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Synthesis of novel, simplified, C-7 substituted eleutheside analogues with potent microtubule-stabilizing activity

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Abstract—The synthesis of a number of novel, simplified, C-7 substituted eleutheside analogues with potent tubulin-assembling and microtubule-stabilizing properties is described, using ring closing metathesis as the key-step for obtaining the 6–10 fused bicyclic ring system. The RCM precursors were synthesized starting from aldehyde **3** [prepared in six steps on a multigram scale from *R*-(−)-carvone in 30% overall yield] via multiple stereoselective Hafner–Duthaler allyltitanations and/or Brown allylborations. 'Second generation' RCM-catalyst **15** gave the desired ring closed ten-membered carbocycles as single *Z* stereoisomers in good yields. The RCM stereochemical course (100% *Z*) is likely to reflect thermodynamic control. Molecular mechanics and semi-empirical calculations also show that the *Z* stereoisomers of these ten-membered carbocycles are consistently more stable than the *E*. The crucial role of the homoallylic and allylic substituents and of their protecting groups for the efficiency of the RCM reactions is discussed. In particular, we have found that *p*-methoxyphenyl (PMP) protected allylic alcohols, the products of a stereoselective oxyallylation, are compatible with the RCM reaction and give better yields than the corresponding free allylic alcohols. One of the simplified analogues of the natural product (**44**, lacking inter alia the C-4/C-7 ether bridge) retains potent microtubule-stabilizing activity. However, the cytotoxicity tests did not parallel the potent tubulin-assembling and microtubule-stabilizing properties: limited cytotoxicity was observed against three common tumor cell lines (human ovarian carcinoma, human colon carcinoma and human leukemia cell lines, IC_{50} in the μM range), approximately two orders of magnitude less than paclitaxel (IC_{50} in the nM range). The mechanism of cell cycle arrest induced by compound **44** is similar to that obtained with paclitaxel.

1. Introduction

Sarcodictyins[1,2] A (**1a**) and B (**1b**) and eleutherobin[3,4] (**2**) (the 'eleutheside' family of microtubule-stabilizing drugs, Fig. 1) are active against paclitaxel resistant tumor cell lines and therefore hold potential as second generation microtubule-stabilizing anticancer agents.[4,5] The scarce availability of **1**–**2** from natural sources makes their total syntheses vital for further biological investigations.[5] To date, sarcodictyins A and B have been synthesized successfully by Nicolaou et al.[6] who have also exploited a similar route for accessing eleutherobin.[7] A subsequent report by Danishefsky and co-workers details an elegant alternative access to eleutherobin.[8] A number of partial syntheses and approaches have also been described.[9,10]

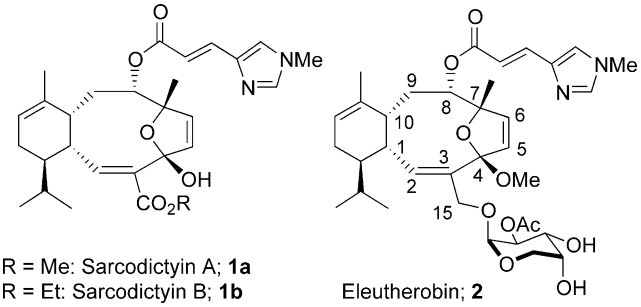

Figure 1. Marine diterpenoids sarcodictyin A (**1a**), B (**1b**) and eleutherobin (**2**).

The total syntheses of the eleutheside have generated very limited diversity in the diterpenoid core, with major variations reported only in the C-15 functionality and C-8

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side-chain.[5–8] We previously described the synthesis of a number of eleutheside analogues with potent tubulin-assembling and microtubule-stabilizing activity.[9h,m,n] However, the cytotoxicity assays did not parallel the potent tubulin-polymerizing properties: limited cytotoxicity was observed against three common tumor cell lines (human ovarian carcinoma and human colon carcinoma cell lines, IC_{50} in the μM range), two-to-three orders of magnitude less than paclitaxel (IC_{50} in the nM range).[9n] These results were attributed to an easy esterase-mediated hydrolytic cleavage of the *N*-methylurocanic ester side-chain in living cells (it is known that the natural eleuthesides are devoid of any cytotoxicity when the *N*-methylurocanic ester side-chain is lacking in position 8).[5] The simplified analogues, in fact, had an unsubstituted $–CH_2–$ in position 7, while natural eleutheSides have a fully substituted quaternary carbon, which is likely to hinder the hydrolysis of the adjacent ester at C-8.

In this paper, we describe the synthesis of a number of eleutheside analogues substituted at C-7, using ring closing metathesis (RCM) as the key-step for obtaining the 6–10 fused bicyclic ring. We also report the tubulin-polymerizing activities (ED_{50} and ED_{90} values) and the cytotoxicity tests (IC_{50} values) performed on these compounds using several different tumor cell lines.

