB system further coupled, J=11.7, 6.8 and 11.7, 4.1, respectively, CH_2(12)-OAc), 4.01 (1H, m, H-10), 3.92 (1H, dt, J=7.2, 2.8, H-7), 3.88 (1H, m, H-6), 3.74 (1H, m, H-11), 2.30, 2.16 (1H, each, m's, H_2-4), 2.09, 2.06 (3H each, s's, acetates), 2.05–1.85 (4H, m's, H_2-8, H_2-9), 1.48 (2H, m, H_2-5). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.6 (2×carbonyl), 135.2 (CH-3), 124.6 (CH-2), 83.2 (CH-7), 78.7 (CH-10), 72.0 (CH-11), 71.9 (CH-6), 66.3 (CH_2-12), 65.0 (CH_2-1), 32.0 (CH_2-5), 28.7 (CH_2-4), 28.2 (CH_2-8, CH_2-9), 21.0 (2×CH_3 acetates). MS=*m*/*z* 369 (40, [M+K]$^+$), 353 (81, [M+Na]$^+$). HRMS: calcd for $C_{16}H_{26}O_7Na$ 353.1569, found 353.1577.

4.1.10.6. Acetic acid 6-[5-(2-acetoxy-1-hydroxy-ethyl)-tetrahydro-furan-2-yl]-6-oxo-hex-2-enyl ester 27. IR (neat): ν_{max} 3403, 1733, 1716 cm^{-1} ^1H NMR (600 MHz,

attributions by 2D-NMR): δ 5.76 (1H, dt, J=20.5, 6.8, H-3), 5.62 (1H, dt, J=20.5, 6.8, H-2), 4.56 (1H, dd, J=8.7, 3.9, H-7), 4.55 (2H, d, J=6.0, C(1)H_2OAc), 4.24 (2H, m, C(12)H_2OAc) 4.18 (1H, m, H-10), 3.74 (1H, m, H-11), 2.61, 2.53 (1H each, m's, H_2-5), 2.37, 2.41 (1H each, m's, H_2-4), 2.09, 2.06 (3H each, s's, acetates), 2.05–1.85 (4H, overlapped m's, H_2-8, H_2-9). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 211.4 (C-6), 171.6, 171.0 (2×acetate carbonyls), 133.5 (CH-3), 125.2 (CH-2), 82.6 (CH-7), 80.4 (CH-10), 70.2 (CH-11), 65.1 (CH_2-12), 64.9 (CH_2-1), 38.2 (CH_2-5), 29.0, 27.5 (CH_2-8, CH_2-9), 25.5 (CH_2-4), 21.0, 20.9 (2×acetate methyls). MS m/z 367 (31, M+K)$^+$, 351 (93, M+Na)$^+$. HRMS: calcd for $C_{16}H_{24}O_7Na$ 351.1413, found 351.1406.

4.1.11. Synthesis of mono-THF olefin 26 from triene 21. To a solution of 19.5 mg (0.070 mmol) of triene **21** in CH_2Cl_2 (500 μL) were added TMEDA (1 equiv, 10.5 μL) and OsO_4 (1 equiv, 17.7 mg) under stirring at rt. Immediate TLC analysis ($CHCl_3$–MeOH, 9:1) revealed the formation of two coloured spots (R_f=0.2 and 0.4), likely attributable to the two possible osmate ester, along with a minor amount of unreacted triene. The mixture was taken to dryness after some 2 h and subjected to two successive HPLC runs ($CHCl_3$–MeOH, 9:1 then 95:5). The material eluted after 9 min (6.5 mg) in the second solvent mixture was identified as the osmate ester at one of the terminal double bonds. Starting triene (4.2 mg, 22%) was recovered as well.

3.4 mg of the above material was dissolved in CH_2Cl_2–AcOH (2:1, 700 μL). After 2 h, 10 drops of AcOH were added and the mixture left at 5 °C for two days. Then a saturated $NaHCO_3$ solution was dropwise added, the mixture was diluted with $CHCl_3$ (1 mL) and extracted with the same solvent (3×2 mL). The organic phase was washed with water, dried and taken to dryness to give 1.0 mg (12% from **21**) of a very pure compound that showed to be identical to mono-THF olefin **26** by NMR and chromatographic methods.

4.1.12. Dihydroxylation of 26 to 24. To a solution of **26** (3.0 mg, 0.009 mmol) in acetone–H_2O (5:1) (600 μL) was added OsO_4 1.2 equiv (12 μL from a 1 M stock solution in acetone–H_2O, 5:1). TLC analysis carried out within 10 min revealed the disappearance of the starting product. Excess NMO (3 equiv, 2.7 mg) was then added and the mixture stirred for 15 min. TLC analysis indicated the formation of a single spot at the R_f expected for tetrols **24**. The mixture was dried under a nitrogen flow and $CHCl_3$ was added. The $CHCl_3$ solution was recovered through a small piece of cotton wool, taken to dryness and separated by HPLC (250×4.6 mm column, $CHCl_3$–MeOH, 9:1; flow 0.9 mL/min) to give two partially overlapped peaks eluted at t_R=21.5 and 22.5 min (together 0.5 mg, 15%). This material showed to be identical to tetrols **24** by ^{1}H NMR analysis and co-injection in the same solvent mixture.

4.1.13. Synthesis of lactols 23 from mono-THF olefin 26. To a solution of **26** (2.0 mg, 0.006 mmol) in THF–H_2O (4:1, 500 μL), was added OsO_4 (1.3 equiv, 2.0 mg) under stirring. After 5 min $NaIO_4$ (5 equiv, 6.5 mg) was added and the mixture stirred for 2.5 h. Then a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (500 μL) was added and the mixture, after a further 10 min stirring, was extracted with EtOAc (3×3 mL). The organic phase was dried and evaporated to give 2.4 mg of a crude product that was further purified by HPLC (hexane–EtOAc, 2:8, flow 2.5 mL/min). 1.4 mg (90%) of a pure product was obtained that showed to be identical to the mixture of lactols **23**.

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