Mimicking Halimane-Synthases: Monitoring a Cascade of Cyclizations plus Rearrangements from Epoxypolyprenes.

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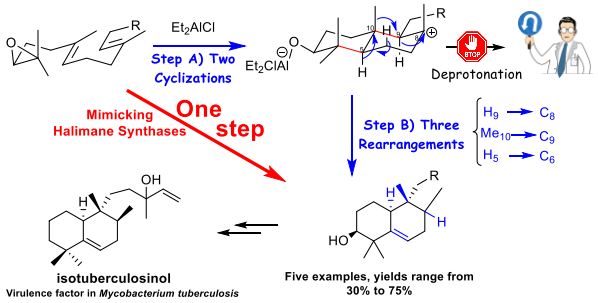


ABSTRACT: We have developed and rationalized a biomimetic transformation mimicking halimane-synthases based on a Lewis acid-catalyzed cascade of cyclizations plus rearrangements of epoxypolyprenes. Two rings, three stereogenic centers and a new double bond were generated in a single chemical operation. Based on this cascade transformation, we achieved a unified strategy toward the stereoselective total syntheses of halimene-type terpenoids and analogues as a proof-of-concept

study. This method has been applied to the rapid synthesis of diterpene isotuberculosinol, a virulence factor of *Mycobacterium tuberculosis* as representative example.

INTRODUCTION

Biomimetic strategies allow the construction of complex natural products in a minimum of steps. The benefits of these processes are recognized worldwide, with the ‘‘atom and step economy’’ approach of green chemistry which are of special interest. [1–4] In the field of terpenoid biogenesis, the generation of the hopanoid skeleton by squalene cyclases, where five new cycles and up to nine stereogenic centers are created constitutes an excellent example of the spectacular and potentiality of this process.[3,5] Challenged by these fascinating transformations, researchers have been trying to replicate the action of these enzymes for over a century.[3] Although the use of either Brönsted or Lewis acids have been by far the most common method to achieve biomimetic polycyclizations of isoprenoids in the lab,[3,6–16] other astonishing protocols including those involving enzymes[17–20] and radical cyclizations have also been reported.[21–23] An outstanding milestone in this synthetic effort was the achievement of enantioselective cyclization protocols of some polyenes.[24–29]

Often oxidosqualene- and other terpene cyclases, in addition to cyclization processes, give rise to a series of hydride and methyl shifts before releasing the final natural product. Up to seven of these rearrangements take place in the biosynthesis of triterpene cucurbitanes.[30] Obviously, the difficulty of reproducing these processes using chemical reagents involving cyclizations and rearrangements increases significantly. In this regard, van Tamelen and Sharpless reported in 1969 that the treatment of squalene 2,3-oxide with stannic chloride led to a mixture of cyclized products, including a rearranged bicyclic alcohol possessing the halimane core.[31] Apart from van Tamelen´s seminal work, to the best of our knowledge, no precedents exist on addressing rationalized synthesis of “rearranged terpenes” using this approach. However, efficient rearrangements of carbocations generated on previously cyclized structures can be found in the literature.[31–37] Some of these non-enzymatic rearrangements can be

considered as nice examples of the minimal-enzymatic-assistance hypothesis,[4,38] thus encouraging the biomimetic pursuit of these complex reactions.

The bicyclic backbone **B** present in diterpene halimene–type skeleton is a common molecular fragment conserved in important biologically active natural products[39–44] (Figure 1a). Biosynthetically, it must be derived from (*E*,*E*,*E*)-geranylgeranyl diphosphate through "halimane synthases" catalysis. This process starts with a class II diterpene cyclase (DTC) mediated protonation of the terminal isopropylidene to give a bicyclic carbocation intermediate which later suffers several rearrangements of hydride and methyl groups.[45] Other common DTCs (such as copalyl synthases for example) only produce diterpenes as labdanes by deprotonation of the labda-13-en-8-yl$^+$ intermediate **A**. Among the many substances presenting the halimene framework, diterpenes such as isotuberculosinol (**1**) and 1-tuberculosinyladenosine were reported to be the virulence factors[42] isolated from *Mycobacterium tuberculosis* the causative agent of the human disease tuberculosis, a worldwide health threat responsible for approximate 1.7 million deaths annually.[46] Due to their interest and structural complexity of these substances, multistep synthesis or semi-synthesis has been developed.[47–48]

Here, we describe our efforts to know to what extent the action of "halimane synthases" can be mimicked in the laboratory *in vitro*, that is, to generate the bicyclic halimene skeleton starting from a simple acyclic epoxypolyprene in a one-step cascade process including two head-tail cyclizations and two or three 1,2-Wagner-Meerwein rearrangements (Figure 1b).

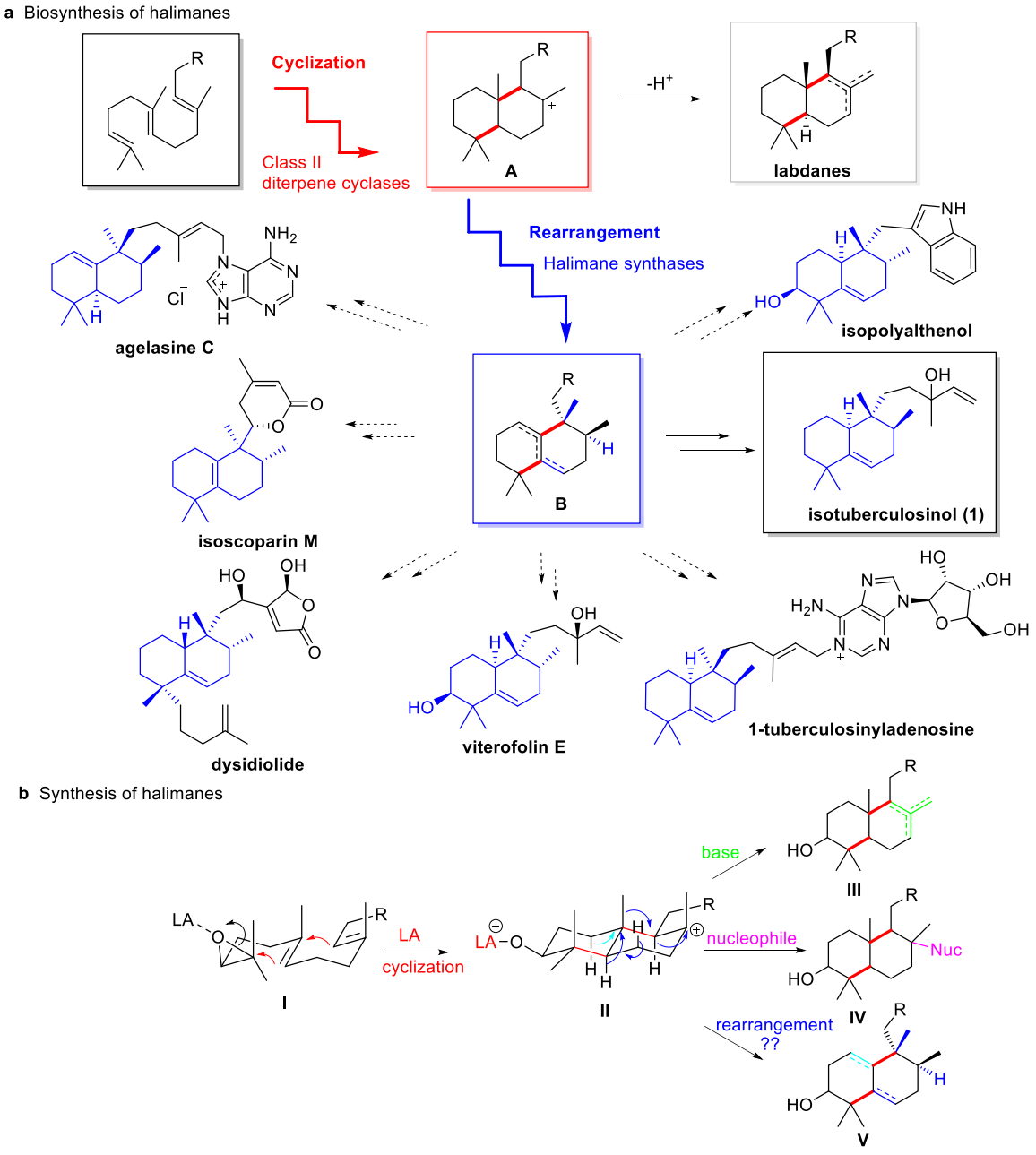


Figure 1. Accessing to the halimane skeleton. **a**, Biosynthesis of the halimanes: some representative halimane–type terpenoids. **b**, Bionspired synthesis of halimanes: Is it achievable a tandem cyclization-rearrangement process leading to halimenes?

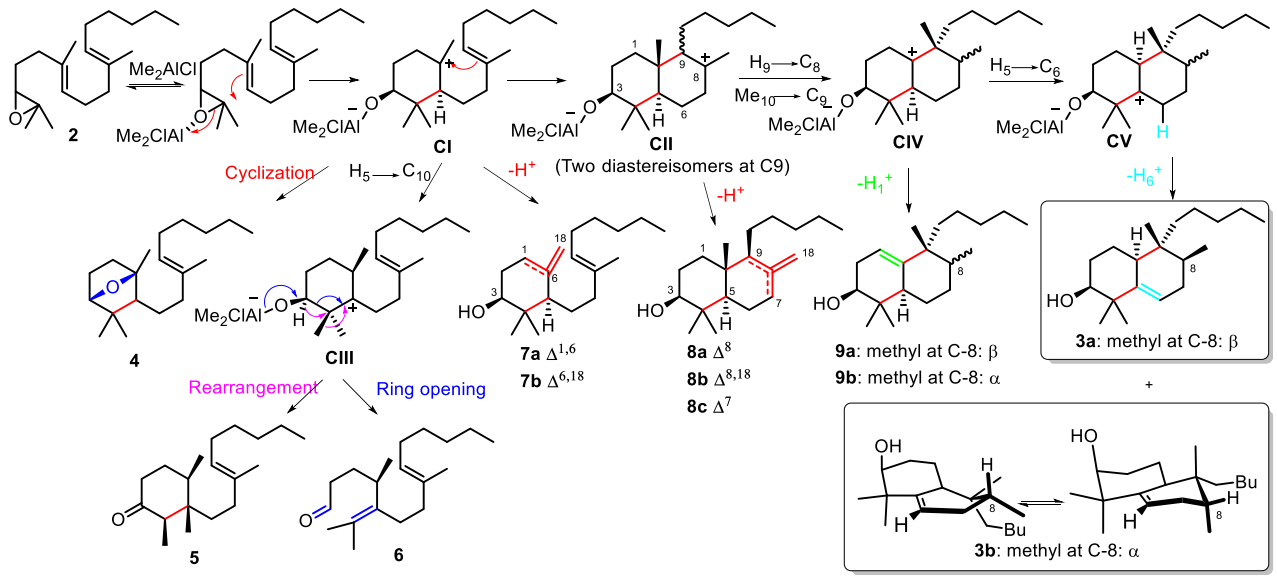
Taking advantage of the tremendous effort devoted by chemists for decades to comprehend carbocationic polycyclizations and before starting any experimental tests, we evaluated and analysed the possible requirements that each of the agents involved in the cyclization process. Selection of the oxyrane group as an initiator is fundamental in this strategy because it must provide the selective and soft formation of the initial acyclic carbocation by oxyrane opening. Concerning the structural

requirements the acyclic precursor, the presence of unsaturations in the terminal "R" moiety, as in the case of C20 geranylgeraniol derivatives or longer polyprenes, or functions containing heteroatoms located close to the C–8 carbocation **II** should be avoided since they could favour subsequent cyclizations or E1 deprotonations respectively (Figure 1b).[26,49] With regard to the reaction medium, the use of non-basic and poor nucleophilic solvents and low temperatures should help to induce the rearrangement process by avoiding the E1 processes. Finally, considering the requirements for the acid that mediates the process, it should be a Lewis acid that, after coordination to the oxirane, should permit its opening and subsequent cyclization, and most importantly, should prevent any fast ligand dissociation in the generated intermediate zwitterionic species resulting from the oxyrane opening (**II**, Figure 1b). This zwitterion possesses a carbocation and a metalanion-alkoxide, which will bear the negative charge during the whole process. Thus, when the cyclization is over, the cation at C–8 in the absence of any base or nucleophile could evolve to the rearranged products if the process is energetically favourable. Although different rearrangements could be conceivable, the series of 1,2-migrations of hydride and methyl groups leading to the different expected halimene skeletons seems to be, a priori, stereoelectronically favoured (Scheme 2). Additionally, in our opinion, the negative charge located at the metal bound to the oxygen may exert an electrostatic attraction on the bicyclic cation at C–8, thus-favouring those rearrangements that bring the charges closer. This reasoning regarding the role that the Lewis acid should exert in this process parallels the interesting rationalization provided by Shenvi to account for their results on the aluminium Lewis acids-mediated tail-to-head transformations of a nerolidol-based vinyl epoxide, mimicking class I terpene cyclases.[14] Thus, the authors claim that key to the success of their approach was the "*sequestration of the counteranion using non-dissociating ligands*". Eventually, and after prolonged reaction times, the dissociation of a chloride ion from the aluminate anion could be responsible for the ultimate deprotonation leading to the halimene skeleton.

RESULTS AND DISCUSSION

To verify the experimental viability of our hypothesis, we started this biomimetic approach by choosing the monoepoxide of farnesylbutane **2** as a simple model of a starting material. For the Lewis acid, we selected initially Me_2AlCl.[50] When **2** was made to react with 1.0 equiv of Me_2AlCl at -78 ºC in DCM (0.1 M) for 40 min, an equimolecular mixture of epimers at C–8, **3a–3b** possessing the rearranged skeleton of halima-5-ene and *syn*- halima-5-ene was obtained in 51% yield (Table 1, entry 1), together with minor proportions of the non-rearranged monocyclic (**7b**) and bicyclic products (**8b**) (3% and 2%, respectively), as well as the acyclic aldehyde **6** (1.5%). The different mechanistic steps rationalizing the generation of the products obtained in this transformation are depicted in Scheme 1.

Scheme 1. Mechanistic Steps Leading to the Generation of 3–9.



Compound **3b** turned out to present a restricted conformational equilibrium at rt on ring B and as consequence the resolution of NMR spectra, especially in ^{13}C NMR, is low. A complete characterization of this isomer was only possible after conducting the NMR experiences at 90 ºC in deuterated DMSO. Molecular Mechanics conformational search first and quantum chemical calculations then performed on **3a** and **3b** revealed the existence of two pairs of main conformers of similar stability (≤1 kcal/mol) for

each epimer. The energetic barrier calculated for **3a** (7.2 Kcal/mol) supports a rapid rate of interconversion in agreement with the experimental data in NMR, whereas the interconversion barrier between the two conformers of **3b** (14.0 kcal/mol) may well account for a slow conformational equilibrium between these two species (see Supplementary Information). This phenomenon was reported in related natural products presenting the stereochemistry assigned to **3b**.[19,40a]

In order to gain a comprehensive mechanistic and energetic understanding of the different steps of the bicyclization-rearrangement cascade from **2** to **3a**–**3b**, quantum chemical calculations were carried out using 14,15-epoxygeranylcitronelene (**I**) as a diterpene model and Me_2AlCl as a catalyst. Previous inexpensive SCW calculations allowed us to find two main productive prochiral conformations (**Ia** and **Ib**) of the acyclic precursor, namely, chair-boat and chair-chair conformations, both possessing similar stabilities (difference 0.3 Kcal/mol, Figure 2). The results obtained from the computational study of the entire process are represented in Figure 2 (see Supplementary Information for details).