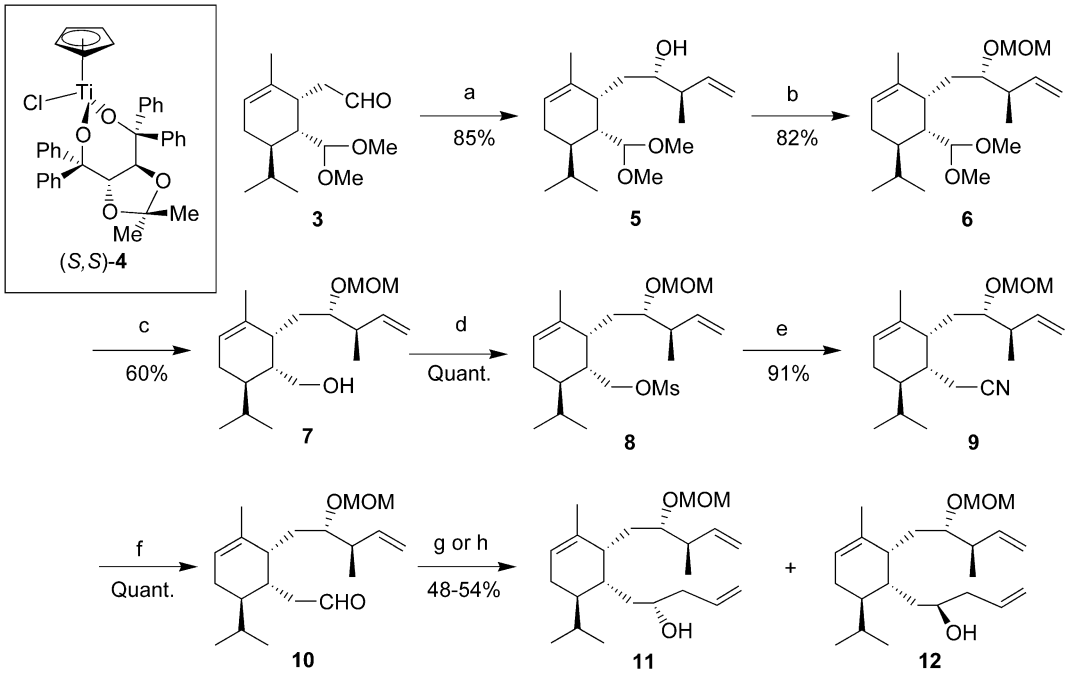
2. Results and discussion

2.1. Synthesis of the eleutheside analogues substituted at C-7

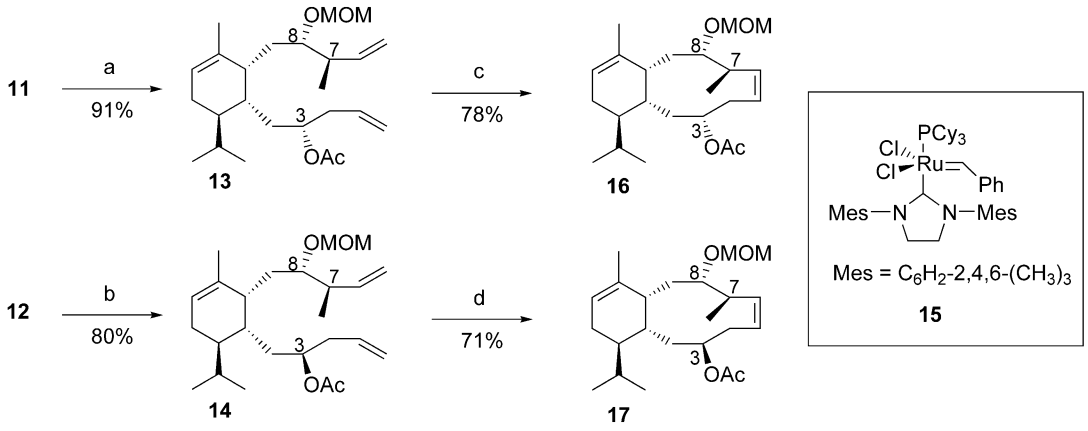
Aldehyde **3** (prepared in six steps on a multigram scale from *R*-(−)-carvone in 30% overall yield)[9a,g] was submitted to a stereoselective titanium-mediated Hafner–Duthaler crotylation,[11] generating alcohol **5** (Scheme 1).

The crotylation reaction proceeded in high yield (85%) and with complete stereocontrol in favor of the desired stereoisomer (diastereomeric purity >95% by ^1H and ^{13}C NMR).[12] After standard alcohol protection, an efficient and well established sequence of steps[8c] led to the homologated aldehyde **10**, on which a Brown allylation procedure was applied.[13] Addition of the allyl borane derived from (+)-α-pinene to aldehyde **10** gave a mixture of the two homoallylic alcohols (**11** and **12**) in a 3:1 ratio.[12] The use of the allyl borane derived from (−)-α-pinene gave the opposite stereochemical outcome (**11**/**12**=1:6).[12] Homoallylic alcohols **11** and **12** were acetylated and the resulting dienes (**13** and **14**) were subjected to ring closing metathesis[14] using the 'second generation' RCM-catalyst[15] **15** (CH_2Cl_2, reflux) to give the desired cyclized products **16** and **17** as single *Z* stereoisomers in 71–78% yields (Scheme 2). The stereochemistry at C-3 appears not to have a dramatic effect on the reaction, as similar yields were achieved. The *Z* stereochemistry of the double bond was unequivocally assigned by detection of the olefinic $^3J_{cis}$ coupling constant (10.8–10.9 Hz) in 400 MHz ^1H NMR experiments, and by detection of a NOE contact between these protons in 400 MHz NOESY experiments.

The reports that describe application of the RCM reaction to medium-sized—particularly ten-membered—rings, are still very rare, especially when dense functionality close to the reaction centre is involved.[16] The stereochemistry of the double bond created by our RCM reactions appears to be



Scheme 1. Reagents and conditions: (a) (i) 2-ButenylMgCl, (*S*,*S*)-TaddolCpTiCl [(*S*,*S*)-**4**], Et_2O, −78 to 0 °C; (ii) solution of **3** in Et_2O, −78 °C, 16 h; (iii) NH_4F (45% aqueous solution), rt, 4 h, 85% (>95% diastereomeric purity). (b) MOMCl, DIPEA, TBAI, CH_2Cl_2, rt, 16 h, 82%. (c) (i) $LiBF_4$, CH_3CN/H_2O (98/2), rt, 1 h; (ii) $NaBH_4$, EtOH, rt, 20 min, 60% over two steps. (d) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, quant. (e) KCN, 18-crown-6, MeCN, 80 °C, 5 h, 91%. (f) DIBAL-H, *n*-hexane/toluene (2/1), −78 °C, 40 min, quant. (g) (i) AllMgBr, ^{d}Ipc$_2$BOMe, Et_2O-THF, 0 °C to rt; (ii) solution of **10** in Et_2O, −78 °C 15 h, −78 to −20 °C 8 h; (iii) 6 N NaOH, H_2O_2, rt, 16 h, 48% (**11**/**12**=3:1). (h) (i) AllMgBr, ^{l}Ipc$_2$BOMe, Et_2O–THF, 0 °C to rt; (ii) solution of **10** in Et_2O, −78 °C 15 h, −78 to −20 °C 15 h; (iii) 6 N NaOH, H_2O_2, rt, 16 h, 54% (**11**/**12**=1:6).

