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Biomimetic rearrangements of simplified labdane diterpenoids

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ABSTRACT

Simplified ethyl-substituted labdane diterpenoids **14** and **19** have been synthesised from (+)-sclareolide (**18**). Biomimetic rearrangements of these compounds, involving stereospecific 1,2-alkyl and hydride shifts, have been carried out by treatment with a variety of Lewis and protic acids. Halimane compounds, such as **34** and simple dehydration products such as **3**, **32** and **33** have been formed either selectively or as mixtures depending on the reaction conditions. However, further rearrangement to clerodane products such as **1** and **2** was not observed, indicating a high degree of enzymatic control for the in vivo formation of these natural products.

1. Introduction

The labdanes and clerodanes[1] are large families of diterpenoid natural products, mainly isolated from plant sources, featuring the basic hydrocarbon skeletons as shown in Figure 1.

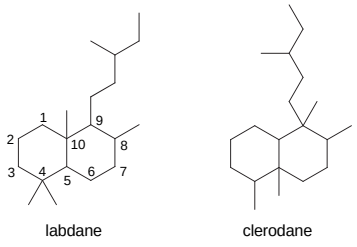


Figure 1. The labdane and clerodane core structures.

Labdane and clerodanes with related structures are often isolated from the same organism, which suggests a biogenetic link between the two families. For example, the hydrocarbons **1**, **2** and **3** were co-isolated from a southern Australian marine sponge, *Mycale* sp., in 1997 (Fig. 2).[2] Although obtained as an inseparable mixture, the structures of **1**, **2** and **3** were assigned by NMR studies.

Clerodane natural products appear to be biosynthetically related to the labdanes via a series of methyl and hydride shifts (Scheme 1).[3] The *trans*-clerodanes **8** and **9** might be produced from labdane carbocation **4** via concerted 1,2-hydride and methyl shifts

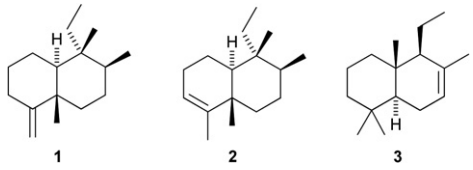
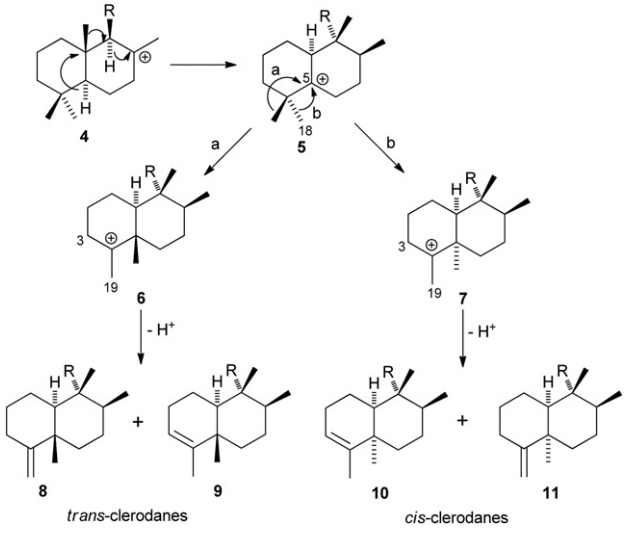


Figure 2. Clerodane and labdane diterpenoids isolated from *Mycale* sp.



Scheme 1. Proposed biosynthesis of clerodanes from labdane carbocation **4**.

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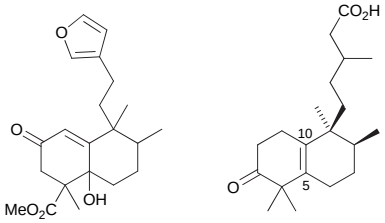
(sequence a). The *cis*-clerodanes **10** and **11**, however, cannot be formed by a concerted process, and their biosynthesis must presumably follow a series of migrations via intermediate **5**, which at this point could lead to *cis* or *trans* compounds depending on which C-4 methyl group migrates. In the synthesis of *cis*-clerodanes, for a steroelectronic shift of C-18 to C-5 (sequence b) a conformational change in the ring would be required. The final carbocations of the rearrangement pathways, **6** and **7**, can lose a proton from either C-3 (to give endocyclic tri-substituted alkenes) or C-19 (to give exocyclic di-substituted alkenes).

Evidence for the proposed biosynthetic rearrangement is derived from isotopic labelling experiments,[4] and the pathway is also supported by the isolation of several partially rearranged labdane compounds such as chettaphanin I[5] (**12**) from *Adenochalaena siamensis*, and salmantic acid[6] (**13**), which contains a halimane-type structure featuring an internal $\Delta^{5,10}$ olefin, from *Cistus laurifolius* (Fig. 3).



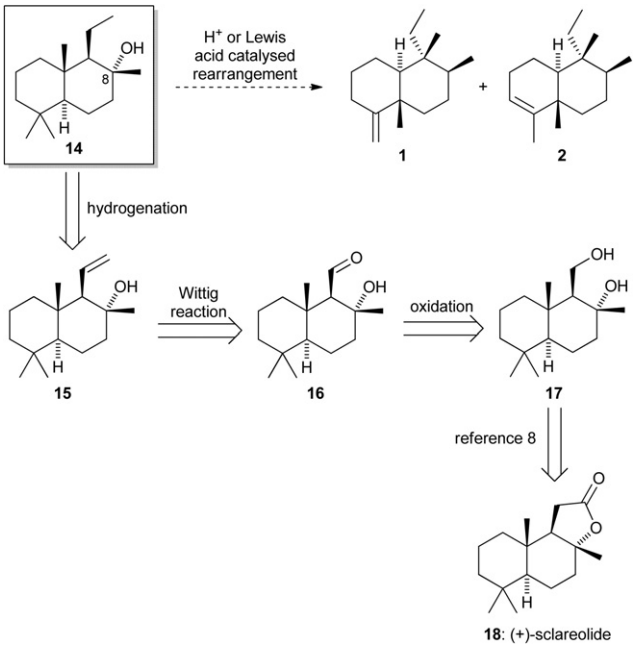
12: chettaphanin **13**: salmantic acid

Figure 3. Partially rearranged labdane natural products.

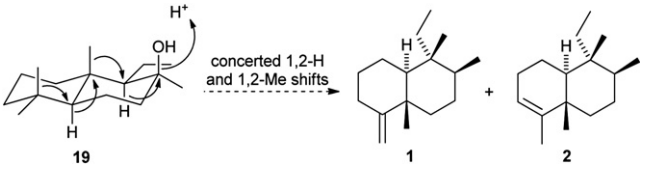
2. Results and discussion

Despite the strong biogenetic link between labdane and clerodane diterpenoid natural products, an in vitro biomimetic synthesis of a clerodane skeleton from a labdane has never been achieved. The aim of this project was to synthesise a simplified labdane structure, such as **14**, in order to fully investigate the possibility of inducing the proposed series of 1,2-methyl and hydride shifts under acid catalysis to give the clerodane ring systems of **1** and **2**. It was anticipated that the use of an unfunctionalised labdane such as **14** would represent the best chance to induce the biomimetic cascade reaction, as there are no functional groups that could interfere with the rearrangement, or trap out early carbocation intermediates as has been previously observed.[7] The retrosynthetic plan for the synthesis of the labdane **14** from (+)-sclareolide **18** is outlined in Scheme 2. Compound **14** could be formed by hydrogenation of alkene **15**, which could in turn be derived from aldehyde **16** via a Wittig-type olefination. Aldehyde **16** could be formed by oxidation of the diol **17**, which has been previously synthesised from the readily available chiral starting material (+)-sclareolide in three steps.[8]

Labdane **14** contains an equatorial hydroxyl group at C-8, but the axially substituted alcohol **19** might also be synthesised by an analogous route, using 8-*epi*-sclaerolide as the starting material. This compound can be obtained from (+)-sclaerolide by isomerisation of the lactone ring junction under strongly acidic conditions.[9] The axially substituted tertiary alcohol **19** might be more pre-disposed towards the biomimetic rearrangement as the C–O bond would be *anti*-periplanar to the migrating C–H bond (Scheme 3). Related 1,2-methyl and hydride shifts of both 3β-friedelanol and estradiols have shown a stereoelectronic requirement for colinearity between the migrating group and the σ* antibonding orbital of the C–O bond.[10]



Scheme 2. Retrosynthetic analysis for synthesis of labdane **14** from (+)-sclareolide.