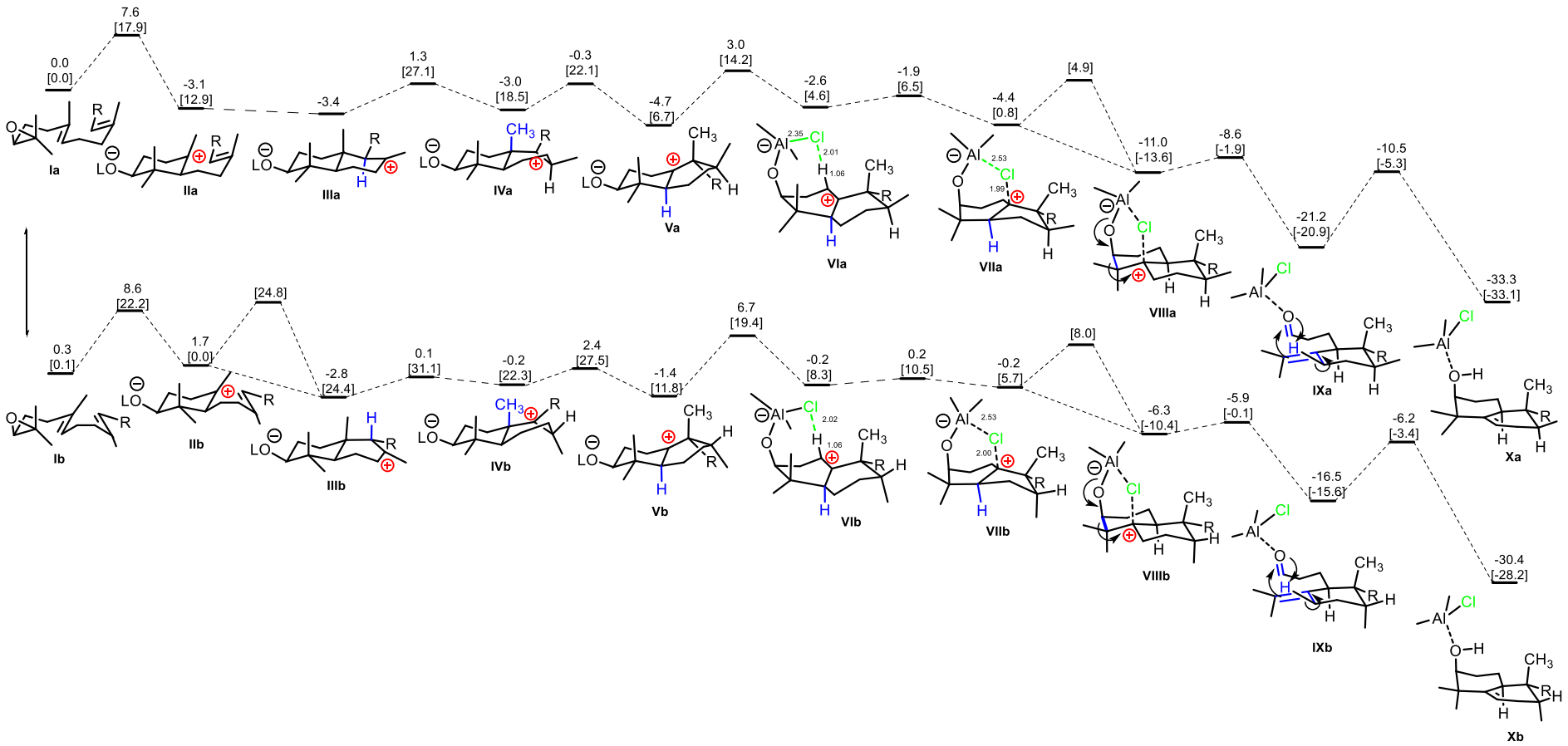
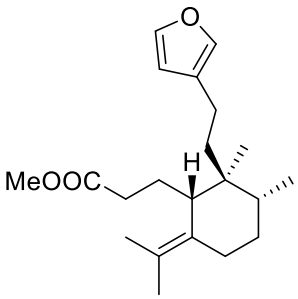


Figure 2. Energy diagram for the formation of species **I**–**X** leading to halimenes **3a**–**b**. Relative energies [kcalmol, B3LYP/6-31+G(d,p) empirical dispersion=gd3b], in normal text for SMD solvation model by a single point energy calculation, and in brackets for calculations in vacuo. Selected distances in Å in TSs. For simplification of the figure, the moiety $ClMe_2Al$-O appears represented by L, and R stands for *n*-butyl.

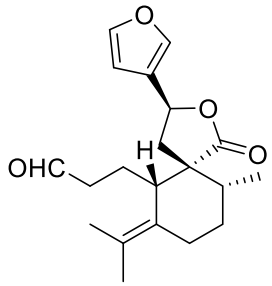
Calculations showed differing results considering the generation of the labdan-8-yl cationic intermediate **III**. Thus, whereas the calculations performed in vacuum showed that the two cyclizations were stepwise, no minimum of energy was found for this first cyclization when the calculations were performed considering the presence of CH_2Cl_2 (concerted process). Although the concerted asynchronous processes were the result obtained when the solvent was included in the calculations,[51–52] the feasibility of a stepwise scenario[53] should not be ruled out, mainly when this mechanism would well account for the generation of minor monocyclic products **4**, **5**, **7** and aldehyde **6**, found in the reaction of **2** with Me_2AlCl.

After the formation of bicyclic cations **IIIa** and **IIIb**, one 1,2 hydride $C_9 \rightarrow C_8$ shift followed by a 1,2-methyl $C_{10} \rightarrow C_9$ migration were predicted to take place, overcoming small barriers leading to the haliman-10-yl carbocations **Va** and **Vb.** Rearranged intermediates **Va** and **Vb** undergo a ring A conformational change implying a variation of the space disposition of the dimethylcholoroaluminate group from equatorial towards an axial arrangement. As consequence of this conformational change, the chlorine atom gradually approaches to C–10 carbocation, thus contributing to the stabilization of the intermediates **VII** due to the favourable electrostatic interactions between the negative charge of the chlorine atom partially detached from the alcoxyaluminate and the carbocation at C–10. In fact, the initial distance of Al–Cl, (2.27Å) when the aluminate was equatorially disposed, is gradually lengthened to 2.53Å when it is axial in both intermediates **VIIa** and **VIIb**, while the distance C10–Cl, 1.99Å, is still far from the 1.85Å of a typical C_{sp3}–Cl bond. The fact that the chlorine atom is not completely detached from the aluminate anion is of paramount importance, since it not only permits the cascade of Warner-Meerwein rearrangements of the molecule to continue; but it also favours the interconversion of carbocations **VII** to **VIII** through $C_5 \rightarrow C_{10}$ hydride shift from the alpha face of the halimane skeleton, a process thermodynamically favourable in 6 kcal/mol. Subsequently, the C3–C4 bond of **VIII** undergoes a gradual elongation until it breaks to give a 10-12 Kcal/mol more stable seco-3,4-halimane monocyclic aldehyde complex intermediates **IX**.

In this regard, a related A contraction of a halima-13*E*-en-15-PP-5-yl^{+} intermediate was proposed to occur in the biosynthesis of premutilin, proposal that was supported by quantum chemical calculations.[54] All that led us to hypothesize that the theoretically-proposed route to aldehydes **IX** may constitute a possible biosynthetic pathway to natural 3,4-seco-halimanes such as secochiliotrin methyl ester or secochiliolide aldehyde.[67]



secochiliotrin
methyl ester



secochiliolide
aldehyde

The unsaturated aldehydes **IX** suffer a concerted process with activation energy near to 10 kcal/mol where A ring is regenerated through a intramolecular Prins reaction with a simultaneous proton transfer from C–6 (Hβ-6) to O–3 to produce the final $\Delta^{5,6}$ halimanes **X**. It is worth noting that the particular space orientation of the oxygen atom resulted in the Prins process in $TS_{IX–X}$, which facilitated the final proton transfer.

These computational calculations are consistent with those recently reported on biosynthetic studies of halimenes not oxigenated at C3[19,55] and, more significantly, they shed some light on the three most relevant figures of our cyclization-rearrangement experimental process. Thus, the solvent CH_2Cl_2 plays an important role provoking a significant decrease in the energetic barriers to cyclizations and rearrangements, probably as consequence of carbocation stabilization. Secondly, the formation of two stereoisomers at C8, **3a** and **3b,** is a consequence of the co-existence of a pre-chair-boat **Ia** acyclic precursor competing against the pre-chair-chair **Ib** precursor (both initial precursors and transition-states structures for the first cyclization step were predicted to be almost isoenergetic, see Supplementary Information). Furthermore, the role played by the oxygen and chlorine atoms in the non-detached

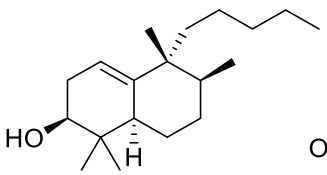
alkoxyaluminate anion, possibilitating the A ring opening and the ensuing concerted Prins reaction and H6-deprotonation, supported the high selectivity observed toward haliman-5-enes among all the possible olefinic regioisomers and also versus other kinds of rearranged products. Finally, the recovery of the Lewis acid unaltered renders the process susceptible to catalysis by the Lewis acid.

Once we proved that the mechanism and the energetic barriers calculated for the cyclization and rearrangement processes supported the experimental results obtained with model **2**, we focused our efforts on optimizing the experimental conditions for this transformation. To this end, a screening of different Lewis acids, concentrations, temperatures and solvents was achieved (Table 1).

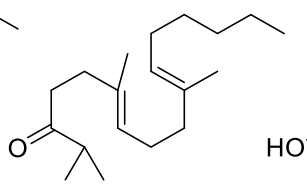
Table 1. Screen of the Cyclization-Rearrangement Experimental Conditions of Epoxide 2

entry	equiv/LA	temp (ºC), C (mM)	solvent	time (min)	3a, 3b yield (ratio)	4, 5, 6 yield (ratio)	7a, 7b yield (ratio)	8a, 8b, 8c yield (ratio)
1	1/Me_2AlCl	-78, 0.03	DCM	45	51% (1:1)	2% (0:0:1)	3% (1:0)	2% (1:0:0)
2	1/Et_2AlCl	-78, 0.03	DCM	45	54% (1:1.1)	3% (1:0:0.2)	ND	10% (0:0.6:1)
3	0.1/$Bi(OTf)_3$	Reflux, 0.03	DCM	40	ND	4% (1:0:0)	4% (1:0)	23% (1:0:0)
4	1/$Cu(OTf)_2$	-78, 0.03	DCM	30	ND	ND	19% (1:0.3)	17% (5.7:0.2:1)
5[a]	1/$InBr_3$	-78, 0.03	DCM	300	27% (1:0.8)	4% (1:0:0)	ND	13% (0:0.3:1)
6[b]	1/$InBr_3$	RT, 0.03	DCM	100	37% (1:0.4)	7% (1:0:0)	9% (1:0.2)	9% (0:0.8:1)
7	**0.5/Et_2AlCl**	**-78, 0.03**	**DCM**	**100**	**53% (1:1)**	**ND**	**ND**	**ND**
8	1.5/Et_2AlCl	-78, 0.03	DCM	50	59% (1:1)	ND	3% (1:0)	2% (1:0:0)
9	**2/Et_2AlCl**	**-78, 0.03**	DCM	**45**	**71% (1:1.1)**	**6%** (1:0:1)	**ND**	**10% (0:0.6:1)**
10	3/Et_2AlCl	-78, v	DCM	40	65% (1:1)	5% (1:0:0.4)	ND	4% (0:0.3:1)
11	5/Et_2AlCl	-78, 0.03	DCM	35	59% (1:1)	ND	ND	ND
12	2/Et_2AlCl	-100, 0.03	DCM	60	34% (1:1)	ND	ND	ND
13	2/Et_2AlCl	0, 0.03	DCM	30	50% ((1:1)	7% (1:0:0.2)	ND	13% (0:0:1)
14	2/Et_2AlCl	-78, 0.3	DCM	25	63% (1:1)	ND	3% (1:0)	ND
15	2/Et_2AlCl	-78, 0.003	DCM	50	58% (1:1)	2% (1:0:0)	ND	ND
16[c]	2/Et_2AlCl	-78, 0.03	Hexane	60	27% (1:1)	ND	ND	ND
17	2/Et_2AlCl	10, 0.03	Bencene	45	54%(1:0.8)	5%(0.7:1:0)	ND	ND
18	2/Et_2AlCl	-78, 0.03	Toluene	45	68% (1:1)	2%(1:0:0)	ND	ND
19	2/Et_2AlCl	-78, 0.03	TBME	50	4% (1:1)	ND	57 (1:1.3)	21%(0:1.6:1)
20[d]	2/Et_2AlCl	-78, 0.03	THF	210	ND	4 (1:0:1)	4 (1.1:1)	ND
21	2/Et_2AlCl	-30, 0.03	DCE	30	40% (1:1.2)	ND	ND	7 (0:1:0)
22	2/Et_2AlCl	-20, 0.03	CCl_4	30	56% (1:0.8)	5%(1:0:0)	ND	3 (0:0:1)
23	2/Et_2AlCl	-60, 0.03	$CHCl_3$	70	59% (1:1.1)	2(1:0:0)	ND	7 (0:0:1)
24[e]	2/Et_2AlCl	-40, 0.03	CH_3CN	65	ND	ND	ND	22 (1:0:0)

[a] Compound **9a** was obtained in 14% yield. Minor proportions of its epimer at C8 was detected by NMR from the mixture. [b] Compound **9a** was obtained in 15% yield. Its epimer at C8 was detected by NMR from the mixture. [c] 60% recovered starting material. [d] Compound **10** was obtained in 91% yield [e] Compound **11** was obtained in 43% yield.