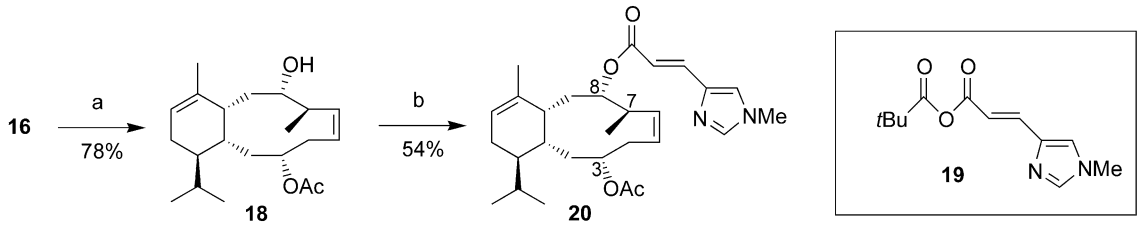


Scheme 2. Reagents and conditions: (a) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 91%. (b) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 80%. (c) **15** (6%), CH_2Cl_2, rt for 16 h, reflux for 7 h, 78% (100% *Z*). (d) **15** (6%), CH_2Cl_2, rt for 16 h, reflux for 7 h, 71% (100% *Z*).

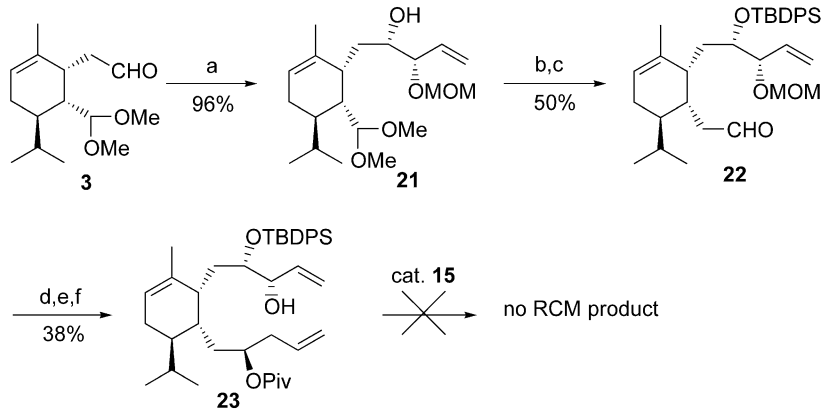
controlled in the desired sense (100% *Z*) by the structure of the new ten-membered carbocycles. This stereochemical course, which was found to be common to the cyclization of several related substrates (previously described)[9h,m,n,o] and of all the substrates reported in the present manuscript (vide infra), is likely to reflect thermodynamic control.[17] Molecular mechanics and semi-empirical calculations (see the relevant section below) also show that the *Z* stereoisomers of these ten-membered carbocycles are consistently more stable than the *E*.

A first simplified eleutheside analogue (**20**) was then synthesized from compound **16** using standard transformations (Scheme 3).

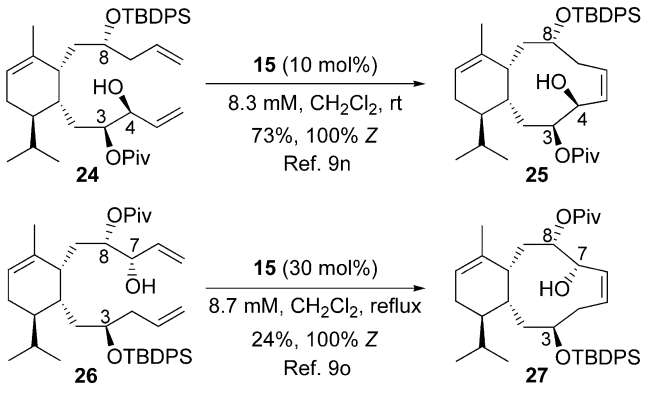
With the goal of synthesizing more C-7 functionalized eleutheside analogues, aldehyde **3** was oxyallylated using Brown's methodology [(*Z*)-γ-(methoxymethoxy)allyldiisopinocampheylborane from (−)-α-pinene][13d] in high yield (96%) and with excellent stereoselectivity (diastereomeric purity >95% by ^1H and ^{13}C NMR, Scheme 4).[12] Compound **21** was transformed into aldehyde **22** via a simple protection/deprotection/homologation sequence (analogous to the sequence described in Scheme 1). Aldehyde **22** was allylated using the allyl borane derived from (−)-α-pinene.[12,13] The protective groups were adjusted to give **23**, with a free allylic alcohol (a free alcohol in the allylic position is known to be important for promoting the cyclization).[9o,18,19] This time, 'second



Scheme 3. Reagents and conditions: (a) *p*-TSA, acetone, rt, 90 h, 78%. (b) **19** (Ref. 6b), $(CH_2Cl)_2$, Et_3N, DMAP, rt, 48 h, 54%.



Scheme 4. Reagents and conditions: (a) $^1Ipc_2BOMe$, AllOMOM, *sec*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C to rt, 16 h, 96% (>95% diastereomeric purity). (b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 16 h, 88%. (c) (i) AcOH/THF/H_2O (3/1/1), rt, 15 h, quant.; (ii) $NaBH_4$, EtOH, rt, 20 min, 71%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 98%; (iv) KCN, 18-crown-6, CH_3CN, 80 °C, 6 h, 91%; (v) DIBAL-H, *n*-hexane/toluene (2/1), −78 °C, 45 min, 90%. (d) $^1Ipc_2BOMe$, AllMgBr, THF, −78 °C, 16 h, 52% (≥95% diastereomeric purity). (e) *t*-BuCOCl (PivCl), DMAP, CH_2Cl_2, 40 °C, 5 h, quant. (f) $BF_3{\cdot}Et_2O$, PhSH, CH_2Cl_2, −78 to −20 °C, 3 h, 73%.



Scheme 5.