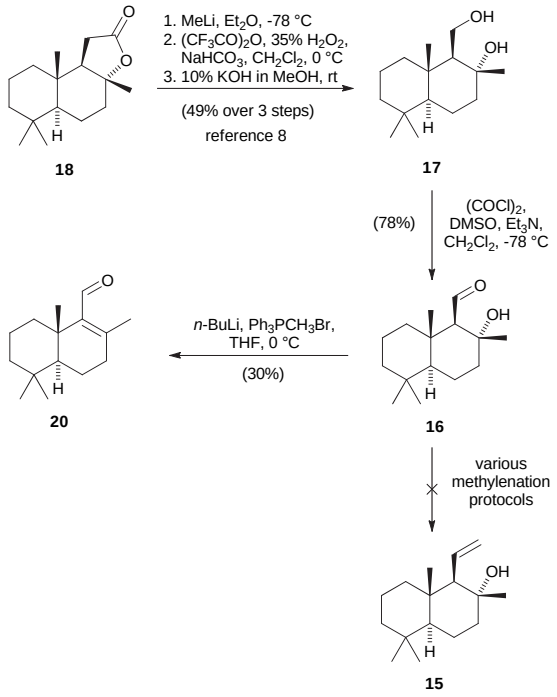


Scheme 3. Possible concerted rearrangement of a labdane with an axial hydroxyl group at C–X.

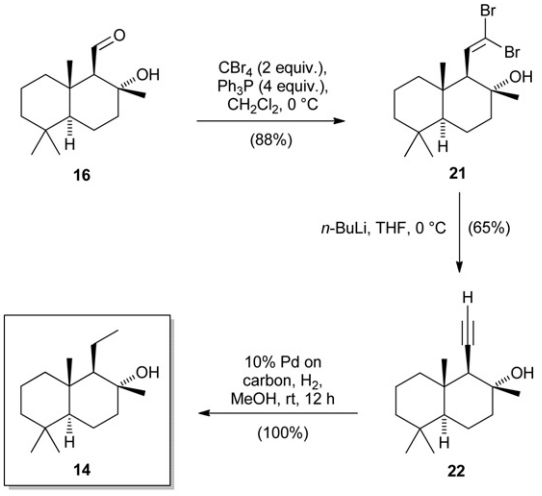
2.1. Synthesis of simplified labdane substrates

The starting point for the synthesis of ladbane **14** was the commercially available terpenoid (+)-sclareolide **18**, which was converted into diol **17** via a three-step sequence, which modified the known procedure of Kuchkova et al.[8] (Scheme 4). Addition of MeLi to **18** at −78 °C gave a ketone, which underwent Baeyer/Villiger oxidation on treatment with in situ generated trifluoroperacetic acid to give an acetate. Basic hydrolysis of this intermediate then gave **17**, which was subjected to a Swern oxidation to give aldehyde **16** in 78% yield.[11] However, efforts to methylenate this aldehyde to give alkene **15** proved to be problematic. Firstly, an attempted Wittig olefination of **16** with methylenetriphenylphosphorane, generated in situ from *n*-butyllithium and methyltriphenylphosphonium bromide, was unsuccessful, with the α,β-unsaturated aldehyde **20** being formed as the main product. Further attempts to methylenate the labile β-hydroxy aldehyde **16**, including use of the Nysted reagent[12] and the Oshimal/Lombardo reaction,[13] were also unsuccessful.

However, a Corey/Füchs reaction[14] of aldehyde **16** with CBr_4 and Ph_3P in CH_2Cl_2 at 0 °C successfully gave the geminal dibromide **21** in 88% yield, with no elimination by-products being formed (Scheme 5). In this process, the phosphorus ylide is generated under relatively non-basic conditions, so the base-labile β-hydroxy aldehyde **16** does not undergo elimination. Treatment of the dibromoolefin **21** with *n*-BuLi then generated the terminal alkyne **22** in 65% yield. Hydrogenation of terminal alkyne **22** gave the desired ethyl labdane alcohol **14** in quantitative yield.

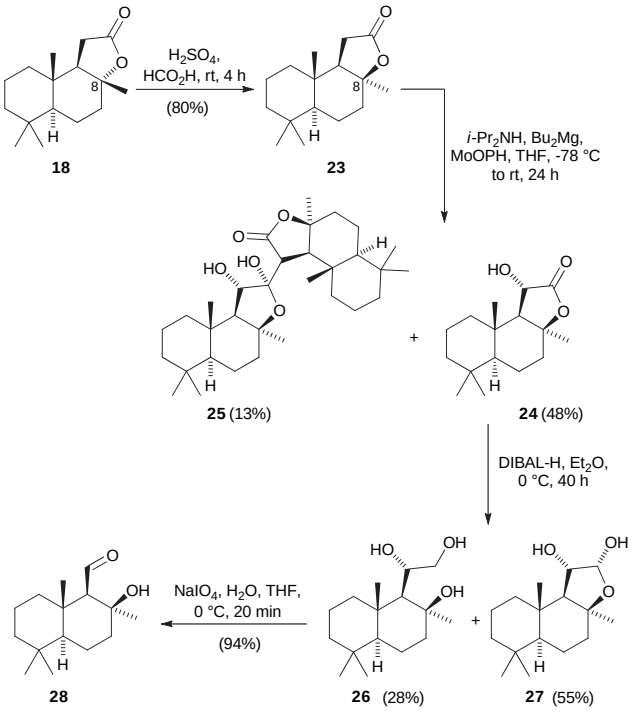


Scheme 4. Attempted synthesis of alkene **15** from (+)-sclareolide.



Scheme 5. Synthesis of ethyl labdane **14**.

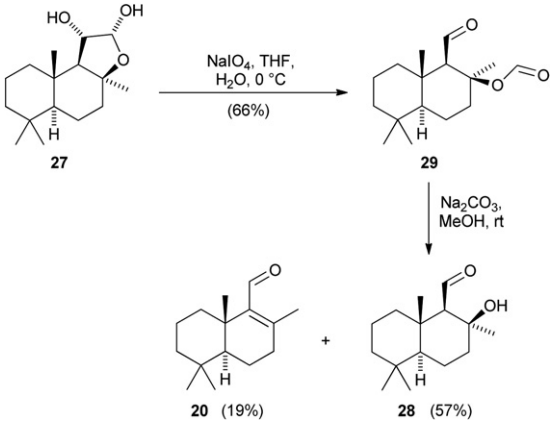
The first step in producing the epimeric labdane **14** was to induce inversion of the C-8 oxygen substituent of (+)-sclareolide **18** (Scheme 6). This was carried out according to the procedure of Quideau et al.,[9] with exposure of (+)-sclareolide to a mixture of sulfuric and formic acids at room temperature giving 8-*epi*-sclareolide **23** in 80% yield after crystallisation from hexane. The ease of this inversion of configuration at C-8 is attributed to the release of 1,3-diaxial interaction between the C-8- and C-10-methyl groups in **18**, as well as the formation of a more stable *cis*-fused lactone. Application of a similar three-step dehomologation procedure to **18**→**17** was unsuccessful with 8-*epi*-slareolide as the starting material because the more stable *cis*-fused lactone is less susceptible to nucleophilic attack by MeLi, and so the ring-opened products were formed in very low yields as under the reaction conditions deprotonation was presumably the favoured outcome. An alternative, more lengthy pathway for the dehomologation of **23** was therefore implemented. Firstly, the lactone of **23** was α-hydroxylated by treatment with base and MoO_5·pyridine·HMPA (MoOPH)[15] to give



Scheme 6. Synthesis of aldehyde **28** from (+)-sclareolide.

24 in 48% yield. In addition to the formation of **24**, some unreacted starting material was also recovered along with an undesired side product **25** resulting from competitive nucleophilic addition of the enolate intermediate to **24**. The stereochemistry of **24** is consistent with the expectation that the MoOPH would preferentially approach the enolate from the less hindered α-face. Reduction of **24** with DIBAL-H gave a mixture of triol **26** (28%) and lactol **27** (55%). The triol **26** could be easily converted to the desired aldehyde **28** by oxidative cleavage of the 1,2-diol functional group with $NaIO_4$ in THF/H_2O.

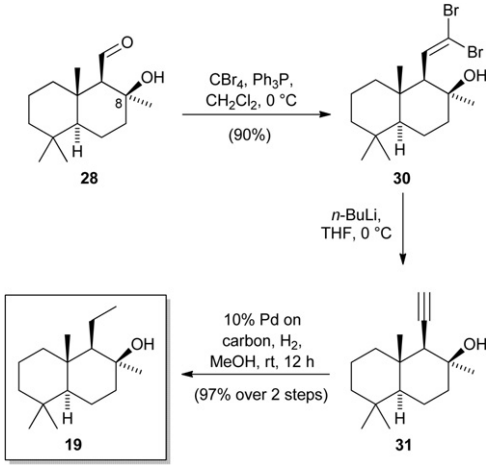
The lactol **27** initially seemed like an unusable side-product, as re-subjection of it to a variety of hydride sources failed to reduce it to the diol. ^{1}H NMR studies of **27** indicated that the hydroxy groups are *cis* to each other, (J=5.0 Hz), which explains the lack of reactivity to DIBAL-H and other hydride sources as a stable chelate with a metal ion could presumably be formed. However, given that the hydroxy groups of lactol **27** are *cis* to each other, it was reasoned that oxidative cleavage of this compound to give a formate ester would be possible. Indeed, treatment of **27** with $NaIO_4$ gave **29** in 66% yield (Scheme 7).