9a



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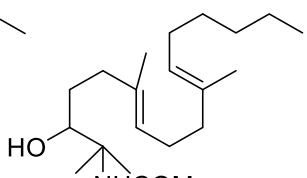

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To start, several Lewis acids were tested to trigger the cyclization-rearrangement process (Table 1, entries 1–6). Although the two alkyl aluminum Lewis acids used led to acceptable yields of **3a** and **3b**, comparatively slight yield improvements were found when Et_2AlCl was used (Table 1, entry 2). Copper(II) and bismuth(III) triflates failed to produce the desired halimane derivatives, and a complex mixture of non-rearranged monocyclic and bicyclic structures was observed (Table 1, entries 3–4). The results obtained with $InBr_3$ deserve a special mention, where together with the previously generated halim-5-ene derivatives **3a** and **3b**, the formation of haliman-1(10)-enes **9a** and **9b** was observed (Table 1, entries 5–6). The greater volume of the Lewis acid in this case, hampering its approach to C–10 and therefore the stabilization of the carbocation at this position, may be postulated to rationalize these results.

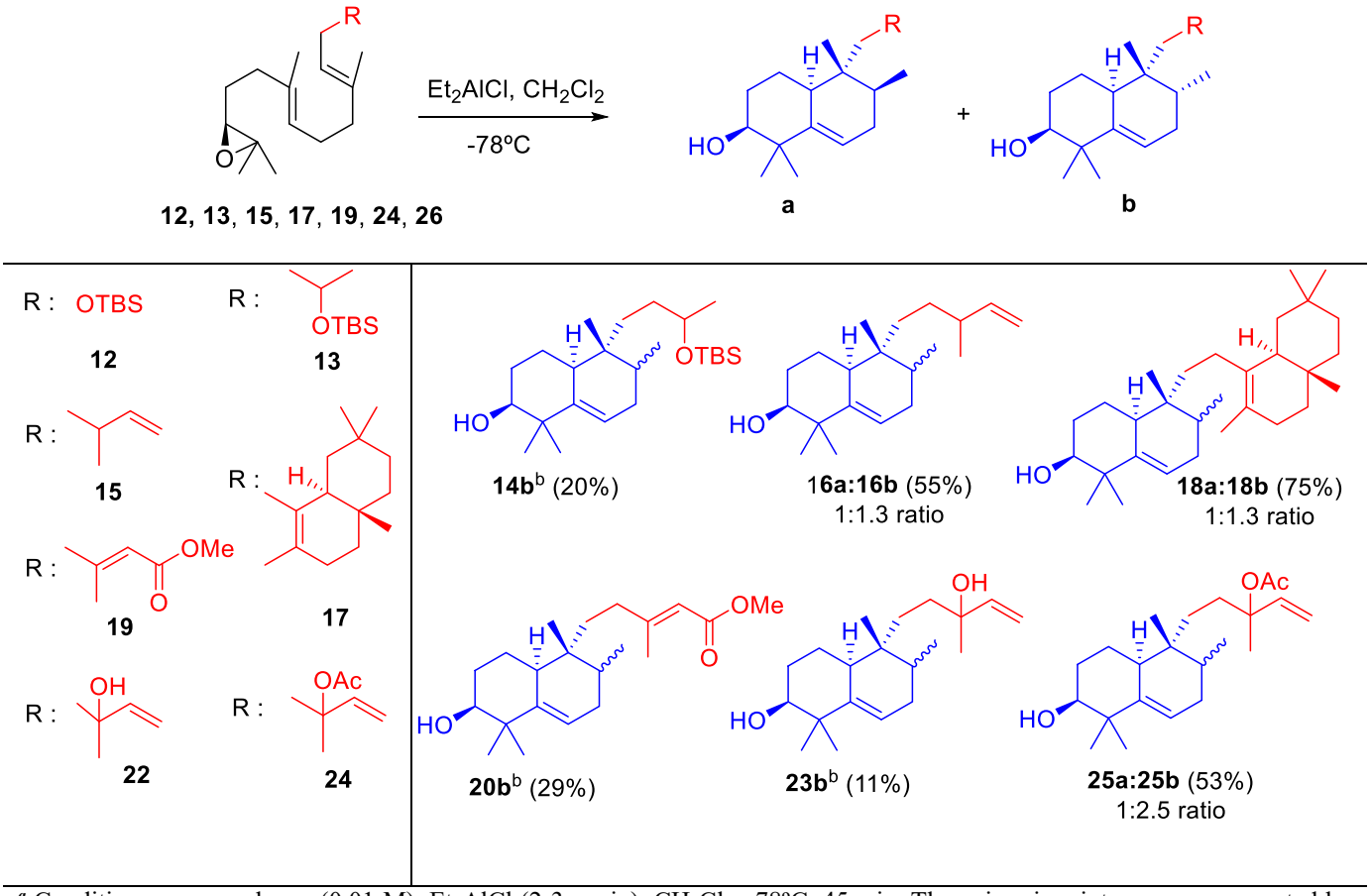
All in all, Et_2AlCl was selected as catalyst of choice. Variations in the quantity of Et_2AlCl used (Table 1, entries 7–11) caused an improvement in the efficiency of the process. Thus, up to a 71% yield of the desired halim-5-enes was obtained when 2 equivalents of Lewis acid were used (Table 1, entry 9). Changes in the temperature do not produce significant yield differences (Table 1, entries 9, 12–13), with the best results being obtained when the reaction was conducted at -78º C. Furthermore, the influence of molar concentration on production of **3a** and **3b** was also moderate as can be concluded from the results obtained in entries 9, 14 and 15 of the Table 1.

Finally, significant alterations of the reaction outcome were revealed when different solvents were tested. Thus, the use of hexane as a solvent slowed down the process significantly, and after 1h, most of the starting material remained mainly unaltered (Table 1, entry 16). Good yields were obtained in benzene and toluene (54% and 68%, respectively) (Table 1, entries 17–18), probably due to the stabilization of carbocation intermediates. The effect of ethereal solvents was counter-productive and mainly regular mono- and unrearranged bicyclization products **7** and **8** were obtained (Table 1, entries 19–20). Easy deprotonation of the corresponding bicyclic cations by solvents acting as Brønsted bases may account for the observed reactivity. The use of THF provoked the production of acyclic ketone **10** as major product as result of a 1,2-hydride shift of the initial acyclic carbocation. Other halogenated

solvents were also tested and, although acceptable yields of the target **3a** and **3b** were produced (Table 1, entries 21–23), the efficiency of the process was slightly worse when compared to that found when using DCM. To conclude, a polar aprotic solvent such as CH_3CN was also made to react with epoxide **2** (Table 1, entry 24) and the initial carbocation was neutralized by a molecule of acetonitrile leading to the hydroxyacetamide **11** as a major product after work-up.

Once the experimental conditions were optimized (Table 1, entry 9), we proceeded to study the scope of the process by altering the side chain of the epoxypolyprene (Table 2)

Table 2. Scope of the Biomimetic Cyclization–Rearrangement of Epoxypolyenes.[a]

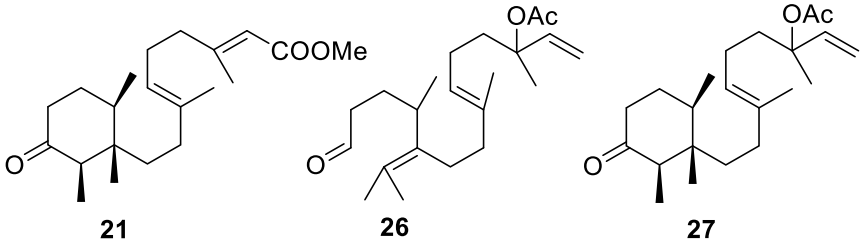


[a] Conditions: epoxypolyene (0.01 M), Et_2AlCl (2-3 equiv), CH_2Cl_2, -78ºC, 45 min. The epimeric mixtures were separated by semipreparative HPLC. [b] Minor proportions of the corresponding epimer at C8 was detected by NMR from the mixture.

First of all the reaction of the *tert*-butyldimethylsilylderivative of 10,11-epoxyfarnesol **12** with Et_2ClAl in CH_2Cl_2 only resulted in a mixture of bicyclization compounds, where no concomitant

rearrangement were produced, in agreement with previous reported results.[13,56] The presence of a silyloxy group at C13 in compound **13** considerably reduced the efficiency of the process towards the halimene type products **14b** (20%), whilst when a double bond is located at C–14, as happens in **15,** an acceptable yield was again obtained (55% of halima-5-enes **16a–b**). In both cases, a certain degree of diastereoselectivity was noticed, favouring the rearranged structured derived from the chair-boat conformation of the starting epoxide (methyl groups at C8 and C9: *anti*). In the reaction of epoxypreoleanatetraene **17** with Et_2AlCl, a good 75 % of a 1:1.3 mixture of the corresponding tetracyclic derivatives (**18a–b**) was obtained, which evidenced a high energetic barrier for a third cyclization in this case.[57]

When the monoepoxy derivative of methyl geranylgeraniate (**19**) was used as a starting material, the diastereomer **20b** resulting from the expected cyclization-rearrangement was obtained in a 29% yield. It should be noted that the monocyclic ketone **21** (5.5%) was also obtained.



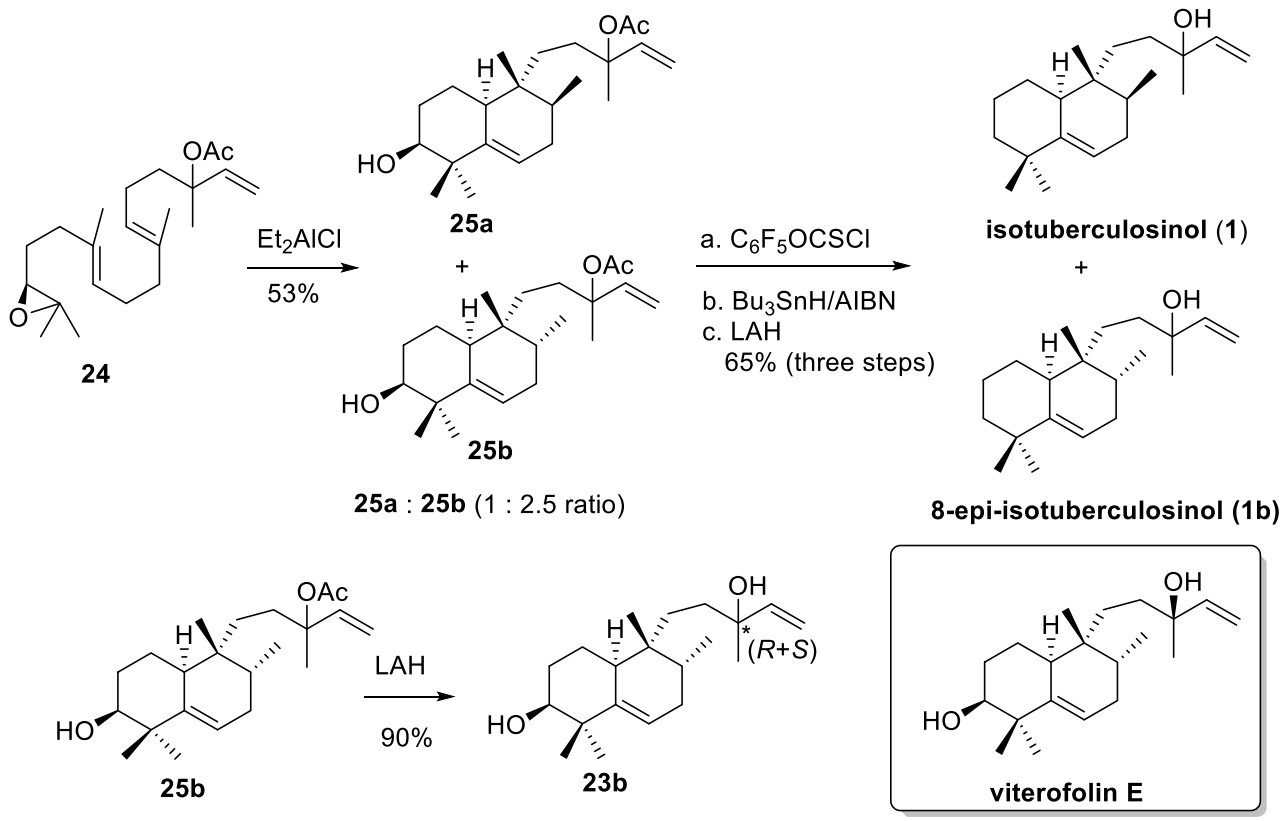
21 **26** **27**

Perhaps the most elegant demonstration of the utility of this cascade of cyclizations plus rearrangements strategy is displayed in the straightforward synthesis of the interesting halim-5-ene isotuberculosinol (**1**). We also anticipated that, while addressing the synthesis of tuberculosinol, the natural halimene viterofolin E,[59] isolated from *Vitex rotundifolia*, could be produced en route (Scheme 2). With these targets in mind, we treated the monoepoxy derivative of geranyllinalool (**22**) with Et_2ClAl in DCM at -78 ºC. Unsurprisingly, the presence of a free hydroxyl group prevented the cyclization-rearrangement process to take place efficiently, and only 12% of the corresponding halim-5-enes (**23**) were produced. However, if the monoepoxy derivative of geranyllinalool acetate **24** was subjected to the same conditions, an acceptable 53% yield of diastereoisomers **25** (1: 2.5) was obtained,

together minor proportions of **26** and **27**. Of these two diastereomers, compound **25a** presents the same stereochemistry at C–8 and C–9 as that exhibited by isotuberculosinol (**1**) (Scheme 2), whereas the second distereomer, **25b**, shares the stereochemistry at C–8 and C–9 with viterofolin E. Reduction of **25b** with LAH allowed to complete the synthesis of viterofolin E as a mixture of epimers at C–13 (**23b**) in only two steps and 34% yield from epoxide **24**.

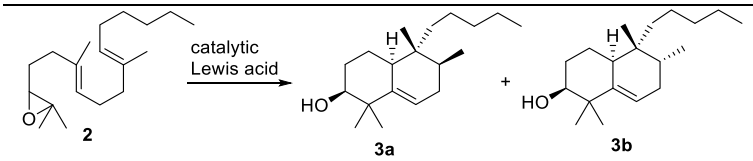
Continuing with the synthesis of isotuberculosinol, the pair of epimers **25** was deoxygenated following the modified Barton-McCombie procedure, and then reduced with LAH. Isotuberculosinol **1** was thus obtained in 65% yield for the last three steps and in an overall 10% yield from monoepoxyderivative **24**. The spectroscopic data of synthetic isotuberculosinol matched completely with those reported for the natural substance.[47] Together with isotuberculosinol, its 8-epi-isomer **1b** was isolated in 25% yield. Although this substance has not been described as natural product so far, it was enzymatically produced.[60]

Scheme 2. Synthesis of (±) isotuberculosinol.