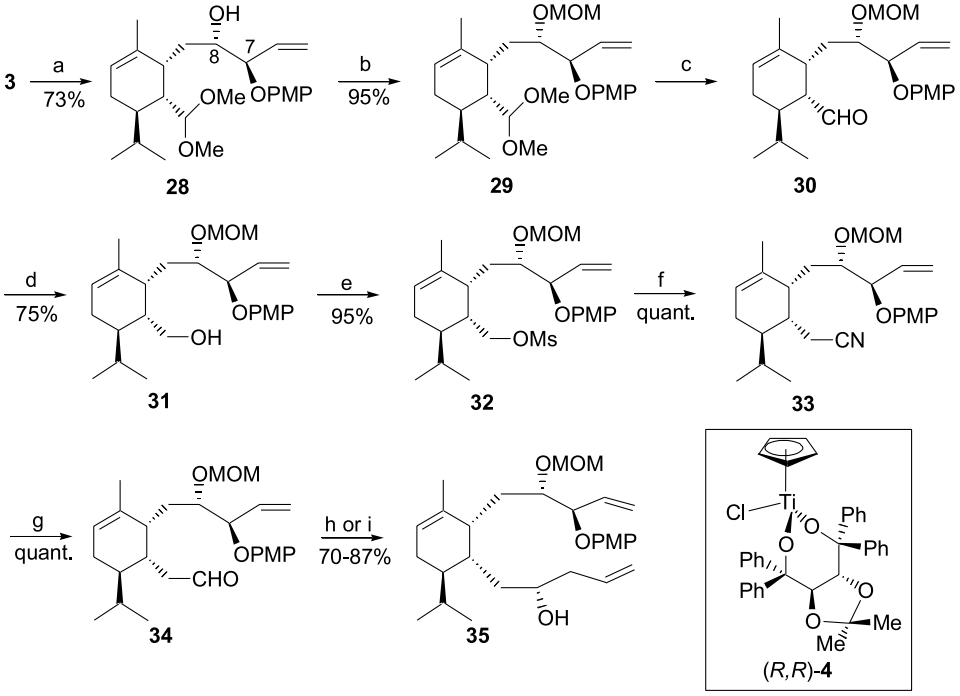
generation' RCM catalyst **15**[15] failed to provide the desired ring closed product, under a variety of experimental conditions.[9o]

This result is striking when compared to the analogous RCM reaction of diene **24** (Scheme 5), which proceeds smoothly to give the ring-closed product **25** in 73% isolated yield.[9n] Interconversion of the homoallylic O-protective groups of diene **23** gave the allylic alcohol **26** which did undergo cyclization to give **27**, albeit in a disappointing 24% yield.[9o]

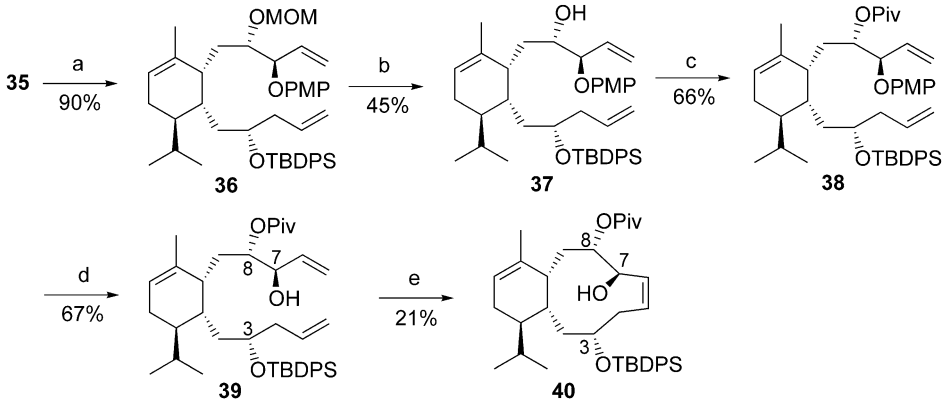
The rationale for this interconversion was that although the substitution pattern in compound **23** is the same as that shown by the successful cyclization precursor **24** (allylic alcohol, homoallylic OPiv and OTBDPS, Schemes 4 and 5), it is not the same with respect to the relationship between the groups [OH adjacent to OTBDPS (**23**) versus OH adjacent to OPiv (**24**)]. Again this observation demonstrates the importance of fine tuning the allylic and homoallylic alcohol protective groups for a successful RCM reaction.

At this point, we decided to change the stereochemistry at C-7, C-8 from *syn* to *anti*, hoping to influence the RCM performance[20] (Scheme 6). Aldehyde **3** was oxyallylated, using the (*S*,*S*)-TaddolCpTiCl complex (**4**),[11] to give the desired stereoisomer **28** in 73% isolated yield with complete stereocontrol (C-7, C-8 *anti* stereochemistry).[12] After standard alcohol protection as methoxymethyl ether (**29**, 95%), dimethylacetal deprotection ($LiBF_4$, CH_3CN/H_2O)[21] and $NaBH_4$ reduction (**31**, 75% over two steps), an efficient and well established sequence of steps[8c,9n] led to the homologated aldehyde **34** (95%). Using Brown allylboration (70%)[13] or better Hafner–Duthaler allyltitanation chemistry (87%),[11] the second olefin fragment was stereoselectively inserted in the south chain to give diene **35**.[12]

Protective group manipulations transformed diene **35** into the desired cyclization precursor **39** (C-7, C-8 *anti*) (Scheme 7) which had the same substitution and protection pattern as shown in compound **26** (C-7, C-8 *syn*). Reaction with the robust 'second generation' RCM-catalyst **15** gave a mixture of compounds, from which the cyclized product **40** could be isolated in a similarly poor yield (21%, Scheme 7). No significant difference was observed in the reactivity of the two diastereomers (**26** and **39**) in the RCM reaction.[20] It was noted, however, that if the RCM reaction was performed with the precursor PMP-protected allylic alcohol (**38**), higher yields could be obtained under similar reaction conditions (52%, 62% considering the recovered starting material, Scheme 8). This is, unexpectedly and unprecedentedly, a result in disagreement with the 'free allylic alcohol' effect,[9o,18,19] that is, allylic ethers are usually found