Scheme 7. Oxidative cleavage of *cis*-lactol **27**.

Hydrolysis of **29** with Na_2CO_3 in MeOH then gave aldehyde **28** in 57% yield and the α,β-unsaturated aldehyde **20** in 19% yield.

Aldehyde **28** was expected to be as sensitive towards base-induced elimination as the epimeric aldehyde **16**, if not more so as the hydroxyl substituent at C-8 is now axial. However, application of a similar Corey/Füchs reaction protocol to that used earlier was successful, with dibromoolefin **30** being formed in 90% yield (Scheme 8). Treatment with *n*-BuLi then gave terminal alkyne **31**, which was hydrogenated to give the saturated labdane **19** in 97% yield over two steps.

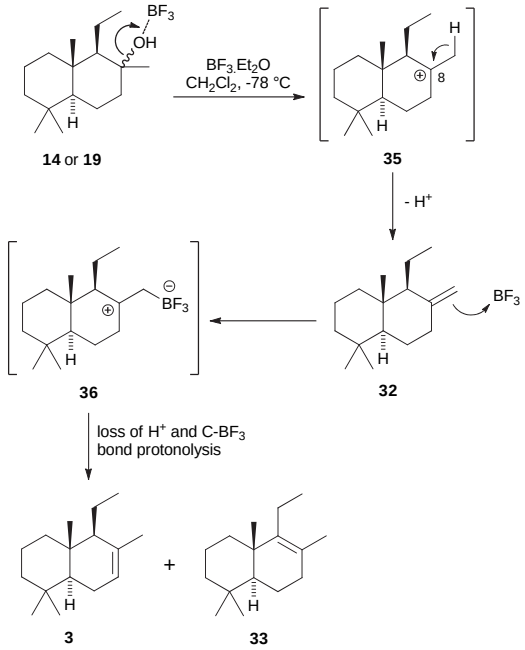


Scheme 8. Synthesis of ethyl labdane alcohol **19**.

2.2. Acid-catalysed rearrangements of labdanes

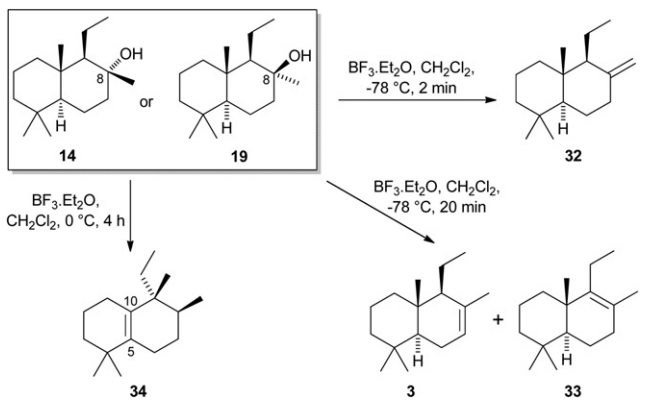
Labdanes **14** and **19** were initially treated with the strong Lewis acid $BF_3 \cdot Et_2O$ in CH_2Cl_2 (Scheme 9). It was envisaged that this reagent would complex with the hydroxyl group of the labdane derivatives, generating either a partial positive charge at C-8 or a full carbocation, which might then rearrange to give a clerodane skeleton. Firstly, **14** and **19** were separately stirred with 5 equiv of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −78 °C for 2 min before being quenched with water. TLC analysis of the crude product showed formation of a very non-polar product. NMR analysis showed that this product was the exocyclic alkene **32**, when the reaction was carried out with both **14** and **19** as the starting material. The ^1H NMR spectrum of this compound showed distinctive singlet peaks at 106.1 and 148.4 ppm indicative of an *exo*-methylene group. When the reactions were left at −78 °C for a longer period of time (20 min), NMR analysis of the crude product showed formation of a mixture of alkenes **3** and **33**, both of which feature an endocyclic double bond. Again it made no difference whether the axial or equatorial labdane alcohol was used. **3** and **33** could not be separated by column chromatography. Finally it was found that when the temperature was raised to 0 °C and the reaction time extended to 5 h, compound **34**, which has a halimane-type skeleton, was the sole product formed (as a single diastereomer). The ^{13}C NMR of this compound showed two quaternary signals at 136.8 and 132.5 ppm characteristic of the $\Delta^{5,10}$ internal carbon–carbon double bond.

Further reactions with $BF_3 \cdot OEt_2$ gave no further rearrangement beyond the halimane structure **34**. A proposed mechanistic reasoning for the reaction of **14** or **19** with BF_3 at −78 °C is shown in Scheme 10. It is thought that the initially formed 3° carbocation at C-8, **35**, undergoes proton loss from the *exo*-methyl group, thus giving rise to the observed *exo*-methylene compound **32**, which can be trapped as the kinetic product by quenching the reaction after 2 min. Further reaction of this alkene with BF_3 can generate the carbocation **36**, which can then lose a proton to give the more stable tri- and tetra-substituted alkenes **3** and **33**.

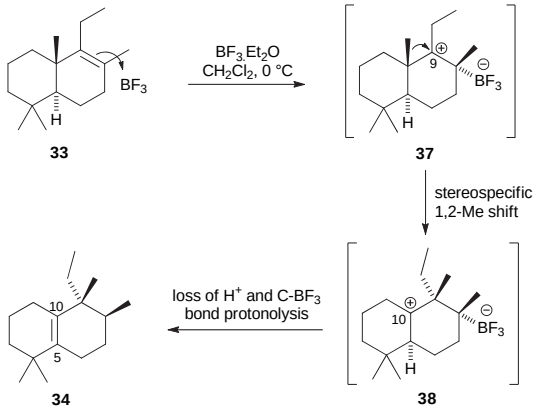


Scheme 10. Mechanism of BF_3-mediated rearrangement of **14** and **19** at −78 °C.

At higher temperature, the alkene **33** can go through further rearrangement by reaction with BF_3 to generate a carbocation centred at C-9, **37** (Scheme 11). This species can undergo



Scheme 9. BF_3-mediated rearrangement of labdanes **14** and **19**.

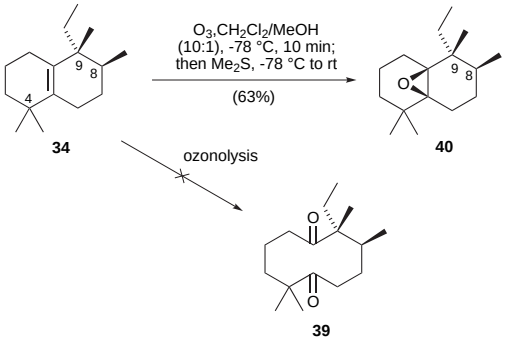


Scheme 11. Mechanism of BF_3-mediated rearrangement of **33** at 0 °C.

a stereospecific 1,2-methyl shift to form a carbocation centred at C-10, **38**, which can lose a proton to form the $\Delta^{5,10}$ double bond of the halimane skeleton. Importantly, the intermediacy of alkene **33** indicates that the rearrangements of **14** and **19** to **34** is not a concerted process, but proceeds via a series of rapidly interconverting carbocations.

TMSOTf was used as an alternative Lewis acid reagent, and in this case reaction of **14** and **19** with 2 equiv of TMSOTf in CH_2Cl_2 at 0 °C for 24 h formed mainly the halimane compound **34**, as observed by NMR analysis of the crude product.

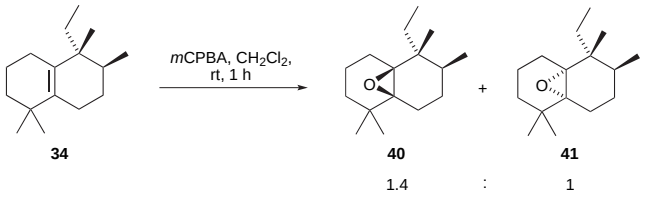
Given these results and our proposed mechanism for the rearrangement, the stereochemistry at C-8 and C-9 in the halimane structure **34** is clearly not derived from a concerted, stereospecific set of 1,2-methyl and hydride shifts. Rather, the stereochemistry at C-8 is due to attack of BF_3 at the α-face of **33**, opposite the axial Me group at C-10. To verify this stereochemical outcome, confirmation of the *cis* C-8, C-9 dimethyl configuration of **34** was sought. Thus, NOE NMR experiments were attempted on **34**, but due to the unfunctionalised nature of the hydrocarbon, the signals of the two methyl peaks at C-4, the methyl peak at C-8 and the methyl and ethyl peaks at C-9 were heavily overlapped in a variety of deuterated solvents, and the results were inconclusive. Attempted ozonolysis of **34** did not give the expected diketone product **39**. Instead, a single product was isolated in 63% yield; ^{13}C spectrum of this compound showed quaternary carbon signals at 68.8 and 69.9 ppm, which suggested that the epoxide **40** had been formed. The high resolution mass spectrum of **40** showed a molecular ion of formula $C_{16}H_{28}ONa^+$, which supported this assignment. The ^1H and ^{13}C NMR showed that the epoxide **40** was formed as a single stereoisomer, which indicates a surprising degree of stereoselectivity in this oxidation process. Epoxidation of **34** had significantly altered the chemical shifts of the methyl and ethyl peaks and a NOESY NMR experiment could be carried out on **40**, which showed that the Me groups attached to C-8 and C-9 are *syn* to each other and that the epoxide is *anti* to the C-9 ethyl substituent. It appears that the alkene **34** is too hindered to undergo ozonolysis due to the difficulty in forming the primary ozonide by a cycloaddition process. Instead ozone acts as an electrophilic oxygen source in the formation of the epoxide **40** (Scheme 12). Similar reactions of hindered alkenes with ozone are known.[16]



Scheme 12. Attempted ozonolysis of **34**—unexpected formation of epoxide **40**.