Once we proved that rearranged diterpenes can be produced after a tandem process of cyclization and rearrangements, we turned back (our attention) to one of the conclusions inferred from the computational calculations, namely, (that) the process is susceptible to catalysis by the Lewis acid. Thus, we treated epoxide to substoichiometric quantities of different Lewis acids (Table 3). Although the use of 50% mmol of dimethylaluminium chloride also produced **3a** and **3b** with acceptable yield (table 3, entry 1), when the quantity of dimethylaluminium chloride was lowered up to 0.2 equiv, the process showed no completion after 5h of reaction time, and 31% of starting material remained unaltered (Table 3, entry 2). We decided then to test different gallium[66] and indium halides. Although the use of indium halides (Table 3, entries 3–4) led to low yields of the rearranged products **3a** and **3b**, the use of 0.2 equiv of different gallium halides led, gratifyingly, to acceptable yields of the desired halim-5-ene derivatives (Table 3, entries 5–7). We finally found that the quantity of $GaCl_3$ could be reduced to 0.01 equiv without decreasing the yield of the halim-5-enes produced (Table 3, entry 8).

Table 3. Generation of Halim-5-enes derivatives (3a–3b) from Epoxide 2 Using Catalytic Quantities of Lewis Acids[a]

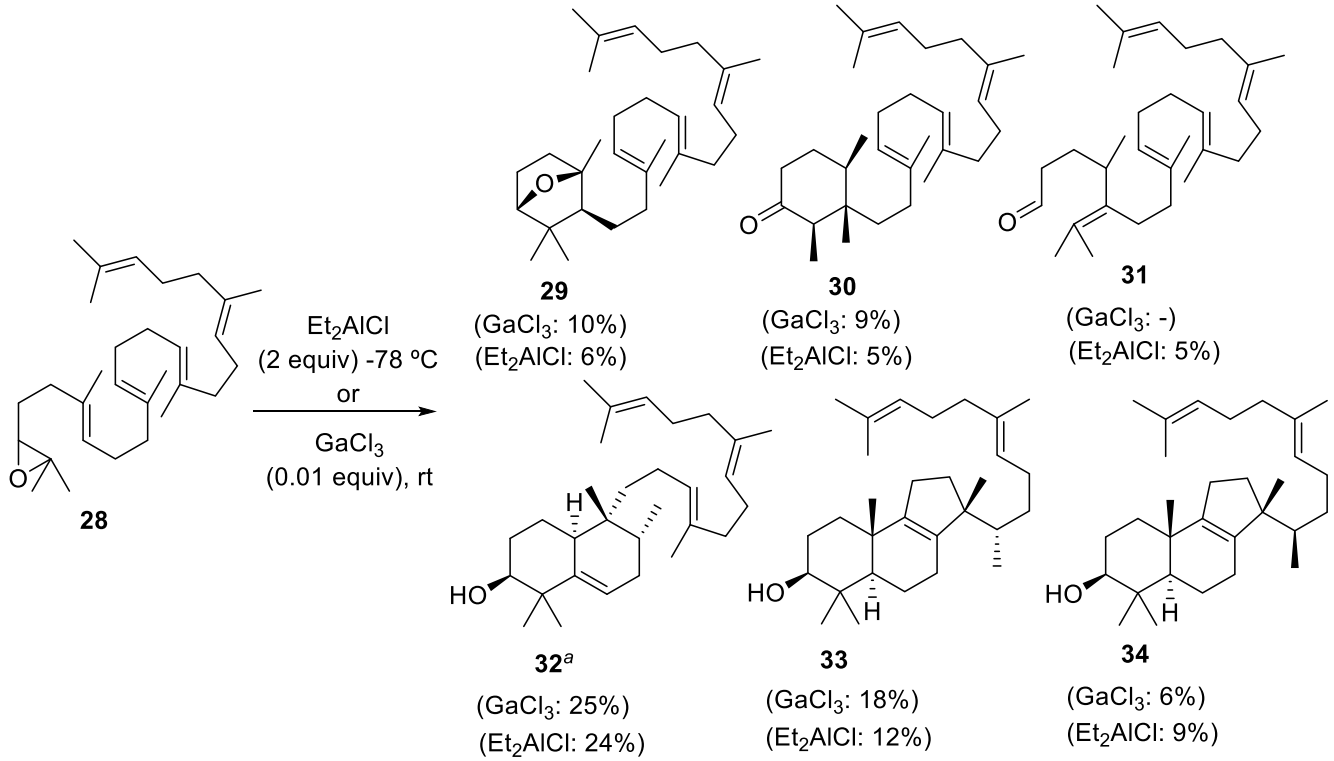


entry	equiv/LA	temp (°C), time (min)	3a, 3b yield (ratio)
1	0.5/Me_2AlCl	-78, 100	53% (1:1)
2[b]	0.2/Me_2AlCl	-78, 180	32% (1:1.7)
3	0.2/InI_3	rt, 15	28 %(1:0.8)
4	0.2/$InCl_3$	rt, 55	12% (1:2)
5	0.2/$GaCl_3$	rt, 5	56% (1:1)
6	0.2/GaI_3	rt, 5	53% (1:1)
7	0.2/$GaBr_3$	rt, 5	54% (1:1)
8	0.1/$GaCl_3$	rt, 5	55% (1:1)
9	0.01/$GaCl_3$	rt, 5	51% (1:1)

[a] DCM was used as solvent, 0.03 C (mM). [b] ·31% of starting material was recovered.

Finally, considering both the enormous biosynthetic importance of the cyclization of squalene-2,3-oxide and the fact that its cyclization with $SnCl_4$ supposed the only precedent so far reported of cyclization and rearrangement to produce halim-5-enes, we decided to study the behavior of squalene-2,3-oxide (**28**) in the presence of aluminium and gallium Lewis acids. The results obtained are summarized in Scheme 3.

Scheme 3. Cyclization of oxidoaqualene with Et_2AlCl and $GaCl_3$.

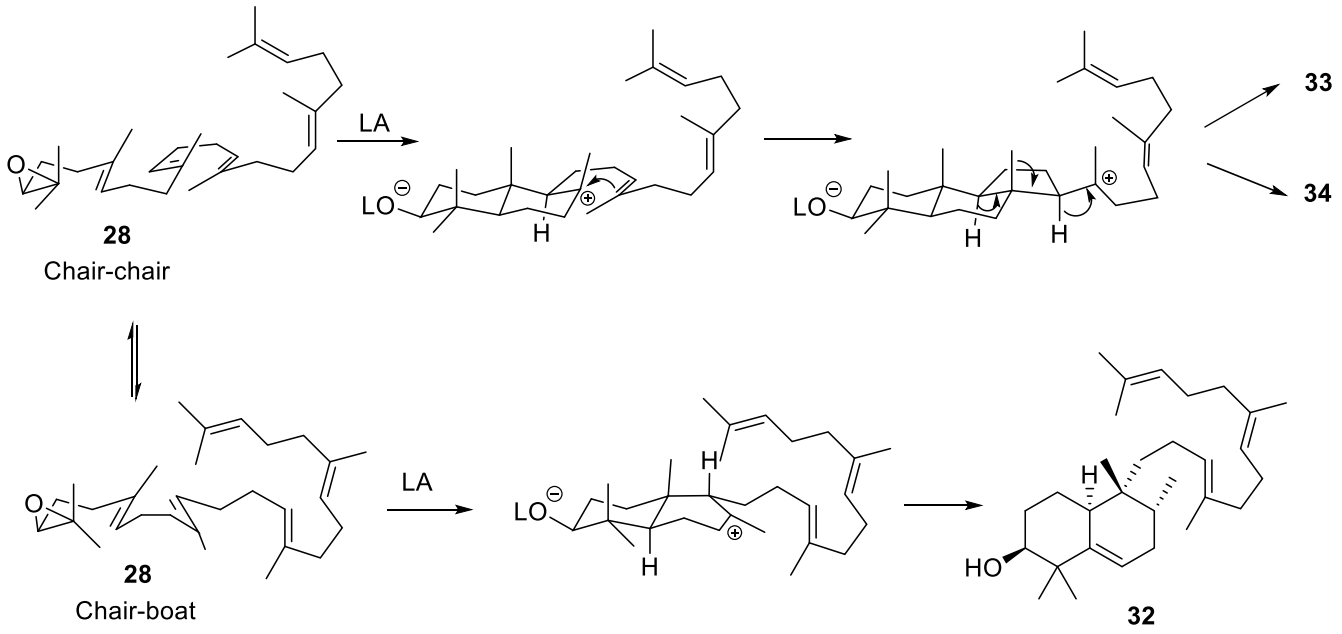


[a] Minor proportions of the corresponding epimer at C8 was detected by NMR from the mixture.

Although no reported by van Tamelen, monocycles **29** and **30** were found previously in the cyclizations of **28**, either triggered by different acids or in processes involving cyclases.[62,63] Aldehyde **31** was described for the first time. Halim-5-ene **32** presented the same ^1H NMR signals to that of the halimene described by van Tamelem, which allowed us to assign unambiguously the stereochemistry of

the product reported by these authors. It should be noted that van Tamelen and Sharpless suggested the opposite configuration at C9 for this compound in their seminal contribution. Finally, the rearranged malabaricanes thalianol (**33**) and 14-epithalianol (**34**) were also produced in these transformations.[64,68] Although van Tamelen amazingly assigned in 1966 the same rearranged malabaricane to the tricyclic compound generated in the reaction of squalene-2,3-oxide with $SnCl_4$, our work suggest that the same mixture of thalianol and 14-epithalianol could have been generated in the $SnCl_4$-mediated cyclization. To conclude, the yields of **32**-**34** and their corresponding stereochemistries seem to indicate that, on the one hand, the bicyclic cation derived from the chair-chair conformation of squalene-2,3-oxide evolves via a third cyclization to produce the rearranged malabaricanes **33** and **34**, after a hydride and methyl shift, and a proton elimination (Scheme 4). On the other hand, the bicyclic intermediated derived from chair-boat conformation of the acyclic precursor would undergo the corresponding 1,2-shifts to generate the halim-5-ene derivative **32**.

Scheme 4. Formation of 32-34 from epoxide 28.



CONCLUSIONS

Nature produces numerous examples of rearranged diterpenes and triterpenes. In this regard, we prove that rearranged halima-5-enes can be produced in a single synthetic step by reacting monoepoxy-geranylgeraniol derivatives with appropriate Lewis acids, via a cascade of two cyclizations and three rearrangements. The fact that we were capable to generate "in vitro" the halima-5-ene skeleton constitutes a nice illustration of the theory of "minimal enzymatic assistance", which was postulated to define the action of cyclases in the generation of related natural products. Quantum chemical calculations revealed, on the one hand, that the energetic barriers calculated for the cyclization and rearrangements processes were low enough to support our mechanistic proposal and, on the other hand, that the process was susceptible to catalysis by the Lewis acid. This last inference was confirmed experimentally, and acceptable yields of rearranged halim-5-ene derivatives could be produced after employing 0.01 equiv of $GaCl_3$.

EXPERIMENTAL SECTION

General Remarks.

All air- and water-sensitive reactions were performed in flaks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon. Anhydrous dichloromethane was distilled from calcium hydride (5 % w/v) under positive pressure of nitrogen. THF was freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under Argon. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35-70 μm) was used for flash column chromatography. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and solutions of phosphomolybdic acid in ethanol. HPLC with UV detection was used. Semi-preparative HPLC separation were carried out on a column (5 μm Silica, 10 X 250 mm) at a flow rate of 2.0 mL/min in an Agilent Series 1100 instrument. NMR spectra

were performed with a Varian Direct Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), Varian Direct Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and Varian Inova Unity (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. High-resolution MS were determined on an Autospec-Q VG-Analytical (FISONS) mass spectrometer. DEPT 135 and two-dimensional (COSY, HSQC, HMBC, NOESY) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

Preparation of polyenic precursors 35–38.

*(6E,10E)-2,6,10-Trimethylhexadeca-2,6,10-triene (**35**).* To a solution of farnesyl acetate (1000 mg, 3.78 mmol) in 20 mL of THF cooled at 0ºC was added 3.8 mL of Li_2CuCl_4 (0.38 mmol). The resulting solution was cooled at -30 ºC and then, 2.83 mL of butylmagnesium chloride were added dropwise (5.67 mmol). After stirring for 4 h, the reaction mixture was diluted with *tert*butyl methyl ether (MTBE) (120 mL) and then washed with saturated aqueous NH_4Cl and brine. The organic layer was then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography with hexane (H) provided 971 mg of compound **35** (97%). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15–5.08 (m, 3H), 2.11–2.04 (m, 4H), 2.01–1.97 (m, 6H), 1.68 (s, 3H), 1.60 (s, 9H), 1.36–1.26 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 134.8 (C), 134.7 (C), 131.2 (C), 124.8 (CH), 124.4 (CH), 124.3 (CH), 39.7 (CH_2), 39.7 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 22.6 (CH_2), 17.7 (CH_3), 16.0 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}$ 263.2739, found 263.2732.

*Tert-butyldimethyl(((5E,9E)-6,10,14-trimethylpentadeca-5,9,13-trien-2-yl)oxy)silane (**36**).* To a solution of farnesyl ketone (1147 mg, 4.38 mmol) in 24 mL of THF cooled at 0ºC was added 141 mg of LAH (3.72 mmol). The resulting solution was stirred for 20 min, and then, diluted with MTBE. To this solution, 0.1 mL of H_2O, 0.1 mL of 5N NaOH and 0.3 mL of H_2O were added successively. The resulting mixture was filtrated through a pad Na_2SO_4 and silica gel and concentrated under reduced pressure. To a stirred solution of this reaction crude oil in 70 mL of DMF were added imidazole (627

mg, 9.2 mmol) and TBSCl (1384 mg, 9.2 mmol). After consumption of the starting product (12 h), the mixture was diluted with MTBE and water and extracted with MTBE. The combined organic layer was washed with 2N HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (H:MTBE, 3:1) afforded 1460 mg of compound **36** (88%). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17–5.08 (m, 3H), 3.80 (sext, *J* = 6.1 Hz, 1H), 2.12–1.92 (m, 10H), 1.69 (s, 3H), 1.61 (s, 9H), 1.53–1.67 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.0 (C), 134.9 (C), 131.2 (C), 124.4 (CH), 124.3 (CH), 124.2 (CH), 68.4 (CH), 39.9 (CH_2), 39.7 (CH_2), 39.7 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.9 (3 x CH_3), 25.7 (CH_3), 24.3 (CH_2), 23.8 (CH_3), 18.2 (C), 17.7 (CH_3), 16.0 (CH_3), 16.0 (CH_3), -4.4 (CH_3), -4.7 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{47}OSi$ 379.3396, found 379.3391.