Scheme 6. Reagents and conditions: (a) *sec*-BuLi (1.3 M in cyclohexane), PMPOAllyl, (*S*,*S*)-TaddolCpTiCl [(*S*,*S*)-**4**], THF/Et_2O (57/43), −78 to 0 °C, 73%. (b) DIPEA, TBAI, MOMCl, CH_2Cl_2, 25 °C, 95%. (c) $LiBF_4$, CH_3CN/H_2O (98/2), 25 °C. (d) $NaBH_4$, EtOH, 25 °C, 75% over two steps. (e) MsCl, TEA, CH_2Cl_2, 0 to 25 °C, 95%. (f) KCN, 18-crown-6, CH_3CN, 80 °C, quant. (g) DIBAL-H, toluene/*n*-hexane (1/2), −78 °C, quant. (h) AllMgBr, $^dIpc_2BOMe$, Et_2O/THF (11/79), −78 °C, 70%. (i) AllMgBr, (*R*,*R*)-TaddolCpTiCl [(*R*,*R*)-**4**], Et_2O, −78 °C, 87%.



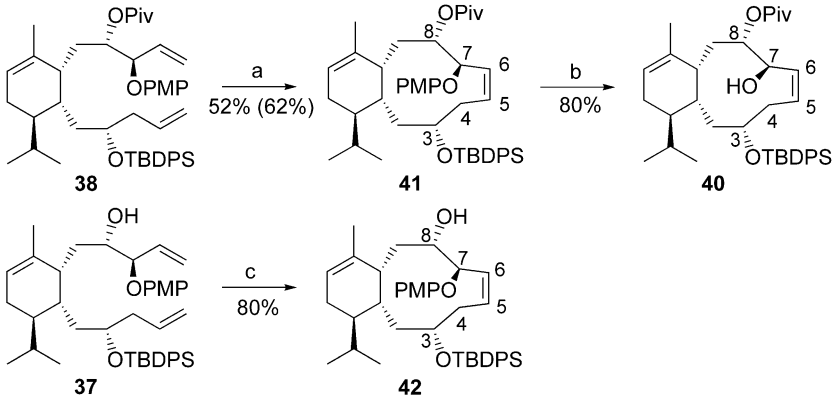
Scheme 7. Reagents and conditions: (a) imidazole, TBDPSCl, CH_2Cl_2, rt, 90%. (b) Me_2S, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C, 45%. (c) DMAP, PivCl, CH_2Cl_2, rt, 66%. (d) CAN, CH_3CN/H_2O (4/1), 0 °C, 67%. (e) **15** (10%), CH_2Cl_2, rt, 7.5 mM, 21% (100% *Z*).

to retard the RCM reaction while a rate acceleration is associated with allylic alcohols. Given the success of diene **38** in the RCM reaction, attempts were made to cyclize precursor **37**. Reaction of diene **37** with a free homoallylic alcohol and a PMP-protected allylic alcohol with the 'second generation' RCM-catalyst **15** gave the desired 6–10 fused bicycle **42** in 80% yield and 100% *Z*-selectivity (Scheme 8).

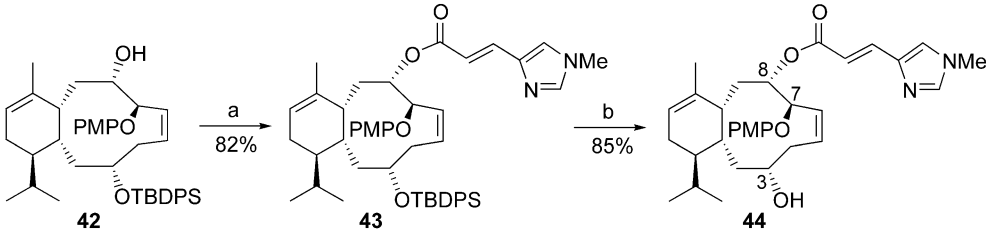
The improved results given by diene **37** compared to **38** may be due to the use of a higher boiling solvent.[22] An extensive analysis of compounds **41** and **42** was carried out using NMR spectroscopy. The olefinic $^3J_{cis}$ coupling constants suggested the *cis* configuration of the new double bonds ($^3J=11.4$ Hz for **41**, $^3J=11.4$ Hz for **42**). Furthermore, extensive NOESY experiments also suggested formation of the *Z*-olefin: a strong NOE was observed between C-7 methine and C-4 methylene protons and between H-5 and H-6.

At present, the reasons why the allylic OPMP group facilitates the RCM reaction are not completely understood. Sterically, the PMP can be considered relatively small, even smaller than a Me group (effective van der Waals radius of Ph = 1.62 Å compared to Me = 1.80 Å),[23] but definitely not smaller than a hydrogen. The true reason must be electronic, but difficult to rationalise.

A simplified eleutheside analogue (**44**) was then synthesized from compound **42** using standard transformations



Scheme 8. Reagents and conditions: (a) **15** (10%), CH_2Cl_2, reflux, 11 mM, 52% (62% considering the recovered starting material) (100% *Z*). (b) CAN, CH_3CN/H_2O (4/1), 0 °C, 80%. (c) **15** (10%), benzene, reflux, 10 mM, 80% (100% *Z*).



Scheme 9. Reagents and conditions: (a) **19** (Ref. 6b), $(CH_2Cl)_2$, Et_3N, DMAP, 80 °C, 82%. (b) TBAF, THF, rt, 85%.