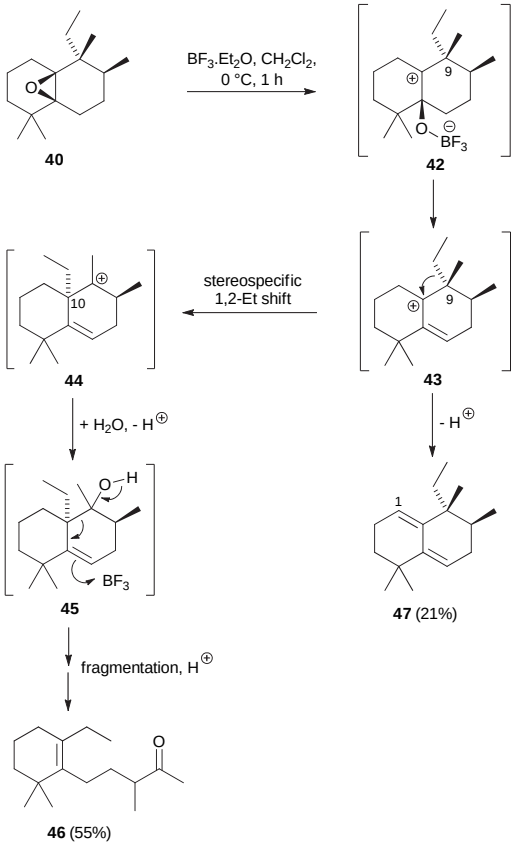
That the ozonolysis product **40** was the epoxide was further confirmed by reaction of alkene **34** with *m*CPBA in CH_2Cl_2. This gave a 1.4:1 inseparable mixture of **40** and its diastereomer **41** in 90% overall yield (Scheme 13).

Treatment of epoxide **40** with $BF_3 \cdot Et_2O$ was then carried out in an attempt to induce migration of one of the C-4 methyl groups to C-5. However, the only isolated products were tetra-substituted cyclohexene **46** (55%) and diene **47** (21%) (Scheme 14). In this case, attack of BF_3 at the epoxide appears to generate the allylic carbocation **43**, via **42**. Stereospecific 1,2-migration of the C-9 ethyl



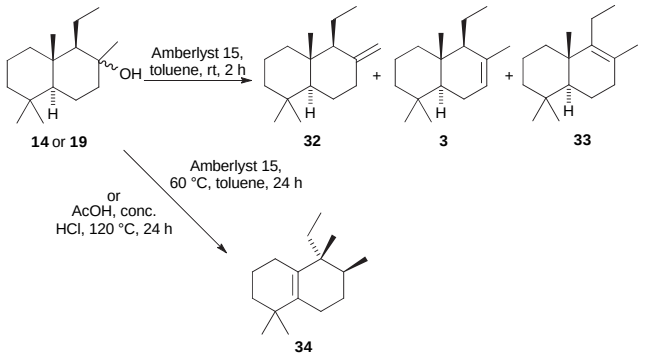
Scheme 13. Epoxidation of **34** with *m*CPBA.

substituent to C-10 could then give tertiary carbocation **44**, which could be trapped by trapped by H_2O to form tertiary alcohol **45**. Lewis-acid induced fragmentation of **45** could then give the tetra-substituted alkene **46**, the major reaction product. Alternatively, loss of a C-1 proton from **43** gives diene **47** as the minor product.



Scheme 14. BF_3-mediated rearrangement of epoxide **40**.

No further rearrangement of the halimane structure **34** was observed during the BF_3-mediated reactions, which indicates that **34** represents a thermodynamic sink for the overall reaction. Conversion of halimane **34** to clerodanes **1** or **2** is possibly hindered by formation of unfavourable 1,3-diaxial interactions between the C-5 and C-9 methyl substituents. The use of harsher reagents (such as strong protic acids) and higher temperatures to induce further rearrangement was also investigated. Stirring **14** and **19** with Amberlyst-15 in toluene at room temperature for 2 h gave an inseparable mixture of alkene products (Scheme 15). Heating the reaction at 60 °C for 24 h gave the halimane **34** as the main product (approx. 90% yield), with traces of other alkene by-products. Similar results were obtained when treating **14** and **19** with a mixture of acetic acid and concd HCl at 120 °C for 24 h. The protic acid induced rearrangements did not yield pure **34** (approx. 90% yield) as the $BF_3 \cdot Et_2O$ reaction had done, despite the higher temperature and

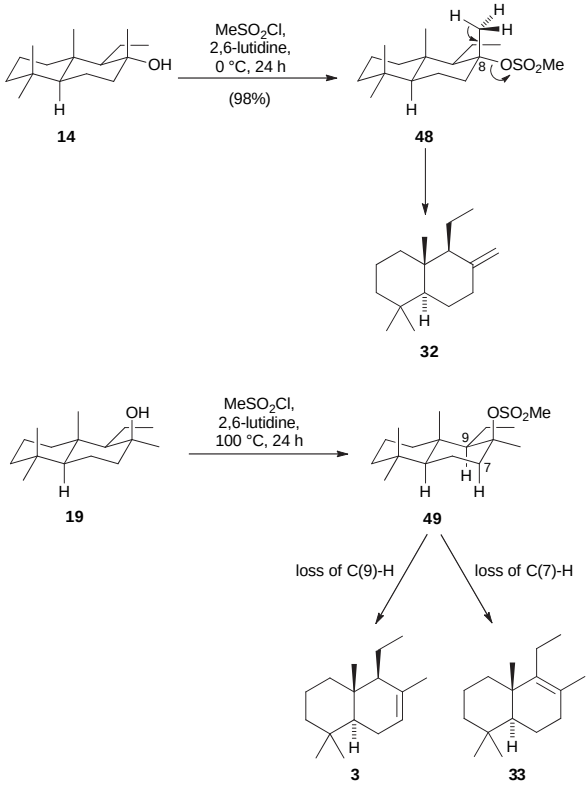


Scheme 15. Reactions of **14** and **19** with protic acids.

longer reaction time, which indicates that strong Lewis acids such as BF_3 are better reagents for this type of transformation.

The results so far indicate that the rearrangement of the labdanes **14** and **19** is occurring via a series of non-concerted 1,2-hydride and Me-shifts, even when the leaving group is *anti*-periplanar to the C–H bond. A dynamic equilibrium of carbocations is thus formed, with the major alkene product being dictated by thermodynamic stability of the molecule.

Up to this point, no difference had been observed in the reactions of the two epimers **14** and **19**. However, when the two compounds were separately treated with mesyl chloride in 2,6-lutidine at 0 °C the α-labdane alcohol **14** was found to react to give a non-polar product after 24 h, while the β-ladbane alcohol **19** showed no reaction. This is presumably because **19** has a more hindered axial hydroxyl group (due to 1,3-diaxial interactions). The product of the reaction of **14** with MsCl was found to be the *exo*-methylene compound **32** (Scheme 16). This alkene is selectively formed via an E2 mechanism as the only H atom *anti*-periplanar to the equatorial –OMs group of the intermediate mesylate **48** is situated on the C-8 methyl group. When the more hindered labdane alcohol **19** was heated at 100 °C, alkenes **3** and **33** were formed by a similar E2 elimination reaction, with in this case the *anti*-periplanar H atoms at C-7 and C-9 of mesylate **49** being removed.

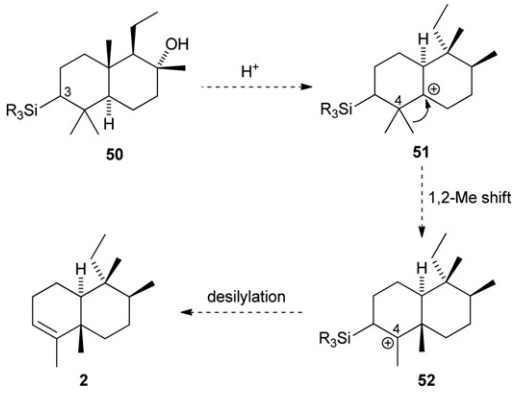


Scheme 16. Mesylation and subsequent E2 elimination of labdanes **14** and **19**.