*(6E,10E)-3,7,11,15-Tetramethylhexadeca-1,6,10,14-tetraene (**37**).* A mixture of Cp_2TiCl_2 (4124 mg, 16.56 mmol) and Mn dust (3163 mg, 57.61 mmol) in deoxygenated THF 100 mL) was stirred at rt until the red solution turned green, under an argon atmosphere. Then, a solution of geranylgeraniol (2092 mg, 7.2 mmol) in strictly deoxygenated THF (5.0 mL) was added to the solution of Cp_2TiCl_2. The reaction mixture was refluxed for 20 h. Then, the solution was diluted with MTBE, filtrated and the solid washed with ethyl acetate. The organic layer was washed with HCl 2N, then with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude was flash chromatographed (H) to give 1007 mg (51%) of compound **37**. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (ddd, *J* = 17.2, 10.3, 7.5 Hz, 1H), 5.16–5.08 (m, 3H), 4.96 (ddd, *J* = 17.2, 2.0, 1.2 Hz, 1H), 4.92 (ddd, *J* = 10.3, 2.0, 0.9 Hz, 1H), 2.17–1.96 (m, 11H), 1.68 (s, 3H), 1.60 (s, 9H), 1.38–1.27 (m, 2H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 145.0 (CH), 135.1 (C), 131.5 (C), 124.8 (CH), 124.7 (CH), 124.5 (CH), 118.5 (C), 112.7 (CH_2), 46.0 (CH), 40.0 (CH_2), 37.6 (CH_3), 37.0 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.0 (CH_3), 25.9 (CH_2), 20.4 (CH_3), 17.9 (CH_3), 16.3 (CH_3), 16.3 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{35}$ 275.2739, found 275.2727.

*Methyl (2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenoate (**38**).* To a stirred solution of geranylgeraniol (1000 mg, 3.45 mmol) in 40 mL in CH_2Cl_2 under Argon was added Dess-Martin

reagent (2925 mg, 6.9 mmol). After 2 h at rt the reaction was quenched with a saturated solution of $Na_2S_2O_3$–$NaHCO_3$ that was added slowly to the mixture, the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Filtration on silica gel (H: MTBE, 1:2) afforded the allylic aldehyde, which was dissolved in 30 mL of *tert*-butyl alcohol and 15 mL of 2-methyl-2-butene. A solution of sodium chlorite (1910 mg, 21.22 mmol) and sodium dihydrogenphosphate (2200 mg, 15.92 mmol) in 15 mL of water was added dropwise over a 25 min period. The pale yellow reaction mixture was stirred at room temperature for 2 h. Volatile components were then removed under vacuum. The residue was dissolved in 150 mL of water and extracted with two 100 mL portions of MTBE. The combined organic layers were washed with brine, dried and concentrated. To a stirred solution of this reaction crude oil in 8.5 mL of benzene and 2.1 mL of MeOH, 1.6 mL (3.2 mmol) of a 2M solution of $TMSCH_2N_2$ in hexanes was added dropwise. After consumption of the starting product (30 min), the mixture was concentrated under reduced pressure. Purification by flash chromatography (H/MTBE, 10:1) afforded 556 mg of compound **38** (51%). The spectroscopic data of compound **38** coincide with those reported in the literature.[58]

General procedure for the synthesis of epoxy-derivatives 2, 13, 15 and 19

Powdered NBS (1.1 mmol) was added to a solution of the corresponding polyene (**35–38**) (1.0 mmol) in a mixture of THF:H_2O (12 mL, 5:1) at 0 ºC. The mixture was stirred for 30 min, diluted with MTBE, washed with water, dried with anhydrous Na_2SO_4 and the solvent concentrated under reduced pressure. The residue was dissolved in 8 mL of MeOH containing 1.2 mmol of K_2CO_3 (20 mL) and stirred for 10 min. The methanolic solution was then diluted with MTBE, washed with water, brine, dried with anhydrous $Na_2SO_4$and the solvent removed, giving a residue which was flash chromatographed to give the corresponding epoxides.

*(3-((3E,7E)-3,7-Dimethyltrideca-3,7-dien-1-yl)-2,2-dimethyloxirane (**2**).* Following the general procedure, successive reaction of polyene **28** with NBS and K_2CO_3/MeOH provided compound **2** (45%). This compound was separated by flash chromatography (H:MTBE, 95:5). Colourless oil. ^1H

NMR (300 MHz, $CDCl_3$): δ 5.17–5.11 (m, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.19–2.06 (m, 4H), 2.04–1.94 (m, 4H), 1.70–1.63 (m, 2H), 1.62 (s, 3H), 1.59 (s, 3H), 1.33–1.27 (m, 6H), 1.30 (s, 3H), 1.26 (s, 3H), 0.88 (t, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 134.5 (C), 133.9 (C), 124.9 (CH), 124.9 (CH), 64.2 (CH), 58.3 (C), 39.6 (CH_2), 36.3 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 24.9 (CH_3), 22.6 (CH_2), 18.7 (CH_3), 16.0 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, found 279.2681.

*Tert-butyl(((5E,9E)-12-(3,3-dimethyloxiran-2-yl)-6,10-dimethyldodeca-5,9-dien-2-yl)oxy)dimethyl silane (**13**).* Following the general procedure, successive reaction of polyene **29** with NBS and K_2CO_3/MeOH provided compound **13** (45%). This compound was separated by flash chromatography (H:MTBE, 95:5). Colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 5.17 (bt, *J* = 6.8 Hz, 1H), 5.13 (bt, *J* = 6.9 Hz, 1H), 3.80 (sext, *J* = 6.0 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.19–1.92 (m, 8H), 1.71–1.57 (m, 2H), 1.63 (s, 3H), 1.61 (s, 3H), 1.53–1.39 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.6 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 134.9 (C), 134.0 (C), 124.9 (CH), 124.4 (CH), 68.4 (CH), 64.2 (CH), 58.3 (C), 39.8 (CH_2), 39.6 (CH_2), 36.3 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 25.9 (3 x CH_3), 24.9 (CH_3), 24.3 (CH_2), 23.8 (CH_3), 18.8 (CH_3), 18.2 (C), 16.0 (CH_3), 16.0 (CH_3), -4.4 (CH_3), -4.7 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{47}O_2Si$ 395.3345, Found 395.3355.

*2,2-Dimethyl-3-((3E,7E)-3,7,11-trimethyltrideca-3,7,12-trien-1-yl)oxirane (**15**).* Following the general procedure, successive reaction of polyene **30** with NBS and K_2CO_3/MeOH provided compound **15** (58%). This compound was separated by flash chromatography (H:MTBE, 95:5). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74–5.63 (m, 1H), 5.17–5.08 (m, 2H), 4.97–4.89 (m, 2H), 2.69 (t, *J* = 6.2 Hz, 1H), 2.15–2.04 (m, 6H), 2.00–1.92 (m, 5H), 1.66–1.63 (m, 2H), 1.61 (s, 3H), 1.58 (s, 1H), 1.35–1.30 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 145.0, 135.0, 134.2, 125.1, 124.9, 112.7, 64.4, 58.5, 39.9, 37.6, 37.0, 36.6, 27.7, 26.8, 25.9, 25.1, 20.4, 19.0, 16.3, 16.2; HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{35}O$ 291.2688, Found 291.2677.

*Methyl (2E,6E,10E)-13-(3,3-dimethyloxiran-2-yl)-3,7,11-trimethyltrideca-2,6,10-trienoate (**19**).* Following the general procedure, successive reaction of polyene **31** with NBS and K_2CO_3/MeOH

provided compound **19** (34%). This compound was separated by flash chromatography (H:MTBE, 10:1). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 (bs, 1H) 5.15 (bt,*J* = 6.9 Hz, 1H), 5.10 (m, 1H), 3.69 (s, 3H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.19–1.97 (m, 10H), 2.17 (d, *J* = 1.3 Hz, 3H), 1.67–1.59 (m, 2H), 1.62 (s, 3H), 1.61 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 167.2 (C), 160.1 (C), 136.1 (C), 134.1 (C), 124.7 (CH), 122.9 (CH), 115.2 (CH), 64.2 (CH), 58.3 (C), 50.8 (CH_3), 40.9 (CH_2), 39.6 (CH_2), 36.3 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 24.9 (CH_3), 18.8 (CH_3), 18.7 (CH_3), 16.0 (CH_3), 16.0 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{35}O_3$ 335.2586, Found 335.2593.

Epoxides **12**, **17**, **22**, **24** and **28** were obtained following methods previously reported in the literarure.[13, 57, 61, 65]

General procedure for the cyclization plus rearrangement of epoxypolyprenes 2, 12, 13, 15, 17, 19, 24 and 26.

A solution of starting material (0.5 mmol) in dry DCM (50 mL) was cooled at -78 ºC, To a separate flask was added dry DCM (15 mL) followed by 1 mL of a 1M solution Et_2AlCl in DCM (1 mmol). This solution of Et_2AlCl was slowly added to a cooled solution of starting material (approximately for 1h). The reaction crude oil was further stirred until disappearance of the starting material. Then, 1.5 mL of Et_3N and 0.7 mL of a 4:1 mixture of MeOH/H_2O were added. The reaction mixture was taken out of the cooling bath and a saturated solution of NH_4Cl (60 mL) was then added. After separation of the organic layer, the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (3 x 50 mL), dried over Na_2SO_4, concentrated under reduced pressure and then purified by column chromatography.

Cyclization of epoxypolyprene 2

Using DCM as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl at -78 ºC for 1 h provided after flash chromatography (H:MTBE, 6:1) compounds **3a** and **3b** (71%, 1:1 ratio), compound **4** (3%), compound **6** (3%) and compounds **8b** and **8c** (10%, 0.6:1 ratio). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

(2S,4aS,5R,6S)-1,1,5,6-Tetramethyl-5-pentyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol ***(3a)***. A fraction enriched in **3a** was subjected to HPLC (normal phase, H:TBME 19:1, Rt = 50.1 min) to give pure **3a**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.53 (dt, *J* = 5.1, 2.2 Hz, 1H), 3.47 (t, *J* = 2.8 Hz, 1H), 2.27 – 2.22 (m, 1H), 1.92 – 1.85 (m, 2H), 1.79 (dddd, *J* = 17.7, 10.6, 3.5, 2.3 Hz, 1H), 1.70 (dq, *J* = 14.0, 3.5 Hz, 1H), 1.57–1.45 (m, 3H), 1.36 – 1.17 (m, 8H), 1.14 (s, 3H), 1.06 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.66 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 142.4 (C), 120.8 (CH), 76.4 (CH), 41.3 (C), 38.8 (CH), 37.0 (C), 36.8 (CH_2), 33.5 (CH), 32.8 (CH_2), 31.8 (CH_2), 28.3 (CH_3), 28.3 (CH_2), 25.5 (CH_3), 22.7 (CH_2), 22.2 (CH_2), 20.0 (CH_2), 16.3 (CH_3), 15.1 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2682.

(2S,4aS,5R,6R)-1,1,5,6-Tetramethyl-5-pentyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol ***(3b)***. A fraction enriched in **3b** was subjected to HPLC (normal phase, H:MTBE 19:1, Rt = 50.1 min) to give pure **3b**. Colourless oil. ^{1}H NMR (600 MHz, DMSO–d_6, 85 ºC): δ 5.27 (bt, *J* = 3.9 Hz, 1H, H6), 3.32 (t, *J* = 3.1 Hz, 1H, H3), 2.06 (bd, *J* = 17.4 Hz, 1H, H7a), 1.98 (bd, *J* = 12.2 Hz, 1H, H10), 1.92 (tdd, *J* = 13.2, 4.9, 2.6 Hz, 1H, H2a), 1.68 – 1.55 (m, 3H, H7b, H8, H2b), 1.52 – 1.40 (m, 2H, H1), 1.31 – 1.13 (m, 8H, H11, H12, H13, H14), 1.01 (s, 3H, H19), 0.98 (s, 3H, H18), 0.85 (t, *J* = 7.1 Hz, 3H, H15), 0.78 (s, 3H, H20), 0.75 (d, *J* = 6.7 Hz, 3H, H17); ^{13}C{^{1}H} NMR (150 MHz, DMSO–d_6, 85 ºC): δ 148.6 (C6), 121.7 (C5), 80.2 (C3), 45.8 (C4), 45.1 (C10), 41.0 (C9), 39.7 (C11), 37.8 (C8), 37.7 (CH_2), 36.0 (C7), 34.8 (C2), 32.3 (C18), 30.2 (C19), 27.6 (CH_2), 27.2 (CH_2), 27.0 (C20), 26.7 (C1), 19.7 (C17), 19.0 (C15); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688; Found 279.2679.

*(1R,4S)-1,3,3-Trimethyl-2-((E)-3-methylnon-3-en-1-yl)-7-oxabicyclo[2.2.1]heptane (**4**).* Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.17 (tm, *J* = 6.9 Hz, 1H), 3.70 (d, *J* = 5.4 Hz, 1H), 2.00 – 1.86 (m, 5H), 1.69 – 1.63(m, 1H), 1.57 (s, 3H), 1.50 – 1.22 (m, 10H), 1.31 (s, 3H), 1.17 (dd, *J* = 8.7, 5.8 Hz, 1H), 1.03 (s, 3H), 1.00 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 135.0 (C), 133.8 (C), 125.0 (CH), 88.7 (C), 86.0 (CH), 55.1 (CH), 45.2 (C), 39.8 (CH_2), 39.0 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 26.1 (CH_2), 26.1 (CH_3), 25.7 (CH_2), 23.9 (CH_3), 22.6 (CH_2), 18.9 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2710.

*(R,E)-4,8-Dimethyl-5-(propan-2-ylidene)tetradec-8-enal (**6**).* Aldehyde **6** was purified and characterized as its primary alcohol derivative **6a**. To a solution of a fraction enriched in **6** (18 mg) in 5 mL of MeOH:H_2O (4:1 ratio) was added 3 mg of $NaBH_4$ and the mixture was stirred for1 h 30 min at 0ºC. The reaction was concentrated under reduced pressure and the residue dissolved in MTBE and washed with water, quenched with acetone, and concentrated under reduced pressure. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting crude was purified by HPLC (H:MTBE, 6:1) to afford 12 mg of primary alcohol **6a**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (t, *J* = 7.1 Hz, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 2.71 (h, *J* = 7.1 Hz, 1H), 2.06 – 1.93 (m, 4H), 1.68 (s, 3H), 1.65 (s, 3H) 1.63 (s, 3H), 1.55 – 1.25 (m, 10 H), 0.98 (d, *J* = 6.9 Hz, 3H),0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.7 (C), 135.6 (C), 125.2 (C), 124.3 (CH), 63.4 (CH_2), 40.4 (CH_2), 35.6 (CH), 31.6 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 21.0 (CH_3), 20.1 (CH_3), 19.7 (CH_3), 16.0 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{19}H_{35}$ 263.2739, Found 263.2745.

*(2S,4aR,5S,8aR)-1,1,4a-Trimethyl-6-methylene-5-pentyldecahydronaphthalen-2-ol (**8b**).* A fraction enriched in **8b** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 22.7 min) to give pure **8b**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 (d, *J* = 1.7 Hz, 1H), 4.53 (d, *J* = 1.7 Hz, 1H), 3.27 (dd, *J* = 11.8, 4.4 Hz, 1H), 2.43 – 2.38 (m, 1H), 1.99 (td, J = 13.1, 5.0 Hz, 1H), 1.81 (dt, *J* = 13.1, 3.6 Hz, 1H), 1.77 – 1.06 (m, 15H), 1.01 (s, 3H), 0.92 (s, 1H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.78 (s, 3H), 0.68 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.4 (C), 106.5 (CH_2), 78.9 (CH), 56.6 (CH), 54.6 (CH),

39.3 (C), 39.1 (C), 38.2 (CH_2), 37.1 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 28.3 (CH_3), 28.0 (CH_2), 24.0 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 15.4 (CH_3), 14.4 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2597.