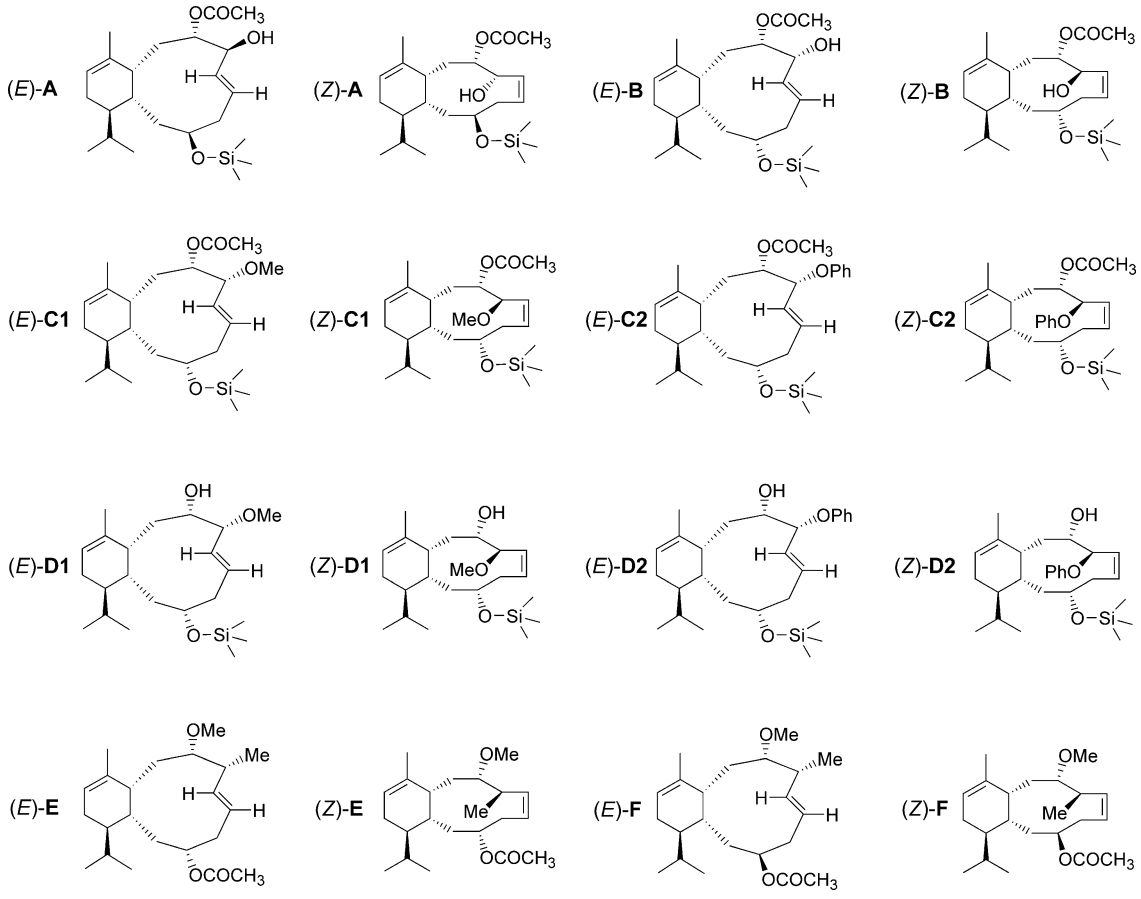


Figure 2. List of structures studied by molecular mechanics and semi-empirical PM3 calculations.

(Scheme 9). It is worth noting that the formation of the (*E*)-*N*-methylurocanic ester in refluxing 1,2-dichloroethane had a beneficial effect on the yield of **43** (82%).

2.2. Molecular mechanics and semi-empirical calculations

Molecular mechanics and semi-empirical PM3[24] calculations were undertaken in order to investigate if the stereochemical outcome of the various RCM reactions could possibly be due to thermodynamic control. Compounds **27**, **40**, **41**, **42**, **16** and **17** were simplified into structures **A**–**F** (*Z* and *E* stereoisomers, Fig. 2) in order to reduce the number of rotatable bonds and of low-quality torsional parameters,[25] by making the following changes in the protective groups: OPiv into OAc, OTBDPS into OTMS,[25] OPMP into either OMe (**C1** and **D1**) or OPh (**C2** and **D2**),[26] OMOM into OMe. Initially, conformational searches were carried out with MacroModel[27] (MM2*, $CHCl_3$ GB/SA) on each of the structures represented in Figure 2. In all cases, the *Z* stereoisomers of structures **A**–**F** were found to be consistently more stable than the corresponding *E* stereoisomers by ca. 1.8–12.7 kJ mol^{-1} (Table 1). The structures generated with MacroModel were then optimized at the PM3 level[24] with the Gaussian 03 package.[28] These calculations also show that the *Z* stereoisomers of structures **A**–**F** are more stable than the *E* stereoisomers, with energy differences ranging from 9.8 to 28.2 kJ mol^{-1} (Table 1). It is therefore highly likely that the selective formation of the *Z* ten-membered carbocycles in the RCM reactions is due to thermodynamic control.[17]

Table 1. Global minimum energy differences between the (*E*) and the (*Z*)-stereoisomers of structures **A**–**F**

Structure	E_E–E_Z (MM2*)[a]	E_E–E_Z (PM3)[a]
A	1.8	9.8
B	4.3	18.0
C1	6.6	17.4
C2	5.0	18.6
D1	7.4	12.3
D2	6.2	18.6
E	7.7	22.4
F	12.7	28.2

[a] Energy differences in kJ mol^{-1}.

Figure 3 shows the lowest energy conformers and relative energies of stereoisomer (*Z*)-**C1** (corresponding to **41**) and of stereoisomer (*E*)-**C1**, obtained at the PM3 level.

2.3. Biological assays

The effect of these new eleutheside analogues on the assembly of tubulin and on the stability of the formed microtubules was assessed at the University of Salford (UK), using the potent microtubule-stabilizing agent paclitaxel as a reference (Table 2).[2b,29] Eleutheside analogue **44** was shown to be at least as potent as paclitaxel. Microtubules were generated in the presence of $CaCl_2$ at 37 °C and were stable (i.e., did not depolymerize) at 10 °C. Although there is a general agreement that the