3. Conclusion

The ethyl-substituted labdane alcohols **14** and **19** have been synthesised in an efficient manner from (+)-sclareolide. Attempts to induce a full rearrangement of these compounds with Lewis or protic acids to give clerodane derivatives was not possible, with either halimanes such as **34** or simple dehydration products such as **3** being formed instead. The fact that labdane **19** (with an axial hydroxyl group at C-8) and **14** (which has an equatorial hydroxyl group at C-8) display identical reactivity towards acidic reagents, combined with the intermediacy of alkenes such as **32** and **33**, indicates that the 1,2-hydride and methyl shifts that are observed proceed via an unconcerted mechanism involving an equilibrium of rapidly interconverting carbocations. In nature, the labdane to clerodane rearrangement presumably occurs under enzymatic control, with a carbocation equilibrium being formed inside an enzyme pocket. The C-4 intermediary cation, that is, the direct precursor of the clerodanes must be formed at the end of the rearrangement cascade. Thus, stabilisation of this cation by the enzyme must be required, either through π-cation interactions with aryl groups of side-chains or through electrostatic interactions with negatively charged residues.[17]

In order to execute a successful labdane to clerodane rearrangement, there needs to be a driving force for the second 1,2-methyl shift to prevent the reaction terminating at the halimane stage. Given that the halimane skeleton appears to be inherently more stable than the clerodane structure, a reaction system in which the C-4 centred carbocation precursor to the clerodanes is stabilised relative to the other carbocations in the rearrangement pathway would need to be designed. Trapping out this stabilised carbocation under kinetic control could thus form the clerodane ring system. One possibility for this would be to use a synthetic labdane precursor such as **50**, with a silicon substituent at C-3 (Scheme 17). Treatment of this compound with a Lewis acid should preferentially generate the carbocation **52** via **51**, with the carbocation centre at C-4 being stabilised by the C–Si bond at C-3.



Scheme 17. Possible formation of the clerodane ring system of **2** via Si-stabilised carbocation **52**.

4. Experimental section

4.1. General experimental procedures

All reactions were carried out under an atmosphere of nitrogen in glassware that had been dried at 100 °C overnight, unless otherwise specified. Proton magnetic resonance spectra were recorded on Brüker DPX200 (200 MHz), Brüker DQX400 (400 MHz) and Brüker AVC500 (500 MHz) spectrometers at ambient temperatures. Chemical shifts (δ_H) are reported as a ratio of parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and recorded to ±0.5 Hz. Proton spectra assignments are supported by $^1H-^1H$ COSY and HSQC where necessary. The order of citation is (i) multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br s, broad singlet), (ii) coupling constant (*J*) quoted in Hertz (Hz) to the nearest 0.5 Hz, (iii) number of equivalent nuclei (by integration). Carbon magnetic resonance spectra were recorded on Brüker DQX400 (400 MHz) and Brüker AVC500 (500 MHz) spectrometers at ambient temperatures. Chemical shifts (δ_H) are reported as a ratio of parts per million (ppm) and are referenced to the residual solvent peak. Carbon spectra assignments are supported by DEPT analysis and $^1H-^{13}C$ correlations where necessary. Mass spectra were recorded using Bruker MicroTOF (ES mode) and Micromass GCT (EI mode) spectrometers. Only molecular ions (M^+), fragments from molecular ions and other major peaks are reported. Spectra recorded on a Micromass Autospec spectrometer (EI mode) and Field Ionisation (FI) measurements are accurate to ±0.5 ppm. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film between NaCl plates (oils), and as KBr disks (solids). Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad. Melting points (mp) were recorded on a Reicher/Koffler block apparatus and are uncorrected. Optical rotations were obtained on a Perkin/Elmer 241 polarimeter. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates pre-coated with silica gel 60 F_{254} (1.05554). Visualisation was effected by staining with ceric ammonium molybdate, (CAM), followed by heating. Retention factors (R_f) are reported to ±0.05. Flash chromatography was performed using ICN silica 32–63, 60 Å.

*4.1.1. (1R,2R,4aS,8aS)-2-Hydroxy-2,5,5,8a-tetramethyl-decahydro-naphthalene-1-carbaldehyde (**16**)[11].* To a solution of DMSO (2.61 mL, 36.5 mmol) in CH_2Cl_2 (30 mL) was added oxalyl chloride (1.58 mL, 18.6 mmol) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. A solution of diol **17** (1.68 g, 6.98 mmol) in CH_2Cl_2 (30 mL) was then added and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (10.9 mL, 78.3 mmol) was then added and the reaction mixture was allowed to warm to room temperature over 30 min. The reaction mixture was then diluted with ice water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. Evaporation of the organic solvent under reduced pressure gave a residue, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 5:1) to give aldehyde **16** (1.30 g, 5.45 mmol, 78%) as a colourless oil. Data for **16**: R_f 0.25 (silica gel, hexanes/EtOAc, 4:1); mp 61–63 °C; $[\alpha]_D^{22}$ +37.0 (*c* 1, $CHCl_3$), lit. $[\alpha]_D^{22}$ +39.2; IR (thin film): 3365 (m br), 2930 (s), 1717 (m), 1700 (m), 1461 (s), 1378 (s), 1242 (s), 1191 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.82 (s, 3H), 0.88 (s, 3H), 0.96 (dd, *J*=12.0, 2.5 Hz, 1H), 1.11 (s, 3H), 1.16–1.54 (m, 6H), 1.37 (s, 3H), 1.61–1.74 (m, 2H), 1.81 (dt, *J*=12.5, 3.0 Hz, 1H), 1.95 (m, 1H), 2.07 (s, 1H), 10.01 (d, *J*=1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=17.6, 18.2, 19.9, 21.4, 25.3, 33.2, 33.3, 37.4, 39.8, 41.6, 42.7, 55.1, 71.3, 72.8, 208.2; HRMS calculated for $C_{15}H_{26}O_2$ [$M^{+\bullet}$] 238.1933, found 238.1934.

*4.1.2. (1R,2R,4aS,8aS)-1-(2,2-Dibromo-vinyl)-2,5,5,8a-tetramethyl-decahydro-naphthalen-2-ol (**21**).* Ph_3P (6.42 g, 24.5 mmol) was added to a solution of CBr_4 (4.06 g, 12.2 mmol) in CH_2Cl_2 (25 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. A solution of aldehyde **16** (1.46 g, 6.12 mmol) in CH_2Cl_2 (25 mL) was added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with Et_2O, and the organic layer was washed with brine and dried with $MgSO_4$. Evaporation of the organic solvent gave a residue, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 8:1) to yield the dibromide **21** (2.12 g, 5.38 mmol, 88%) as a white solid. Data for **21**: R_f 0.55 (hexanes/EtOAc, 4:1); mp 75–77 °C; $[\alpha]_D^{22}$ +7.0 (*c* 1, $CHCl_3$); IR (KBr disc): 3439 (w br), 2886 (s), 2725 (m), 1744 (w), 1461 (s), 1377 (s), 1312 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.81 (s, 3H), 0.90 (s, 3H), 0.92 (s, 3H), 0.99 (dd, *J*=12.0, 2.5 Hz, 1H), 1.08 (m, 1H), 1.16 (m, 1H), 1.23 (s, 3H), 1.30 (m, 1H), 1.37–1.62 (m, 6H), 1.70 (m, 1H), 1.93 (dt, *J*=13.0, 3.5 Hz, 1H), 2.29 (d, *J*=11.0 Hz, 1H), 6.45 (d, *J*=11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.2, 18.3, 20.2, 21.6, 24.8, 33.3, 33.4, 38.9, 39.6, 41.8, 43.2, 55.7, 65.9, 73.1, 91.2, 136.3; HRMS calculated for $C_{16}H_{26}Br_2O$ [$M^{+\bullet}$] 394.0331, found 394.0310.