*(2S,4aR,5S,8aR)-1,1,4a,6-Tetramethyl-5-pentyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-2-ol (**8c**).* A fraction enriched in **8c** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 21.5 min) to give pure **8c**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.39 (bs, 1H), 3.26 (dd, *J* = 11.2, 4.5 Hz, 1H), 2.00 – 1.94 (m, 2H), 1.91 (dt, *J* = 13.3, 3.6 Hz, 2H), 1.69 (s, 3H), 1.67 – 1.57 (m, 3H), 1.52 (s, 2H), 1.42 – 1.10 (m, 8H), 0.98 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 3H), 0.76 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 135.6 (C), 121.7 (CH), 79.2 (CH), 54.9 (CH), 49.6 (CH), 38.7 (C), 37.3 (CH_2), 36.5 (C), 32.5 (CH_2), 31.9 (CH_2), 27.9 (CH_3), 27.4 (CH_2), 27.2 (CH_2), 23.5 (CH_2), 22.6 (CH_2), 21.9 (CH_3), 15.1 (CH_3), 14.1 (CH_3), 13.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2608.

Using MTBE as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using MTBE as a solvent for 1 h provided after flash chromatography (H:MTBE, 9:1) compounds **3a** and **3b** (4%, 1:1 ratio), compounds **7a** and **7b** (57%, 1:1.3 ratio) and compounds **8b** and **8c** (21%, 1.6:1 ratio). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(1S,5R)-4,6,6-Trimethyl-5-((E)-3-methylnon-3-en-1-yl)cyclohex-3-en-1-ol (**7a**).* A fraction enriched in **7a** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 20.8 min) to give pure **7a**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.23 (bs, 1H), 5.13 (t, *J* = 6.8 Hz, 1H), 3.45 (dd, *J* = 8.1, 5.5 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.15 (ddd, *J* = 15.1, 10.9, 5.2 Hz, 1H), 1.99 – 1.93 (m, 4H), 1.75 – 1.68 (m, 1H), 1.71 (s, 4H), 1.63 (bs, 1H), 1.60 (s, 3H), 1.37 – 1.23 (m, 7H), 0.95 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.82 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 137.1 (C), 135.0 (C), 125.3 (CH), 118.2 (CH), 75.0 (CH), 48.8 (CH), 42.0 (CH_2), 38.1 (C), 31.8 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 27.9 (CH_2), 27.2 (CH_2), 27.0

(CH), 25.3 (CH_3), 22.6 (CH_3), 16.2 (CH_3), 16.0 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2690.

*(1S,3R)-2,2-Dimethyl-4-methylene-3-((E)-3-methylnon-3-en-1-yl)cyclohexan-1-ol (**7b**).* A fraction enriched in **7b** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 22.6 min) to give pure **7b**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.10 (t, *J* = 7.3 Hz, 1H), 4.88 (s, 1H), 4.61 (s, 1H), 3.41 (dd, *J* = 9.9, 4.2 Hz, 1H), 2.33 (dt, *J* = 13.2, 4.8 Hz, 1H), 2.08 (ddd, *J* = 13.6, 9.6, 4.2 Hz, 2H), 2.02–1.94 (m, 3H), 1.88 – 1.77 (m, 2H), 1.67 – 1.46 (m, 4H), 1.59 (s, 3H), 1.35 – 1.24 (m, 6H), 1.03 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.72 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 149.9 (C), 137.7 (C), 127.6 (CH), 111.0 (CH_2), 80.0 (CH), 53.4 (CH), 43.2 (C), 41.2 (CH_2), 35.8 (CH_2), 34.9 (CH_2), 34.2 (CH_2), 32.2 (CH_2), 30.5 (CH_2), 28.5 (CH_3), 26.3 (CH_2), 25.3 (CH_2), 18.6 (CH_3), 18.1 (CH_3), 16.8 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2578.

Using benzene as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using benzene as a solvent at 10ºC for 45 minutes provided after flash chromatography (H:MTBE, 9:1) compounds **3a** and **3b** (54%, 1:0.8 ratio), compound **4** (2%) and compound **5** (3%). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(2R,3S,4R)-2,3,4-Trimethyl-3-((E)-3-methylnon-3-en-1-yl)cyclohexan-1-one (**5**).* Colourless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (t, *J* = 7.1 Hz, 1H), 2.50 (q, *J* = 6.7 Hz, 1H), 2.37 – 2.33 (m, 2H), 2.14 – 1.80 (m, 6H), 1.68 – 1.55 (m, 1H), 1.63 (s, 3H), 1.48 – 1.23 (m, 8H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 10.2 Hz, 3H), 0.91 (t, *J* = 3.5 Hz, 3H), 0.59 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 214.1 (C), 134.8 (C), 124.9 (CH_2), 50.5 (CH), 43.5 (C), 41.6 (CH_2), 36.1(CH), 36.0 (CH_2), 32.6 (CH_2), 31.6 (CH_2), 31.0(CH_2), 29.5(CH_2), 28.0 (CH_2), 22.6 (CH_2), 16.2 (CH_3), 15.4 (CH_3), 15.0 (CH_3), 14.1 (CH_3), 7.6 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2687.

Using THF as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using THF as a solvent for 1 h provided after flash chromatography (H:MTBE, 9:1) in silica column compounds **6** and **4** (4%, 1:1 ratio), compounds **7a** and **7b** (4%, 1:1.3 ratio) and compound **10** (91%). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(6E,10E)-2,6,10-Trimethylhexadeca-6,10-dien-3-one (**10**).* Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 – 5.10 (m, 1H), 2.61 (hept, *J* = 6.9 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.24 (t, *J* = 7.8 Hz, 2H), 2.08 (q, *J* = 7.3 Hz, 2H), 2.01 – 1.94 (m, 2H), 1.37 – 1.24 (m, 6H), 1.60 (d, *J* = 8.0 Hz, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.0 (C), 133.8 (C), 125.0 (CH), 88.7 (C), 86.0 (CH), 55.1 (CH), 45.2 (C), 39.8 (CH_2), 39.0 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 26.1 (CH_2), 26.1 (CH_3), 25.7 (CH_2), 23.9 (CH_3), 22.6 (CH_2), 18.9 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688; Found 279.2706.

Using CH_3CN as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using acetonitrile as a solvent at -40 ºC for 1 h provided after chromatography in silica column, using mixtures of H and MTBE of increasing polarity, compound **8a** (H:MTBE, 95:5, 22%) and compound **11** (H:MTBE, 2:1. 43%). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(2S,4aS,8aR)-1,1,4a,6-tetramethyl-5-pentyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-2-ol (**8a**).* A fraction enriched in **8a** was subjected to HPLC (normal phase, H:TBME 5:1, Rt = 13.1 min) to give pure **8a**. Colourless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (dd, *J* = 11.7, 4.7 Hz, 1H), 2.10 – 1.94 (m, 3H), 1.88 – 1.81 (m, 2H), 1.75 – 1.56 (m, 3H), 1.57 (s, 3H), 1.46 (ddd, *J* = 24.4, 12.4, 6.3 Hz, 1H), 1.38 – 1.24 (m, 6H), 1.11 (dd, *J* = 12.4, 2.0 Hz, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 140.5 (C), 125.6 (C), 79.0 (CH), 51.1 (CH), 38.8 (C), 38.7 (C), 35.0 (CH_2), 33.8 (CH_2), 32.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 28.1 (CH_3), 27.8 (CH_2), 22.5 (CH_2),

20.1 (CH_3), 19.4 (CH_3), 18.8 (CH_2), 15.5 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2584. A fraction enriched in **8a** was subjected to HPLC (normal phase, H:TBME 5:1, Rt = 13.1 min) to give pure **8a**. Colourless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (dd, *J* = 11.7, 4.7 Hz, 1H), 2.10–1.94 (m, 3H), 1.88 – 1.81 (m, 2H), 1.75 – 1.56 (m, 3H), 1.57 (s, 3H), 1.46 (ddd, *J* = 24.4, 12.4, 6.3 Hz, 1H), 1.38 – 1.24 (m, 6H), 1.11 (dd, *J* = 12.4, 2.0 Hz, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 140.5 (C), 125.6 (C), 79.0 (CH), 51.1 (CH), 38.8 (C), 38.7 (C), 35.0 (CH_2), 33.8 (CH_2), 32.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 28.1 (CH_3), 27.8 (CH_2), 22.5 (CH_2), 20.1 (CH_3), 19.4 (CH_3), 18.8 (CH_2), 15.5 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2584.

*N-((6E,10E)-3-hydroxy-2,6,10-trimethylhexadeca-6,10-dien-2-yl)acetamide (**11**).* Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (t, *J* = 6.9 Hz, 1H), 5.14 (t, *J* = 7.1 Hz, 1H), 4.01 (dd, *J* = 9.9, 3.7 Hz, 1H), 2.24 – 1.93 (m, 8H), 1.98 (s, 3H), 1.73 – 1.56 (m, 2H), 1.63 (s, 3H), 1.60 (s, 3H), 1.37 – 1.24 (m, 6H), 1.28 (s, 3H), 1.12 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.9 (C), 134.6 (C), 133.8 (C), 125.1 (CH), 125.0 (CH), 88.7 (CH), 66.6 (C), 39.6 (CH_2), 36.7 (CH_2), 31.6 (CH_2), 29.6 (CH_2), 29.1 (CH_3), 28.6 (CH_2), 27.9 (CH_2), 26.6 (CH_2), 22.8 (CH_3), 22.6 (CH_2), 16.0 (CH_3), 15.9 (CH_3), 14.3 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{21}H_{38}NO$ 320.2983, Found 320.2953.

Cyclization of epoxypolyprene 12

Following the general procedure, reaction of epoxide **12** with Et_2AlCl for 1 h provided a mixture which was a complex mixture of drimanes structures, in good agreement with the results described by Corey *et al.*[13]

Cyclization of epoxypolyprene 13

Following the general procedure, reaction of epoxide **13** with Et_2AlCl for 1 h provided after flash chromatography (H:MTBE, 6:1) compounds **14a** and **14b** (30% combined, 1:2 ratio). Ratios were determined by integration of the ^1H spectrum of the mixture.

*(2S,4aS,5R,6R)-5-(3-((Tert-butyldimethylsilyl)oxy)butyl)-1,1,5,6-tetramethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**14b**).* Compound **14b** was purified and characterized as its alcohol derivative **14b´**. A fraction enriched in **14b** was desilylated with TBAF (3 equiv) for 13 h and the resulting crude subjected to HPLC (normal phase, H:MTBE 1:1, Rt = 21.1 min) to give pure **14b´**. Colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 5.46 (t, *J* = 3.9 Hz, 1H), 3.72 (dq, *J* = 11.9, 6.0 Hz, 1H), 3.44 (m, 1H), 2.20 – 2.00 (m, 2H), 1.91 (tdd, *J* = 14.0, 4.4, 2.5 Hz, 1H), 1.79 – 1.12 (m, 9H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.13 (s, 6H), 0.83 (s, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): only distinguishable signals δ 76.8 (CH), 69.1 (CH), 40.0 (CH), 35.8 (CH), 33.3 (CH_2), 32.8 (CH_3), 23.6 (CH_3), 22.2 (CH_3), 14.6 (CH_3). HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{33}O_2$ 281.2481, Found 281.2462.

Cyclization of epoxypolyprene 15

Following the general procedure, reaction of epoxide **15** with Et_2AlCl for 1 h provided after flash chromatography (H:TBME, 6:1) compounds **16a** and **16b** (55% combined, 1:1.2 ratio). Ratios were determined by integration of the ^1H spectrum of the mixture. These two compounds were produced as a mixture of epimers at C–13).

*(2S,4aS,5R,6S)-1,1,5,6-Tetramethyl-5-(3-methylpent-4-en-1-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**16a**).* A fraction enriched in **16a** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 37.8 min) to give pure **16a**. Colourless oil.^1H NMR (500 MHz, $CDCl_3$): δ 5.74-5.66 (m, 1H), 5.54 (m, 1H), 4.99 – 4.91 (m, 2H), 3.48 – 3.47 (m, 1H), 2.22 (m, 1H), 2.06 – 1.99 (m, 1H), 1.90 – 1.68 (m, 4H), 1.54-1.49 (m, 3H), 1.37-1.20 (m 4H), 1.14 (s, 3H), 1.06 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H) (epimer I), (0.81, d, *J* = 6.8 Hz, 3H) (epimer II), 0.66 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 144.9 (CH) (epimer I), 144.8 (CH) (epimer II), 142.4 (C) (epimer I), 142.3 (C) (epimer II), 120.8 (CH)

(epimer II), 120.8 (CH) (epimer I), 112.6 (CH_2) (epimer II), 112.6 (CH_2) (epimer I), 76.4 (CH), 41.3 (C), 38.7 (CH) (epimer II), 38.7 (CH) (epimer I), 38.6 (CH) (epimer II), 38.5 (CH) (epimer I), 37.0 (C) (epimer II), 36.9 (C) (epimer I), 34.1 (CH_2), 33.4 (CH) (epimer I), 33.4 (CH) (epimer II), 31.9 (CH_2), 29.5 (CH_2), 28.4 (CH_3), 28.3 (CH_2), 25.6 (CH_3), 20.3 (CH_3) (epimer II), 20.3 (CH_3) (epimer I), 19.8 (CH_2) (epimer II), 19.8 (CH_2) (epimer I), 16.3 (CH_3), 15.0 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{20}H_{33}$ 273.2582, Found 273.2589.

*(2S,4aS,5R,6R)-1,1,5,6-Tetramethyl-5-(3-methylpent-4-en-1-yl)-1,2,3,4,4a,5,6,7-octahydro naphthalen-2-ol (**16b**).* A fraction enriched in **16b** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 38.9 min) to give pure **16b**. Colourless oil. ^{1}H NMR (500 MHz, DMSO-D_6, 78 ºC): δ 5.76–5.67 (m, 1H), 5.29 – 5.26 (m, 1H), 4.97 – 4.88 (m, 2H), 3.32 (t, *J* = 3.1 Hz, 1H), 2.11–1.94 (m, 3H), 1.87 – 1.79 (m, 1H), 1.68 – 1.39 (m, 5H), 1.36 – 1.11 (m 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.97 (d, *J* = 4.9 Hz, 3H) (epimer I), 0.95 (d, *J* = 4.9 Hz, 3H) (epimer II), 0.78 (s, 3H) (epimer I), 0.77 (s, 3H) (epimer II), 0.76 (d, *J* = 6.6 Hz, 3H) (epimer I), 0.74 (d, *J* = 6.6 Hz, 3H) (epimer II); $^{13}C\{^1H\}$ NMR (125 MHz DMSO–D_6): δ 149.9 (CH) 121.5 (CH), 117.7 (CH_2) (epimer I), 117.6 (CH_2) (epimer II), 80.1 (CH), 46.3 (C), 45.0 (CH), 43.0 (CH) (epimer I), 42.9 (CH) (epimer II), 40.8 (C) 37.7 (CH) (epimer I), 37.7 (CH) (epimer II), 35.9 (CH_2), 35.0 (CH_2), 34.6 (CH_2), 32.3 (CH_3), 30.2 (CH_3), 26.9 (CH_3) (epimer I), 26.89 (CH_3) (epimer II), 26.6 (CH_2) 25.1 (CH_3), 19.6 (CH_3) (epimer I), 19.61 (CH_3) (epimer II); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{20}H_{33}$ 273.2582, Found 273.2589.