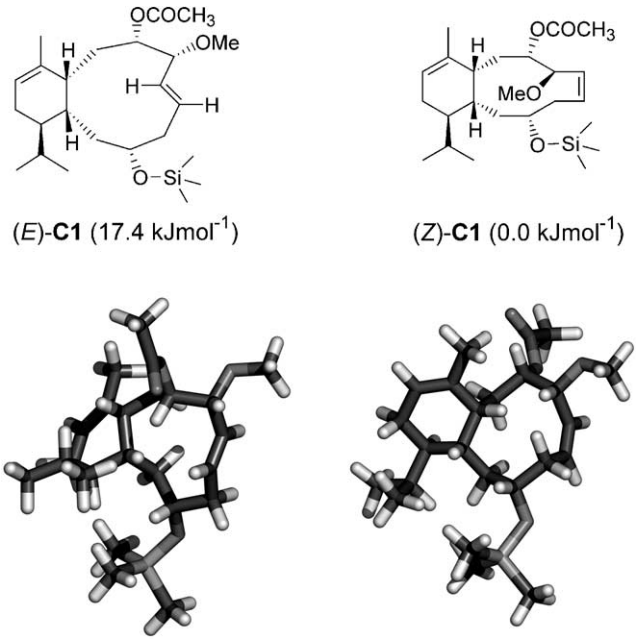


Figure 3. Lowest energy conformers and relative energies of stereoisomer (*Z*)-**C1** (corresponding to **41**) and of stereoisomer (*E*)-**C1**, obtained at the PM3 level.

Table 2. Tubulin polymerizing activities[a]

Compound	ED_{50} [μM]	ED_{90} [μM]
20	3.0	>20.0
44	0.1	0.5
Paclitaxel	1.0	2.5

[a] ED_{50}, effective dose that induces 50% tubulin polymerization; ED_{90}, effective dose that induces 90% tubulin polymerization (see Ref. 2b). ED values may vary depending on the tubulin batch (from pig brain): the same batch is used for the paclitaxel reference assay. For a more detailed experimental procedure, see Ref. 9n.

(*E*)-*N*-methylurocanic side-chain, the C-4/C-7 ether bridge, and the cyclohexene ring are important determinants of antimitotic activity,[5] it is interesting to note that this simplified analogue of the natural product (lacking inter alia the C-4/C-7 ether bridge) retains potent microtubule stabilizing activity. Given the dramatic impact that the furanose oxygen deletion is likely to have on the conformation of the ring system, the fact that some of these compounds retain activity comparable to paclitaxel in the tubulin polymerization assay is remarkable.[9n]

Table 3. Cytotoxicity assays: IC_{50} values on A2780, HCT116, K562 tumor cell lines[a]

Compound	IC_{50} [μM] (A2780)	IC_{50} [μM] (HCT116)	IC_{50} [μM] (K562)
20	10.9[b]	n.d.[c]	4.3[d]
44	1.9[b]	0.9[e]	2.3[d]

[a] IC_{50} values: concentration inhibiting cell growth by 50%. Cell proliferation was determined by the ATPlite assay (Perkin Elmer). A2780: human ovarian carcinoma cell line; HCT116: human colon carcinoma cell line; K562: human leukemia cell line.
[b] Paclitaxel IC_{50}=15 nM.
[c] Not determined.
[d] Paclitaxel IC_{50}=25 nM.
[e] Paclitaxel IC_{50}=7 nM.

However, the cytotoxicity assays did not parallel the potent tubulin-assembling and microtubule-stabilizing properties: limited cytotoxicity was observed for **44** (IC_{50} in the μM range) against three common tumor cell lines (human ovarian carcinoma, human colon carcinoma and human leukemia cell lines, Table 3),[30] approximately two orders of magnitude less than paclitaxel (IC_{50} in the nM range).

The mechanism of cell cycle arrest was studied in the case of compound **44**.[31] When tested on asynchronously proliferating HCT116 cells, compound **44** produced cell cycle perturbations similar to that obtained with paclitaxel: a 2.5-fold increase in the percentage of cells in G2/M phase (the mitotic phase) was observed with **44** at 4 μM and a 2-fold increase was obtained with paclitaxel at 50 nM.[31]

Despite their excellent microtubule-stabilizing activity, which is often superior to paclitaxel, and a mechanism of cell cycle arrest similar to that obtained with paclitaxel, high concentrations of our analogues (in the μM range) are needed to inhibit tumor cell growth.[9n] Thus, with this new class of eleutheside analogues, we succeeded, at least in part, in the separation of the tubulin mechanism from the cytostatic/cytotoxic action.[32] Although the application of these compounds as monotherapeutics in tumor indications will be limited, they might be of value as tools and wherever the stabilization of microtubules without other cell-toxic effects are advantageous. One of these potential applications might be the treatment of Alzheimer's disease.[33] It has been demonstrated very recently that paclitaxel protects very efficiently against β-amyloid toxicity in primary neurons.[34] This will open new therapeutic areas for compounds which are able to stabilize microtubules.

3. Experimental

3.1. General procedures

All reactions were carried out in flame-dried glassware under argon atmosphere. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_3CN (CaH_2), CH_2Cl_2 (CaH_2), $(CH_2Cl)_2$ (CaH_2), MeOH (CaH_2), Et_3N (CaH_2), *i*Pr_2EtN (CaH_2), $HN(TMS)_2$ (CaH_2), THF (Na), Et_2O (Na), benzene (Na), toluene (Na), *n*-hexane (Na). Organic extracts were dried over anhydrous Na_2SO_4. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness) or basic alumina supported on aluminium foils. TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm, following the procedure by Still and co-workers.[35] Proton NMR spectra were recorded on 400, 300, or 200 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ 7.26 ppm; d_6-DMSO, δ 2.50 ppm). The following abbreviations are used to describe spin multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br,

broad signal; dd, doublet of doublet; dt, doublet of triplet; ddd, doublet of doublet of doublet. Carbon NMR spectra were recorded on 400 (100 MHz), 300 (75 MHz) or 200 (50 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0). Infrared spectra were recorded on a standard Infrared Spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter at the sodium D line. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. A Reserpine solution 100 pg/μL (about 100 count/s), 0.1% HCOOH/CH_3CN 1:1, was used as reference compound (Lock Mass).