*4.1.3. (1R,2R,4aS,8aS)-1-Ethynyl-2,5,5,8a-tetramethyl-decahydro-naphthalen-2-ol (**22**).* A solution of *n*-butyllithium (1.6 M in hexane, 10.1 mL, 16.1 mmol) was added to a solution of dibromide **21** (2.12 g, 5.38 mmol) in anhydrous THF (25 mL) at −78 °C and the resulting mixture was stirred at this temperature for 45 min. The reaction mixture was then quenched by the addition of saturated aqueous NH_4Cl solution (25 mL). Et_2O (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2×50 mL). The combined organics were then washed with water and brine, dried over Mg_2SO_4 and filtered. Concentration under reduced pressure gave a residue, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 10:1) to give alkyne **22** as a colourless oil (0.82 g, 3.50 mmol, 65%). Data for **22**: R_f 0.40 (silica gel, hexanes/EtOAc, 4:1); mp 91–93 °C; $[\alpha]_D^{22}$ +3.0 (*c* 1, $CHCl_3$); IR (KBr disc): 3553 (s), 3442 (br s), 3296 (s), 3270 (s), 2924 (s), 2098 (w), 1386 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.79 (s, 3H), 0.86 (m, 1H), 0.87 (s, 3H), 0.97 (s, 3H), 0.98 (s, 1H), 1.11–1.28 (m, 2H), 1.33 (s, 3H), 1.36–1.49 (m, 3H), 1.55–1.69 (m, 2H), 1.86 (m, 1H), 1.92 (dt, *J*=12.5, 3.5 Hz, 1H), 2.12 (br s, 1H), 2.21 (d, *J*=2.5 Hz, 1H), 2.29 (d, *J*=2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.0, 18.5, 19.9, 21.4, 25.1, 33.2, 33.3, 37.9, 40.5, 40.8, 42.0, 54.8, 57.8, 71.8, 73.7, 82.9; HRMS calculated for $C_{16}H_{26}O$ [$M^{+\bullet}$] 234.1984, found 234.1984.

*4.1.4. (1R,2R,4aS,8aS)-1-Ethyl-2,5,5,8a-tetramethyl-decahydro-naphthalen-2-ol (**14**).* A catalytic amount of 10% Pd on carbon (70 mg) was added to a solution of **22** (689 mg, 2.94 mmol) in anhydrous MeOH under a nitrogen atmosphere at room temperature. The reaction flask was then purged with hydrogen gas and left stirring at room temperature for 24 h. The resulting solution was filtered through Celite and the filtrate was evaporated to give **14** as a white solid (700 mg, 2.94 mmol, 100%). Data for **14**: R_f 0.45 (silica gel, hexanes/EtOAc, 4:1); mp 78–79 °C; $[\alpha]_D^{22}$ −13.2 (*c* 1, $CHCl_3$); IR (KBr disc): 3418 (br s), 2927 (s), 2869 (s), 1465 (m), 1386 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.79 (apparent br s, 6H), 0.87 (s, 3H), 0.90–1.06 (m, 6H), 1.13 (s, 3H), 1.14 (m, 1H), 1.18–1.51 (m, 7H), 1.55–1.72 (m, 3H), 1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.4, 18.1, 18.3, 18.5, 20.6, 21.5, 23.8, 33.2, 33.5, 39.2, 39.7, 42.0, 44.5, 56.1, 64.4, 74.5; HRMS calculated for $C_{16}H_{30}O$[$M^{+\bullet}$] 238.2297, found 238.2296.

*4.1.5. (1S,3aS,5aS,9aS,9bS)-1-Hydroxy-3a,6,6,9a-tetra-methyl-decahydro-naphtho[2,1-b]furan-2(3aH)-one (**24**)[9].* To a stirred solution of diisopropylamine (20.2 mL, 144.1 mmol) in anhydrous THF

(100 mL) was added dropwise a 1.0 M solution of Bu_2Mg in hexane (72.0 mL, 72.0 mmol). The resulting solution was heated at reflux for 1 h, after which time it was allowed to cool to room temperature. A solution of 8-*epi*-sclareolide **23**[9] (5.17 g, 20.7 mmol) in anhydrous THF (25 mL) was then added dropwise. The reaction mixture was stirred at room temperature for 1 h, then cooled to −78 °C for 2 h before the addition of solid oxodi-peroxymolybdenum(pyridine)-(hexamethylphosphoric triamide) MoOPH (20.95 g, 48.0 mmol) in one portion. The mixture was allowed to warm up to −25 °C overnight. Addition of water (7 mL) to the resulting brown solution gave a white precipitate, which was filtered, and the filtrate was extracted with Et_2O (4×50 mL). The combined extracts were washed with 10% aqueous HCl solution and brine, then dried over $MgSO_4$, filtered and evaporated to give a beige solid. This crude product mixture was purified by flash chromatography (silica gel, hexanes/EtOAc, 10:1) to yield **24** (2.65 g, 9.95 mmol, 48%) as a white solid. Data for **24**: R_f 0.20 (silica gel, hexanes/EtOAc, 4:1); mp 83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (s, 3H), 0.90 (s, 3H), 0.94 (s, 3H), 1.02–1.23 (m, 3H), 1.39–1.67 (m, 5H), 1.53 (s, 3H), 1.71–1.85 (m, 3H), 2.06 (m, 1H), 3.64 (br s 1H), 4.39 (d, J=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.6, 18.0, 18.1, 21.8, 31.6, 32.8, 33.2 (two peaks superimposed), 35.8, 41.8, 42.1, 48.7, 61.3, 71.3, 86.4, 177; HRMS calculated for $C_{16}H_{25}O_3[M-H]^-$ 265.1809, found 265.1812.

Second product **25** also obtained as a white solid (689 mg, 1.33 mmol, 13%). Data for **25**: R_f 0.65 (silica gel, hexanes/EtOAc, 4:1); mp 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85 (s, 6H), 0.90 (s, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.00–1.05 (m, 1H), 1.07 (s, 3H), 1.09–1.27 (m, 5H), 1.39 (s, 3H), 1.41–1.47 (m, 4H), 1.49 (s, 3H), 1.52–1.77 (m, 11H), 1.86–1.99 (m, 2H), 2.74 (d, J=4.0 Hz, 1H), 2.80 (d, J=8.5 Hz, 1H), 4.18 (t, J=9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.2, 17.7, 17.9, 18.1, 18.2, 18.6, 21.1, 21.8, 29.1, 31.7, 31.9, 32.2, 32.2, 33.3, 33.4, 34.0, 36.6, 36.9, 41.9, 42.3, 42.6, 44.4, 46.2, 47.8, 50.2, 57.3, 62.5, 75.9, 81.4, 88.0, 100.6, 178.9 ppm; HRMS calculated for $C_{32}H_{51}O_5[M-H]^-$ 515.3742, found 515.3740.

*4.1.6. (1S,3aS,5aS,9aS,9bS)-3a,6,6,9a-Tetramethyldodeca-hydronaphtho-[2,1-b]furan-1,2-diol (**27**) and (S)-1-((1S,2S,4aS,8aS)-2-hydroxy-2,5,5,8a-tetramethyl-decahydro-naphthalen-1-yl)ethane-1,2-diol (**26**).* To a stirred ice-cold solution of **24** (1.99 g, 7.47 mmol) in dry Et_2O (150 mL) was added dropwise a 1 M solution of DIBAL-H in THF (57.4 mL, 57.4 mmol). The reaction mixture was allowed to warm up to room temperature and stirring was continued for 40 h, after which time it was quenched with a 10% aqueous solution of HCl (100 mL). The organic layers were separated, and the aqueous layer was extracted with Et_2O (4×50 mL). The combined organic extracts were washed with a saturated aqueous solution of K_2CO_3 (100 mL) and brine (100 mL), and then dried over Mg_2SO_4. After filtration, evaporation under reduced pressure gave a white solid, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 8:1) to yield **27** (1.10 g, 4.10 mmol, 55%) as a white solid. Data for **27**: R_f 0.50 (silica gel, hexanes/EtOAc, 1:1); mp 122–125 °C; $[\alpha]_D^{25}$ −63.4 (c 0.74, $CHCl_3$); IR (KBr disc) 3458 (br s), 3330 (br s), 2921 (s), 2863 (s), 2664 (w), 1461 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (s, 3H), 0.91 (s, 3H), 0.95 (s, 3H), 0.96–1.22 (m, 5H), 1.34–1.39 (m, 1H), 1.41 (s, 3H), 1.42–1.65 (m, 6H), 1.80–1.92 (m, 2H), 4.20 (t, J=4.5 Hz, 1H), 5.26 (d, J=5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 18.1, 18.4, 21.9, 32.5, 33.2, 33.4, 34.0, 35.6, 42.1, 42.9, 48.8, 64.3, 74.5, 82.6, 96.1; HRMS calculated for $C_{16}H_{28}NaO_3[M^{+\bullet}]$ 291.1931, found 291.1923.

Further elution gave **26** as a white solid (568 mg, 2.10 mmol, 28%). Data for **26**: R_f 0.25 (silica gel, hexanes/EtOAc, 1:1); mp 143–146 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ=0.86 (s, 3H), 0.87 (s, 3H), 1.22 (s, 3H), 1.31 (s, 3H), 3.50 (s, 1H), 3.75–3.87 (m, 3H), 4.21–4.25 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ=17.2, 19.0, 19.2, 22.2, 32.7, 34.0, 34.1, 40.1, 41.2, 42.5, 45.1, 57.2, 62.0, 67.7, 73.5, 74.3; HRMS calculated for $C_{16}H_{30}NaO_3[M^{+\bullet}]$ 293.2087, found 293.2084.