Cyclization of epoxypolyprene 17

Following the general procedure, reaction of epoxide **17** with Et_2AlCl for 30 min provided after flash chromatography (H:MTBE, 9:1) compounds **18a** and **18b** (75% combined, 1:1 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

*(2S,4aS,5R,6S)-1,1,5,6-Tetramethyl-5-(2-((4aS,8aR)-2,4a,7,7-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**18a**).* A fraction enriched

in **18a** subjected to HPLC (normal phase, H:TBME 6:1, Rt = 18.9 min) to give pure **18a**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (m, 1H), 3.48 (t, *J* = 2.9 Hz, 1H), 2.22 (bd, *J* = 12.1 Hz, 1H), 2.12 (dt, *J* = 13.1, 8.4 Hz, 1H), 2.01 – 1.66 (m, 8H), 1.62 – 1.44 (m, 6H), 1.56 (s, 3H), 1.40 – 0.96 (m, 7H), 1.14 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.67 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.5 (C), 133.8 (C), 123.5 (C), 120.9 (CH), 76.5 (CH), 43.2 (CH_2), 42.5 (CH), 41.5 (C), 38.6 (CH), 37.1 (C), 36.6 (CH_2), 35.2 (CH_2), 34.6 (CH_2), 33.6 (CH), 33.2 (CH_3), 31.9 (CH_2), 31.5 (C), 31.1 (C), 29.6 (CH_2), 28.5 (CH_2), 28.5 (CH_3), 27.1 (CH_3), 26.6 (CH_2), 25.6 (CH_3), 24.7 (CH_2), 24.2 (CH_3), 20.4 (CH_2), 18.6 (CH_3), 16.3 (CH_3), 15.4 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{30}H_{49}$ 409.3834, Found 409.3829.

*(2S,4aS,5R,6R)-1,1,5,6-Tetramethyl-5-(2-((4aS,8aR)-2,4a,7,7-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**18b**)*. A fraction enriched in **18b** subjected to HPLC (normal phase, H:MTBE 6:1, Rt =20.2 min) to give pure **18b**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): only distinguishable signals δ 5.46 (t, *J* = 3.8 Hz, 1H), 3.45 (m, 1H), 2.12 (m, 1H), 2.06 (dt, *J* = 12.6, 4.9 Hz, 1H), 2.00 – 1.80 (m, 7H), 1.77 – 1.64 (m, 3H), 1.61 – 0.92 (m, 10H), 1.51 (s, 3H), 1.10 (m, 3H), 0.89 (m, 3H), 0.88 (m, 9H), 0.82 (m, 3H), 0.81 (m, 3H).; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): only distinguishable signals δ 134.0 (C), 123.2 (C), 120.7 (CH), 76.6 (CH), 43.1 (CH_2), 42.5 (CH), 39.9 (CH), 36.5 (CH_2), 35.9 (C), 34.6 (CH_2), 33.1 (CH_3), 32.7 (CH), 31.5 (CH_2), 31.0 (C), 29.4 (CH_2), 29.2 (CH_2), 26.9 (CH_3), 26.5 (CH_2), 25.1 (CH_2), 24.8 (CH_3), 24.1 (CH_3), 22.6 (CH_2), 22.2 (CH_3), 18.3 (CH_3), 14.5 (CH_3), 14.1 (CH_3); HRMS (FAB) m/z: $[M - OH]^+$ Calcd for $C_{30}H_{49}$ 409.3834, Found 409.3831.

Cyclization of epoxypolyprene 19

Following the general procedure, reaction of epoxide **13** with Et_2AlCl for 50 min provided after flash chromatography (H:MTBE, 4:1) compound **21** (5.5%) and compounds **20a** and **20b** (32%, 1:9 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

*Methyl (2E,6E)-3,7-dimethyl-9-((1S,2R,6R)-1,2,6-trimethyl-3-oxocyclohexyl)nona-2,6-dienoate (**21**)*. A fraction enriched in **21** was subjected to HPLC (normal phase, H:MTBE 6:1, Rt = 20.9 min) to give pure **21**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 (bs, 1H), 5.14 – 5.08 (m, 1H), 3.70 (s, 3H), 2.49 (q, *J* = 6.7 Hz, 1H), 2.37 – 2.33 (m, 2H), 2.20 – 2.16 (m, 7H), 2.06 – 1.97 (m, 2H), 1.90 – 1.81 (m, 2H), 1.67 – 1.60 (m, 1H), 1.64 (s, 3H), 1.43 (ddd, *J* = 14.6, 12.4, 4.8 Hz, 1H), 1.36 (ddd, *J* = 14.4, 13.0, 4.4 Hz, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.59 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 213.9 (C), 167.2 (C), 159.9 (C), 136.4 (C), 122.9 (CH), 115.4 (CH), 50.8 (CH_3), 50.5 (CH), 43.4 (C), 41.6 (CH_2), 40.9 (CH_2), 32.7 (CH), 29.3 (CH_2), 24.6(CH_3), 22.2 (CH_3), 19.1 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M]^+$ Calcd for $C_{21}H_{34}O_3$ 334.2508, Found 334.2513.

*Methyl (E)-5-((1R,2R,6S,8aS)-6-hydroxy-1,2,5,5-tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-methylpent-2-enoate (**20b**).* A fraction enriched in **20b** was subjected to HPLC (normal phase, H:MTBE 4:1, Rt = 26.5 min) to give pure **20b**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.66 (bs, 1H), 5.45 (t, *J* = 3.3 Hz, 1H), 3.68 (s, 3H), 3.45 (bs, 1H), 2.15 (s, 3H), 2.13 – 1.98 (m, 3H), 1.91 (tdd, *J* = 14.1, 4.7, 2.6 Hz, 1H), 1.77 – 1.64 (m, 3H), 1.70 – 1.29 (m, 4H), 1.10 (s, 6H), 0.81 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): only distinguishable signals δ 167.3 (C), 161.7 (C), 120.7 (CH), 114.9 (CH), 76.5 (CH), 50.8 (CH_3), 40.0 (CH), 35.3 (CH_2), 32.7 (CH), 29.3 (CH_2), 24.6 (CH_3), 22.2 (CH_3), 19.1 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{21}H_{33}O_2$ 317.2481, Found 317.2486.

Cyclization of epoxypolyprene 22

Following the general procedure, reaction of epoxide **22** with Et_2AlCl for 40 min provided after flash chromatography (H:MTBE, 2:1) compound **23a** and **23b** (12%, 1:9 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

*(2S,4aS,5R,6R)-5-(3-Hydroxy-3-methylpent-4-en-1-yl)-1,1,5,6-tetramethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**23b**).* Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable

signals δ 5.87 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.44 (t, *J* = 3.3 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.04 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.43 (bs, 1H), 2.09 – 2.01 (m, 1H), 1.89 (tdd, *J* = 13.9, 4.7, 2.6 Hz, 1H), 1.71 (ddd, *J* = 15.0, 7.2, 3.6 Hz, 1H), 1.64 (dq, *J* = 13.6, 6.6 Hz, 1H), 1.50 – 1.32 (m, 3H), 1.40 (td, *J* = 12.9, 3.9 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 0.80 (s, 3H), 0.78 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 145.2 (CH), 111.7 (CH_2), 76.5 (CH), 39.9 (CH), 36.0 (CH_2), 32.8 (CH), 29.3 (CH_2), 27.8 (CH_3), 24.7 (CH_3), 22.1 (CH_3), 14.6 (CH_3).

Cyclization of epoxypolyprene 24

Following the general procedure, reaction of epoxide **24** with Et_2AlCl for 50 min provided after column chromatography aldehyde **26** (H:MTBE, 5:1) (4%), compound **27** (H:MTBE, 5:1) (6%) and compounds **25a** and **25b** (H:MTBE, 4:1) (53% combined, 1:2.5 ratio). Compounds **25a** and **25b** were obtained as a pair of diastereomers. **25a1** and **25a2**, and **25b1** and **25b2**, respectively.

*Compound **25a1***. A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25a1** (Rt = 47.7 min). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.98 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.52 (dt, *J* = 5.0, 2.2 Hz, 1H), 5.14 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.12 (dd, *J* = 11.0, 0.9 Hz, 1H), 3.47 (t, *J* = 2.9 Hz, 1H), 2.22 – 2.17 (m, 1H), 2.00 (s, 3H), 1.91 – 1.83 (m, 2H), 1.81 – 1.66 (m, 4H), 1.52 (s, 3H), 1.51 – 1.42 (m, 3H), 1.38 – 1.31 (m, 1H), 1.25 (ddd, *J* = 14.2, 11.6, 6.0 Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.66 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 169.9 (C), 142.2 (CH), 141.9 (C), 120.7 (CH), 113.1 (CH_2), 83.2 (C), 76.3 (CH), 41.3 (C), 38.5 (CH), 36.8 (C), 33.2 (CH), 32.8 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 28.2 (CH_2), 25.5 (CH_3), 23.7 (CH_3), 22.2 (CH_3), 19.8 (CH_2), 16.3 (CH_3), 14.9 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2518.

*Compound **25a2***. A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25a2 (**Rt = 53.6 min). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.52 (dt, *J* = 5.9, 1.9 Hz, 1H), 5.16 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.12 (dd, *J* = 11.0, 1.0 Hz, 1H),

3.47 (t, *J* = 3.0 Hz, 1H), 2.23 – 2.17 (m, 1H), 2.01 (s, 3H), 1.91 – 1.75 (m, 4H), 1.71 – 1.57 (m, 2H), 1.54 (s, 3H), 1.54 – 1.43 (m, 3H), 1.33 (dt, *J* = 13.5, 4.0 Hz, 1H), 1.25 (ddd, *J* = 14.4, 12.8, 4.9 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.66 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 169.9 (C), 142.2 (CH), 141.9 (C), 120.7 (CH), 113.1 (CH_2), 83.2 (C), 76.3 (CH), 41.3 (C), 38.5 (CH), 36.8 (C), 33.2 (CH), 32.8 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 28.2 (CH_2), 25.5 (CH_3), 23.7 (CH_3), 22.2 (CH_3),19.8 (CH_2), 16.3 (CH_3), 14.9 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2527.

*Compound **25b1***. A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25b1 (**Rt = 41.8 min). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.92 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.44 (t, *J* = 3.7 Hz, 1H), 5.12 (d, *J* = 17.5, 1H), 5.10 (d, *J* = 11.0 Hz, 1H), 3.43 (bs, 1H), 2.09 – 2.01 (m, 1H), 1.99 (s, 3H), 1.90 (tdd, *J* = 13.9, 4.7, 2.4 Hz, 1H), 1.81 (bt, *J* = 13.0 Hz, 1H), 1.75 – 1.68 (m, 1H), 1.67 – 1.60 (m, 2H), 1.51 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 0.80 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 169.8 (C), 141.9 (CH), 113.1 (CH_2), 76.5 (CH), 39.9 (CH), 33.6 (CH_2), 32.8 (CH), 29.2 (CH_2), 24.7 (CH_3), 23.6 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2524.

*Compound **25b2***. A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25b2 (**Rt = 43.7 min). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.95 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.45 (t, *J* = 3.5 Hz, 1H),5.13 (d, *J* = 17.6, 1H), 5.10 (dd, *J* = 11.1, 1H), 3.44 (bs, 1H), 2.07 – 2.01 (m, 1H), 1.98 (s, 3H), 1.91 (tdd, *J* = 14.0, 4.5, 2.5 Hz, 1H), 1.75 – 1.68 (m, 3H),1.64 (dq, *J* = 14.1, 7.4 Hz, 1H), 1.50 (s, 3H), 1.09 (s, 6H), 0.80 (s, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 169.8 (C), 142.0 (CH), 113.1 (CH_2), 76.5 (CH), 39.8 (CH), 33.6 (CH_2), 32.8 (CH), 29.3 (CH_2), 24.8 (CH_3), 23.6 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2530.

*(E)-3,7,11-Trimethyl-13-oxo-10-(propan-2-ylidene)trideca-1,6-dien-3-yl acetate (**26**).* Aldehyde **26** was purified and characterized as its primary alcohol derivative **26a**. To a solution of a fraction enriched in **26** (44 mg) in 22 mL of MeOH:H_2O (4:1 ratio) was added 15 mg of $NaBH_4$ and the mixture was stirred for 30 min at 0ºC. The reaction was concentrated under reduced pressure and the residue dissolved in MTBE and washed with water, quenched with acetone, and concentrated under reduced pressure. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting crude was purified by column chromatography (H/MTBE, 3:1) to afford 21 mg of primary alcohol **26a**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.17 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.13 (dd, *J* = 11.0, 0.9 Hz, 1H), 5.15–5.10 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.71 (sext, *J* = 7.1 Hz, 1H), 2.06 – 1.85 (m, 7H), 2.02 (s, 3H), 1.82–1.76 (m, 2H), 1.82 – 1.76 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H), 1.38 – 1.32 (m, 2 H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.0 (C), 141.8 (CH), 136.3 (C), 135.5 (C), 125.3 (C), 123.1 (CH), 113.1 (CH_2), 82.9 (C), 63.4 (CH_2), 40.2 (CH_2), 39.8 (CH_2), 35.6 (CH), 31.6 (CH_2), 31.2 (CH_2), 26.8 (CH_2), 23.6 (CH_3), 22.2 (CH_2), 22.2 (CH_3), 20.9 (CH_3), 20.1 (CH_3), 19.6 (CH_3), 16.0 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{35}O$ 291.2693, Found 291.2693.

*(E)-3,7-Dimethyl-9-((1S,2R,6R)-1,2,6-trimethyl-3-oxocyclohexyl)nona-1,6-dien-3-yl acetate (**27**).* Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.17 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.14 (dd, *J* = 11.0, 0.8 Hz, 1H), 5.15 – 5.10 (m, 1H), 2.49 (q, *J* = 6.7 Hz, 1H), 2.38 – 2.33 (m, 2H), 2.05 – 1.95 (m, 4H), 2.02 (s, 3H), 1.91 – 1.75 (m, 4H), 1.67 – 1.58 (m, 1H), 1.62 (s, 3H), 1.55 (s, 3H), 1.46 – 1.32 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.59 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 213.9 (C), 169.9 (C), 141.8 (CH), 135.5 (C), 123.8 (CH), 113.1 (CH_2), 82.9 (C), 50.5 (CH), 43.4 (C), 41.6 (CH_2), 39.7 (CH_2), 36.1 (CH), 35.9 (CH_2), 32.5 (CH_2), 31.0 (CH_2), 23.6 (CH_3), 22.3 (CH_2), 22.2 (CH_3), 16.1 (CH_3), 15.4 (CH_3),15.0 (CH_3), 7.6 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2533.