*4.1.7. (1R,2S,4aS,8aS)-1-Formyl-2,5,5,8a-tetramethyl-decahydronaphthalen-2-yl formate (**29**).* To an ice-cold, stirred solution of **27** (497 mg, 1.85 mmol) in THF (25 mL) was added dropwise a solution of $NaIO_4$ (463 mg, 2.17 mmol) in water (25 mL). After stirring for 20 min, the resulting precipitate was filtered and the filtrate was extracted with Et_2O (4×40 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure gave the aldehyde **29** as a white solid (326 mg, 1.22 mmol, 66%). Data for **29**: R_f 0.75 (silica gel, hexanes/EtOAc, 1:1); mp 69–72 °C; $[\alpha]_D^{20}$ +28.8 (c 0.56, $CHCl_3$); IR (KBr disc) 3409 (w), 2963 (s), 2752 (w), 1711 (s), 1460 (m), 1391 (m), 1166 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.83 (d, J=3.0 Hz, 1H), 0.85–0.87 (m, 3H), 0.88 (s, 3H), 1.03–1.21 (m, 2H), 1.29 (s, 3H), 1.31–1.47 (m, 3H), 1.51 (s, 3H), 1.52–1.67 (m, 5H), 2.85 (dt, J=15.0, 3.0 Hz, 1H), 8.12 (s, 1H), 9.92 (d, J=5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.8, 17.8, 18.0, 21.7, 26.1, 33.2, 33.4, 36.9, 38.1, 39.8, 41.5, 55.0, 70.7, 83.2, 159.8, 205.2; HRMS calculated for $C_{16}H_{26}O_3[M^{+\bullet}]$ 266.1882, found 266.1893.

*4.1.8. (1R,2S,4aS,8aS)-2-Hydroxy-2,5,5,8a-tetramethyl-decahydronaphthalene-1-carbaldehyde (**28**).* To an ice-cold stirred solution of **26** (303 mg, 1.12 mmol) in THF (20 mL) was added dropwise a solution of $NaIO_4$ (280 mg, 1.31 mmol) in water (20 mL). After stirring for 20 min at 0 °C, the resulting precipitate was filtered and the filtrate was extracted with Et_2O (4×35 mL). The combined extracts were then washed with aqueous $Na_2S_2O_3$ solution and brine, dried over Mg_2SO_4 and filtered. Evaporation of the solvent under reduced pressure gave the aldehyde **28** as a white solid (250 mg, 1.05 mmol, 94%). Data for **28**: R_f 0.50 (silica gel, hexanes/EtOAc, 5:1); mp 64–68 °C; $[\alpha]_D^{21}$ +122.4 (c 0.37, $CHCl_3$); IR (KBr disc) 3512 (s), 2945 (s), 2849 (m), 2741 (w), 1698 (s), 1459 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=0.84 (s, 3H), 0.88 (s, 3H), 0.89–0.96 (m, 1H), 1.15 (s, 3H), 1.18 (s, 3H), 1.15–1.80 (m, 11H), 2.12 (d, J=3.0 Hz, 1H), 10.04 (d, J=2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.9, 17.9, 18.2, 21.5, 31.0, 33.3, 33.5, 39.8, 40.2, 41.4, 41.6, 55.1, 69.3, 71.3, 209.7; HRMS calculated for $C_{15}H_{26}NaO_2[M^{+\bullet}]$ 261.1825, found 261.1823.

*4.1.9. (1R,2S,4aS,8aS)-1-(2,2-Dibromo-vinyl)-2,5,5,8a-tetramethyldeca-hydronaphthalen-2-ol (**30**).* Ph_3P (1.83 g, 6.96 mmol) was added to a solution of CBr_4 (1.15 g, 3.48 mmol) in CH_2Cl_2 (25 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. A solution of aldehyde **28** (415 mg, 1.74 mmol) in CH_2Cl_2 (15 mL) was then added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The mixture was then diluted with Et_2O (100 mL), washed with brine and dried over $MgSO_4$. Evaporation of the organic solvents under reduced pressure gave a residue, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 8:1) to yield dibromide **30** as a white solid (616 mg, 1.56 mmol, 90%). Data for **30**: R_f 0.70 (silica gel, hexanes/EtOAc, 5:1); mp 66–68 °C; $[\alpha]_D^{23}$ +39.5 (c 1.32, $CHCl_3$); IR (KBr disc) 3614 (w br), 2909 (s), 2846 (s), 1603 (m), 1456 (m), 1388 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (s, 3H), 0.90 (s, 3H), 0.91–0.94 (m, 1H), 1.08 (s, 3H), 1.14 (s, 3H), 1.16–1.23 (m, 1H), 1.36–1.45 (m, 2H), 1.47–1.66 (m, 6H), 1.80 (d, J=7.5 Hz, 1H), 1.99 (d, J=11.0 Hz, 1H), 6.62 (d, J=11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.0, 18.1, 18.2, 21.8, 30.8, 33.3, 33.5, 39.7, 41.9, 42.2, 55.3, 62.9, 72.4, 77.2, 89.4, 137.6; HRMS calculated for $C_{16}H_{26}Br_2O$ $[M^{+\bullet}]$ 394.0331, found 394.0326.

*4.1.10. (1R,2S,4aS,8aS)-1-Ethynyl-2,5,5,8a-tetramethyl-decahydronaphthalen-2-ol (**31**).* A solution of *n*-BuLi in hexanes (1.6 M, 7.45 mL, 11.9 mmol) was added to a solution of dibromide **30**

(1.57 g, 3.98 mmol) in anhydrous THF (25 mL) at −78 °C and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was then quenched by the addition of saturated aqueous NH_4Cl solution (25 mL). The mixture was then extracted with Et_2O (2×50 mL), washed with water (50 mL) and brine (50 mL) and then dried over $MgSO_4$. Filtration and evaporation of the organic solvents in vacuo gave crude alkyne **31**, which was used without further purification. Data for **31**: R_f 0.60 (silica gel, hexanes/EtOAc, 4:1); $[\alpha]_D^{21}$ +18.4 (*c* 0.49, $CHCl_3$); IR (KBr disc) 3519 (s), 3440 (m br), 3289 (s), 2924 (s), 2108 (w), 1460 (m), 1385 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.80 (dd, *J*=12.0, 2.5 Hz, 1H), 0.85 (s, 3H), 0.88 (s, 3H), 0.91–0.99 (m, 1H), 1.16 (s, 3H), 1.28 (s, 3H), 1.30–1.44 (m, 3H), 1.45–1.59 (m, 3H), 1.59–1.69 (m, 1H), 1.87 (dq, 13.0, 3.0 Hz, 1H), 1.94 (dt, *J*=14.0, 3.0 Hz, 1H), 2.05 (d, *J*=2.5 Hz, 1H), 2.26 (d, *J*=2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 18.1, 18.3, 21.6, 31.6, 33.2, 33.3, 37.8, 39.6, 40.5, 42.0, 54.7, 55.1, 71.0, 74.1, 82.7; HRMS calculated for $C_{16}H_{26}O$ [$M^{+\bullet}$] 234.1984, found 234.1975.

*4.1.11. (1R,2S,4aS,8aS)-1-Ethyl-2,5,5,8a-tetramethyl-decahydronaphthalen-2-ol (**19**).* A catalytic amount of 10% palladium on carbon (90 mg) was added to a solution of alkyne **31** (895 mg, 3.82 mmol) in anhydrous MeOH (20 mL) at room temperature under a nitrogen atmosphere. The system was then purged with hydrogen and left stirring for 24 h under a hydrogen atmosphere. Careful TLC analysis showed that the starting material had been consumed and a less-polar product had been formed. The reaction mixture was then filtered through Celite (washed with MeOH) and the filtrate was evaporated to give alkane **19** as a white solid (910 mg, 3.82 mmol) in 97% yield for two steps. Data for **19**: R_f 0.65 (silica gel, hexanes/EtOAc, 4:1); mp 49–51 °C; $[\alpha]_D^{25}$ +6.4 (*c* 0.56, $CHCl_3$); IR (KBr disc) 3520 (m br), 2926 (s), 2866 (s), 1711 (w), 1458 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.71–0.81 (m, 2H), 0.83 (s, 3H), 0.84–0.86 (m, 1H), 0.87 (s, 3H), 0.88–0.92 (m, 1H), 0.94 (s, 3H), 0.98 (t, *J*=15.0, 8.0 Hz, 3H), 1.14 (s, 3H), 1.16–1.23 (m, 1H), 1.28–1.46 (m, 4H), 1.47–1.52 (m, 2H), 1.53–1.56 (m, 1H), 1.56–1.64 (m, *J*=13.0, 3.5, 3.5 Hz, 1H), 1.68–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.0, 17.9, 18.0, 18.2, 18.3, 21.6, 30.5, 33.2, 33.4, 38.9, 39.0, 42.0, 42.1, 55.9, 61.3, 73.2; HRMS calculated for $C_{16}H_{30}O$[$M^{+\bullet}$] 238.2297, found 238.2298.