Cyclization of epoxypolyprene 2 using Br_3In as Lewis acid

To a solution of starting material (0.5 mmol) in dry DCM (10 mL) was added indium tribromide (0.5 mmol) at room temperature. The reaction mixture was further stirred until disappearance of the starting material. Then, solvent was removed under reduced pressure and the crude reaction mixture passed through a short plug of silica gel and celite (4:1) which was washed with EtOAc:H (9:1). Finally the crude resultant was concentrated under reduced pressure and then purified by flash chromatography in silica column (H:MTBE, 95:5), to obtain compounds **3a** and **3b** (37%, 1:0.45 ratio), compound **4** (7%), compounds **7a** and **7b** (9%, 1:0.2 ratio), compounds **8b** and **8c** (9%, 1:0.8 ratio) and compounds **9a** and **9b** (25%, 1:0.7 ratio).

(2S,5R,6S,8aR)-1,1,5,6-Tetramethyl-5-pentyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-ol ***(9a)****.* A fraction enriched in **9a** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 13.4 min) to give **9a** together with some proportion of **3a**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.28 (t, *J* = 4.0 Hz, 1H), 3.40 (dd, *J* = 6.2, 4.9 Hz, 1H), 2.33 (dtd, *J* = 17.5, 4.6, 2.0 Hz, 1H), 2.10 (dddd, *J* = 17.5, 5.9, 3.6, 2.1 Hz, 1H), 1.88 – 1.79 (m, 1H),1.71 (d, *J* = 13.5 Hz, 1H), 1.57 – 1.36 (m, 3H), 1.37 – 1.15 (m, 8H), 1.05 – 0.98 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 145.1 (C), 113.9 (CH), 74.9 (CH), 43.9 (CH), 43.1 (CH), 42.3 (C), 36.5 (C), 32.8 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 29.1 (CH_2), 26.6 (CH_3), 23.2 (CH_2), 22.7 (CH_3), 22.7 (CH_2), 19.3 (CH_3), 16.5 (CH_3), 14.2 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2679.

Catalytic assays of cyclization plus rearrangement of epoxide 2

Using Et_2AlCl as Lewis acid

The reactions were performed following the general procedure and only varying the quantity of catalyst.

Using indium or gallium halides as Lewis acids

To a solution of starting material (0.5 mmol) in dry DCM (15 mL) was added the Lewis acid (0.2-0.01 mmol) at room temperature. The reaction mixture was further stirred until disappearance of the starting material. Then, solvent was removed under reduced pressure and the crude reaction mixture passed through a short plug of silica gel and celite (4:1) which was washed with MTBE. Finally the crude resultant was concentrated under reduced pressure and then column chromatographed to afford the corresponding mixtures of **3a** and **3b** (H:MTBE, 6:1).

Synthesis of isotuberculosinol (1)

A solution of 110 mg (0.31 mmol) of **25a** and **25b** in 3 mL of DCM was treated with 0.09 mL (0.62 mmol) of pentafluorophenyl chlorothionoformate (0.153 mmol) and 115 mg (0.9 mmol) of DMAP. After stirring for 7h at rt, the mixture was concentrated under vacuum and column chromatographed (H:MTBE, 20:1) to afford 151 mg of the corresponding xanthates. To a solution of 88 mg (0.15 mmol) of this mixture in 5 mL of degassed toluene, 9 mg of AIBN and 0.24 mL of tributyltin hydride (0.92 mmol) were added. The mixture was refluxed for 1h and then column chromatographed (H:MTBE, 15:1) to afford 85 mg of a mixture of deoxygenated products. This mixture was dissolved in 2 mL of THF and treated at rt with 38 mg of LAH at 0ºC. The mixture was then stirred for 12 h. After the usual work-up, 58 mg (0.20 mmol) of a mixture of **1** and **1b** (1:2.5 ratio) were obtained (65%). This mixture was subjected to HPLC (normal phase H:MTBE, 10:1) to give **1** (Rt = 24.3 min) and **1b** (Rt = 26.1 min). Compounds **1** and **1b** were obtained both as a pair of diastereomers.

*Isotuberculosinol (**1**).* Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.92 (dd, *J* = 17.4, 10.8 Hz, 2H), 5.43 (bd, *J* = 5.5 Hz, 2H), 5.22 (bd, *J* = 17.3 Hz, 2H), 5.07 (bd, *J* = 10.8 Hz, 2H), 2.13 (dm, *J* = 13.1 Hz, 2H), 1.83 (dt, *J* = 17.7, 5.5 Hz, 2H), 1.74 – 1.68 (m, 4H), 1.60 – 1.33 (m, 14H), 1.30 (s, 6H), 1.29 – 1.17 (m, 4H), 1.06 (s, 6H), 1.01 (qd, *J* = 12.9, 4.2 Hz, 2H), 1.00 (s, 6H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.62 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 146.0, 146.0 (C), 145.1, 145.1 (CH),

116.2, 116.1 (CH), 111.8, 111.8 (CH_2), 73.5, 73.3 (C), 40,9 (CH_2), 39.7 (CH), 36.7 (C), 36.1 (C), 35.2, 35.1 (CH_2), 33.3 (CH), 31.7 (CH_2), 30.1 (CH_2), 29.8 (CH_3), 29.1 (CH_3), 27.7, 27.6 (CH_3), 27.3 (CH_2), 22.2 (CH_2), 16.2, 16.2 (CH_3), 15.0, 15.0 (CH_3).

8-Epi-isotuberculosinol (***1b***). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.91 (ddd, *J* = 17.4, 10.8, 6.9 Hz, 1H), 5.33 (bs, 1H), 5.21 (dd, *J* = 17.1, 2.9 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 1.96 (bd, *J* = 12.9 Hz, 1H), 1.79 – 1.00 (m, 14H), 1.28 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.79 (s, 3H), 0.77 (m, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 145.3, 145.3 (CH), 114.3 (CH), 111.7, 111.6 (CH_2), 73.5, 73.5 (C), 41,9 (CH_2), 40.8, 40.8 (CH), 36.0 (CH_2), 32.9, 32.9 (CH), 29.5 (CH_3), 27.7 (CH_3), 23.0 (CH_2), 22.0 (CH_3), 14.6 (CH_3).

Cyclization of epoxypolyprene 28

Using Et_2AlCl as Lewis acid

Following the general procedure, reaction of epoxide **28** with Et_2AlCl for 50 min provided after flash column chromatography (H:MTBE, 95:5) aldehyde **31** (5%), compound **29** (6%), compound **30** (5%), compound **32** (24%) and compounds **33** (12%) and **34** (9%).

(R,8E,12E,16E)-4,8,13,17,21-pentamethyl-5-(propan-2-ylidene)docosa-8,12,16,20-tetraenal (***31***). *Colourless* oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.73 (t, *J* = 1.8 Hz, 1H), 5.27 – 5.08 (m, 4H), 2.74 (tq, *J* = 7.4, 6.9 Hz, 1H), 2.34 (td, *J* = 7.4, 1.9 Hz, 2H), 2.12 – 1.95 (m, 16H), 1.70 (s, 6H), 1.67 (q, *J* = 7.4 Hz, 2H), 1.66 (s, 6H), 1.63 (s, 3H), 1.62 (s, 6H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 202.9 (CH), 135.8, 135.2, 134.9, 134.5, 131.3, 126.6 (C), 124.4, 124.3, 124.3, 124.0 (CH), 42.5, 40.4, 39.8, 39.8 (CH_2), 35.3 (CH), 28.3, 28.3, 27.8, 26.9, 26.8, 26.7 (CH_2), 25.7, 21.0, 20.1, 19.6, 17.7, 16.1, 16.1, 16.0 (CH_3). HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{50}O$ 427,3862, Found 427.3930.

(1R,2S,4S)-1,3,3-trimethyl-2-((3E,7E,11E)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraen-1-yl)-7-oxabicyclo[2.2.1]heptane (***29***). Colourless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.19 – 5.10 (m,

4H), 3.74 (d, *J* = 5.4 Hz, 1H), 2.14 – 1.88 (m, 16H), 1.70 (s, 3H), 1.62 (s, 12H), 1.51 – 1.39 (m, 4H), 1.35 (s, 3H), 1.20 (dd, *J* = 8.6, 5.7 Hz, 1H), 1.07 (s, 3H), 1.04 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.39, 135.21, 134.94, 131.27 (C), 124.5, 124.4, 124.3, 124.3 (CH), 86.7 (C), 86.1 (CH), 55.2 (CH), 45.3 (C), 39.8, 39.8, 39.8, 39.0, 28.3, 28.2, 26.8, 26.7, 26.2 (CH_2), 26.1 (CH_3), 25.8 (CH_2), 25.7, 23.4, 18.9, 17.7, 16.1, 16.0, 16.0 (CH_3).

*(2R,3S,4R)-2,3,4-trimethyl-3-((3E,7E,11E)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraen-1-yl)cyclohexan-1-one (**30**)*. Colourless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.22 – 5.09 (m, 4H), 2.51 (q, *J* = 6.7 Hz, 1H), 2.40 – 2.34 (m, 2H), 2.13 – 1.98 (m, 15H), 1.92 – 1.81 (m, 2H), 1.70 (s, 3H), 1.65 (s, 3H), 1.63 (s, 9H), 1.47 – 1.36 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.60 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 214.0, 135.3, 135.2, 135.0, 131.3 (C), 124.4, 124.4, 124.3, 124.2, 50.5 (CH), 43.5(C), 41.6, 39.8, 39.8, 36.2 (CH), 36.0, 32.6, 31.0, 28.3, 28.2, 26.8, 26.7 (CH_2), 25.7, 17.7, 16.2, 16.1, 16.0, 15.4, 15.1, 7.6 (CH_3).

*(2S,4aS,5R,6R)-1,1,5,6-tetramethyl-5-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**32**).* Colourless oil. A fraction enriched in **32** was subjected to HPLC (normal phase, H:MTBE 95:5, Rt = 26.8 min) to give pure **32**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.30 (dt, *J* = 3.9, 2.0 Hz, 1H), 5.14 – 5.08 (m, 3H), 3.34 (q, *J* = 3.5 Hz, 1H), 2.12 – 1.81 (m, 14H), 1.66 (s, 3H), 1.65 – 1.60 (m, 2H), 1.58 (s, 9H), 1.54 – 1.44 (m, 2H), 1.37 – 1.27 (m, 1H), 1.25 – 1.16 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 0.84 (s, 3H), 0.79 (d, *J* = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, DMSO) δ 143.7, 134.8, 134.0, 130.9 (C), 125.9, 124.7, 124.5, 117.0, 75.46 (CH), 41.6 (C), 39.7 (CH), 39.6 (CH_2), 36.3 (C), 35.0 (CH_2), 33.0 (CH), 31.3, 30.0, 30.0 (CH_2), 27.4 (CH_3), 26.8, 26.5(CH_2), 25.7, 25.3 (CH_3), 22.2, 22.2 (CH_2), 22.1, 17.9, 16.3, 16.1, 14.9 (CH_3).

*Thalianol (**33**).* A fraction enriched in **33** was subjected to HPLC (normal phase, H:MTBE 95:5, Rt = 45.3 min) to give pure **33**. Colourless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.12 (bt, *J* = 6.9 Hz, 1H), 5.10 (bt, *J* = 6.9 Hz, 1H), 3.26 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.21 – 1.82 (m, 9H), 1.78 – 1.70 (m, 5H), 1.69 (bs, 3H), 1.66 – 1.62 (m, 2H), 1.61 (bs, 6H), 1.57 – 1.42 (m, 3H), 1.35 (ddd, *J* = 9.9, 6.6, 2.8 Hz,

1H), 1.31 – 1.21 (m, 2H), 1.09 – 1.04 (m, 1H), 1.02 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, cdcl$_3$) δ 143.2, 138.2, 134.7, 131.3 (C), 125.0, 124.4, 79.2 (CH), 52.6 (C), 51.5 (CH), 39.7 (CH_2), 38.7 (C), 38.4 (CH), 35.7 (C), 35.6, 31.7, 30.8 (CH_2), 28.2 (CH_3), 27.9, 27.8, 26.8, 26.6 (CH_2), 25.7 (CH_3), 25.2 (CH_2), 23.4 (CH_3), 19.4 (CH_2), 19.0, 17.7, 16.0, 15.5, 14.7 (CH_3).

*14-Epi-thalianol (**34**).* A fraction enriched in **34** was subjected to HPLC (normal phase, H:MTBE 95:5, Rt = 38.3 min) to give pure **34**. Colourless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.11 (bt, *J* = 6.9 Hz, 1H), 5.10 (bt, *J* = 6.9 Hz, 1H), 3.28 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.22 – 1.83 (m, 10H), 1.79 – 1.71 (m, 5H), 1.71 (bs, 3H), 1.69 – 1.64 (m, 3H), 1.62 (d, *J* = 6.1, 1.4 Hz, 6H), 1.47 (ddd, *J* = 12.1, 6.4, 1.8 Hz, 1H), 1.35 – 1.26 (m, 3H), 1.09 (dd, *J* = 12.3, 1.5 Hz, 1H), 1.04 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 6H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.4, 138.0, 134.9, 131.3 (C), 125.0, 124.4, 79.3 (CH), 52.8 (C), 51.6 (CH), 39.8 (CH_2), 38.8 (C), 38.2(CH), 35.8, 35.6 (C), 32.2, 30.8 (CH_2), 28.2(CH_3), 27.9, 27.6, 26.8, 26.5 (CH_2), 25.7, 25.2(CH_3), 23.4 (CH_2), 19.5 (CH_3), 19.0 (CH_2), 17.7, 16.0, 15.5, 14.3 (CH_3).

Using $GaCl_3$ as Lewis acid

To a solution of starting material **28** (1 mmol) in dry DCM (30 mL) was added gallium trichloride (0.01 mmol) at room temperature. The reaction mixture was further stirred until disappearance of the starting material. Then, solvent was removed under reduced pressure and the crude reaction mixture passed through a short plug of silica gel which was washed with TBME. Finally the crude resultant was concentrated under reduced pressure and then purified by flash chromatography in silica column (H:MTBE, 95:5) to obtain compound **29** (10%), compound **30** (9%), compound **32** (25%) and compounds **33** (18%) and **34** (6%).

ASSOCIATED CONTENT

Supporting Information.

This material is available free of charge via on the ACS Publications website at DOI:

Copies of ^{1}H and ^{13}C NMR spectra, and computational data (PDF).

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Notes

The authors declare no competing financial interest.

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