*4.1.12. Preparation of (1R,2S)-1-ethyl-1,2,5,5-tetra-methyl-1,2,3,4,5,6,7,8-octahydro-naphthalene (**34**).* To an ice-cold solution of **14** (53 mg, 0.22 mmol) in CH_2Cl_2 (3 mL), was added dropwise $BF_3{\cdot}OEt_2$ (0.14 mL, 1.11 mmol). After stirring at 0 °C for 5 h, the organic layer was extracted with CH_2Cl_2 (40 mL), dried over $MgSO_4$ and filtered. Evaporation of the solvent gave **34** as a pale yellow oil (47 mg, 0.21 mmol, 95%). Data for **34**: R_f 0.80 (silica gel, hexanes/EtOAc, 20:1); $[\alpha]_D^{24}$ −101.6 (*c* 0.38, $CHCl_3$); IR (film) 2964 (s), 2926 (s), 2877 (s), 1731 (w), 1459 (m), 1380 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=0.67 (t, *J*=7.5 Hz, 3H), 0.80 (s, 3H), 0.83 (d, *J*=7.0 Hz, 3H), 0.97 (s, 3H), 0.99 (s, 3H), 1.27–1.66 (m, 9H), 1.72–1.82 (m, 1H), 1.90–2.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=8.4, 16.1, 20.0, 21.0, 25.2, 25.7, 27.2, 27.7, 28.3, 29.3, 32.7, 34.5, 40.0, 40.7, 132.5, 136.8; HRMS calculated for $C_{16}H_{28}$[$M^{+\bullet}$] 220.2191, found 220.2195.

*4.1.13. Preparation of (4aS,8aS)-8-ethyl-4,4,7,8a-tetra-methyl-1,2,3,-4,4a,5,6,8a-octahydro-naphthalene (**33**) and (4aS,5S,8aS)-5-ethyl-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydro-naphthalene (**3**).* To a solution of **14** (50 mg, 0.21 mmol) in CH_2Cl_2 (3 mL), was added dropwise $BF_3{\cdot}OEt_2$ (0.13 mL, 1.05 mmol). After stirring at −78 °C for 20 min the reaction was quenched with H_2O and the organic layer was extracted with CH_2Cl_2 (40 mL), dried over $MgSO_4$ and filtered. Evaporation of the solvent gave an inseparable mixture of **33** and **3** as a pale yellow oil, which could not be fully assigned due to signal overlap in the NMR spectrum. Data for **33**: R_f 0.80 (silica gel, hexanes/EtOAc, 20:1); ^1H NMR ($CDCl_3$, 400 MHz): no olefinic peaks seen; ^{13}C NMR (100 MHz, $CDCl_3$): δ=142.3, 125.0; HRMS calculated for $C_{16}H_{28}$[$M^{+\bullet}$] 220.2191, found 220.2192 (of mixture of **33** and **3**). Data for **3**: R_f 0.80 (silica gel, hexanes/EtOAc, 20:1); ^1H NMR ($CDCl_3$, 400 MHz): δ=5.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.6, 18.9, 21.9, 22.1, 23.8, 33.0, 33.3, 33.7, 42.2, 57.2, 122.0, 135.6.

*4.1.14. Preparation of (1R,2S)-1-ethyl-1,2,5,5-tetra-methyl-1,2,3,4,5,-6,7,8-octahydro-naphthalene oxide (**40**).* To a solution of **34** (185 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (10 mL) and MeOH (1 mL), O_3 was bubbled through for 10 min at −78 °C. After this time, O_2 was passed through the reaction mixture for 2 min until residual ozone was removed. Me_2S (0.50 mL, 6.81 mmol) was then added at −78 °C and stirring continued until the reaction mixture warmed up to room temperature over 3 h. Evaporation of the organic solvents in vacuo gave a residue, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 50:1) to yield the epoxide **40** as a colourless liquid (126 mg, 0.53 mmol, 63%). Data for **40**: R_f 0.50 (silica gel, hexanes/EtOAc, 20:1); IR (film) 2962 (s), 2920 (s), 2878 (s), 1465 (m), 1383 (m), 1261 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.74 (d, *J*=6.5 Hz, 3H), 0.81 (s, 3H), 0.86 (t, *J*=7.5 Hz, 3H), 0.89–0.93 (m, 1H), 0.96 (s, 3H), 0.98 (s, 3H), 1.00–1.11 (m, 2H), 1.26–1.37 (m, 2H), 1.37–1.45 (m, 4H), 1.64 (ddd, *J*=14.0, 12.0, 4.5 Hz, 1H), 1.68–1.76 (m, 1H), 1.80–1.86 (m, 1H), 1.89 (dt, *J*=14.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.9, 16.4, 17.4, 17.8, 24.3, 24.9, 26.4, 26.4, 26.9, 29.5, 32.8, 33.2, 38.0, 39.3, 68.8, 69.9; HRMS calculated for $C_{16}H_{28}ONa$ [$M^{+\bullet}$] 259.2032, found 259.2035.

*4.1.15. Preparation of (1R,2S)-1-ethyl-1,2,5,5-tetra-methyl-1,2,3,5,6,7-hexahydro-naphthalene (**47**) and 5-(2-ethyl-6,6-dimethylcyclohex-1-en-1-yl)-3-methylpentan-2-one (**46**).* To a stirred solution of **40** (62 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (3 mL) was added $BF_3{\cdot}OEt_2$ (0.1 mL, 0.81 mmol). After stirring at −78 °C for 1 h, the reaction mixture was quenched with H_2O and the organic layer was extracted with CH_2Cl_2 (30 mL), dried over $MgSO_4$ and filtered. Evaporation of the solvent gave a pale yellow oil, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 50:1) to yield **47** (12 mg, 0.06 mmol, 21%). Data for **47**: R_f 0.70 (silica gel, hexanes/EtOAc, 16:1); IR (film) 3041 (w), 2964 (s), 2921 (s), 1456 (m), 1379 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ=0.77 (t, *J*=7.5 Hz, 3H), 0.81 (d, *J*=7.0 Hz, 3H), 0.91 (s, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 1.21–1.33 (m, 2H), 1.36–1.50 (m, 2H), 1.55–1.66 (m, 1H), 1.79 (dt, *J*=18.5, 4.5 Hz, 1H), 2.10–2.24 (m, 1H), 2.32–2.40 (m, 2H), 5.39–5.42 (m, 1H), 5.44–5.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=8.1, 16.1, 21.5, 23.3, 27.2, 28.2, 30.7, 31.1, 33.4, 34.7, 36.9, 40.0, 115.8, 120.6, 138.1, 141.0.

Further elution gave **46** (34 mg, 0.14 mmol 55%) as a colourless oil. Data for **46**: R_f 0.25 (silica gel, hexanes/EtOAc, 16:1); ^1H NMR ($CDCl_3$, 500 MHz): 0.95 (t, *J*=7.5 Hz, 3H), 0.96 (s, 3H), 0.98 (s, 3H), 1.11 (d, *J*=8.0 Hz, 3H), 1.37–1.44 (m, 4H), 1.53–1.58 (m, 2H), 1.65–1.76 (m, 2H), 1.85–1.96 (m, 4H), 2.15 (s, 3H), 2.50 (sextet, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.0, 16.0, 19.5, 26.0, 26.4, 28.0, 28.71, 28.73, 29.4, 34.3, 34.9, 39.9, 48.1, 133.1, 136.1, 212.6; HRMS calculated for $C_{16}H_{28}ONa$ [$M^{+\bullet}$] 259.2032, found 259.2036.

*4.1.16. (4aS,5S,8aS)-5-Ethyl-1,1,4a-trimethyl-6-methylene-decahydro-naphthalene (**32**).* To an ice-cold stirred solution of **14** (52 mg, 0.22 mmol) in 2,6-lutidine (2.5 mL) was added dropwise a solution of $MeSO_2Cl$ (0.1 mL, 1.29 mmol). After stirring for 24 h at 0 °C the reaction mixture was poured onto ice, neutralised with 10% HCl solution and extracted with Et_2O (4×10 mL). The combined extracts were then washed with water and brine, dried over $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure gave the olefin **32** as a pale yellow oil (47 mg, 0.21 mmol, 98%): Data for **32**: R_f 0.80 (silica gel, hexanes/EtOAc, 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ=0.68 (s, 3H), 0.81 (s, 3H), 0.88 (s, 6H), 0.93–1.80 (m, 12H), 1.91–2.10 (m, 1H), 2.40 (ddd, *J*=13.0, 4.5, 2.5 Hz, 1H), 4.51 (d,

J=1.5 Hz, 1H), 4.83 (d, J=1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.5, 14.4, 19.4, 21.7, 24.5, 33.6, 33.6, 38.4, 39.1, 39.7, 42.2, 42.3, 55.5, 59.1, 106.1, 148.4 ppm; HRMS calculated for $C_{16}H_{28}[M^{+\bullet}]$ 220.2191, found 220.2194.

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