3.1.1. (2*S*,3*R*)-1-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-3-methyl-pent-4-en-2-ol (5). To a cold (−78 °C), stirred suspension of (*S*,*S*)-**4**[11] (1.00 g, 1.63 mmol), in Et_2O (24.5 mL), was added 2-butenylmagnesium chloride (0.5 M in THF, 2.9 mL, 1.47 mmol). After stirring for 30 min, the resulting orange solution was warmed to 0 °C and stirred for 3 h, then recooled to −78 °C. A solution of aldehyde **3**[9a,g] (277 mg, 1.09 mmol) in Et_2O (6.0 mL) was added. After stirring for 15 h, the reaction mixture was treated with a NH_4F aqueous solution (45%, 10 mL) and stirred for further 4 h at room temperature. The organic phase was separated and the aqueous layer was extracted with iPr_2O (3×15 mL). The organic extracts were washed with brine. Purification of the crude by flash chromatography (*n*-hexane/EtOAc, 9/1) afforded compound **5** (285 mg, 85%) as a colourless oil. R_f=0.38 (*n*-hexane/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86–5.77 (m, 1H), 5.35 (br, 1H), 5.10–5.03 (m, 2H), 4.35 (d, 1H, J=5.5 Hz), 3.71–3.63 (m, 1H), 3.36 (s, 6H), 2.48 (br, 1H), 2.40 (br, 1H), 2.19–2.10 (m, 1H), 2.06–1.97 (m, 2H), 1.87–1.71 (m, 4H), 1.67 (s, 3H), 1.42 (ddd, 1H, J_1=14.6 Hz, J_2=10.1 Hz, J_3=3.3 Hz), 1.03 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.6 Hz), 0.83 (d, 3H, J=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.1, 136.6, 121.3, 115.2, 106.9, 71.8, 55.1, 54.4, 45.1, 39.8, 36.1, 34.5 (2C), 27.1, 24.5, 22.2, 21.0, 17.3, 16.0; FT-IR (CCl_4): ν 3632, 3583, 3487, 3077, 2961, 2832, 2675, 2290, 2002, 1847, 1638, 1558, 1463, 1386, 1259, 1216, 1159, 1111, 1073, 1007, 914; $[\alpha]_D^{20}$=+48.2 (c=1.03, EtOAc); HRMS (ESI): *m*/*z*: calculated for $C_{19}H_{34}NaO_3$: 333.2406 $[M+Na]^+$; found: 333.2410 (resolution 9000).

3.1.2. (4*R*,5*R*,6*R*)-5-Dimethoxymethyl-4-isopropyl-6-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-1-methyl-cyclohexene (6). To a stirred solution of compound **5** (993 mg, 3.20 mmol), in CH_2Cl_2 (8.1 mL) was added DIPEA (1.23 mL, 7.05 mmol) followed by TBAI (237 mg, 0.64 mmol) and chloromethyl methyl ether (487 μL, 6.41 mmol). After stirring for 15 h, the resulting brown solution was filtered through a plug of silica gel (eluting with CH_2Cl_2). Purification of the crude by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **6** (932 mg, 82%) as a colourless oil. R_f=0.6 (*n*-hexane/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddd, 1H, J_1=17.4 Hz, J_2=10.3 Hz, J_3=7.1 Hz), 5.28 (br, 1H), 5.08–4.97 (m, 2H), 4.78 (d, 1H, J=6.6 Hz), 4.70 (d, 1H, J=6.6 Hz), 4.29 (d, 1H, J=5.3 Hz), 3.80 (dt, 1H, J_1=9.7 Hz, J_2=3.2 Hz), 3.41 (s, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 2.50 (br, 1H), 2.34 (br, 1H), 2.11–1.60 (m, 9H), 1.36 (ddd, 1H, J_1=14.3 Hz, J_2=9.9 Hz, J_3=3.6 Hz), 1.04 (d, 3H, J=6.9 Hz), 0.91 (d, 3H, J=6.8 Hz), 0.82 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.2, 138.3, 120.2, 113.8, 107.0, 97.4, 81.4, 55.7, 55.1, 54.3, 42.0, 40.4, 36.3, 34.2, 32.1, 27.1, 24.4, 22.3, 21.3, 17.2, 14.4; FT-IR (CCl_4): ν 3075, 2959, 2931, 2842, 2830, 2674, 2291, 2009, 1831, 1736, 1639, 1558, 1464, 1442, 1376, 1369, 1259, 1214, 1152, 1103, 1078, 1049, 1013, 979, 914; $[\alpha]_D^{20}$=+74.0 (c=0.5, EtOAc); HRMS (ESI): *m*/*z*: calculated for $C_{21}H_{38}NaO_4$: 377.2668 $[M+Na]^+$; found: 377.2667 (resolution 10,000).

3.1.3. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-methanol (7). $LiBF_4$ (246 mg, 2.63 mmol) was dissolved in a mixture of CH_3CN/H_2O (5.2 mL, v/v: 98/2) and added to compound **6** (932 mg, 2.63 mmol). After stirring for 1 h, the reaction mixture was filtered through a plug of silica gel (eluting with CH_2Cl_2) and the filtrate concentrated in vacuo to give the crude aldehyde (768 mg), which was used without further purification. To a stirred solution of the crude aldehyde, in EtOH (28.0 mL), was added $NaBH_4$ (149 mg, 3.94 mmol). After stirring for 20 min, the reaction mixture was treated with NH_4Cl (1.41 g, 26.36 mmol) followed by Na_2SO_4 and iPr_2O, and stirred for further 20 min. The salts were removed by filtration and washed with iPr_2O. Purification by flash chromatography (*n*-hexane/EtOAc, 85/15) afforded alcohol **7** (505 mg, 60% over two steps) as a colourless oil. R_f=0.25 (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.93–5.72 (m, 1H), 5.34 (br, 1H), 5.16–5.01 (m, 2H), 4.75 (d, 1H, J=6.9 Hz), 4.69 (d, 1H, J=6.9 Hz), 3.75 (dd, 1H, J_1=11.2 Hz, J_2=5.1 Hz), 3.67–3.42 (m, 5H), 2.65–2.42 (m, 1H), 2.33 (br, 1H), 1.98–1.37 (m, 12H), 1.06 (d, 3H, J=6.9 Hz), 0.91 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.5, 137.4, 120.9, 115.1, 97.0, 81.3, 61.9, 55.9, 41.9, 41.6, 35.9, 34.2, 30.9, 24.2, 22.3, 21.1, 16.3, 14.1; FT-IR (CCl_4): ν 3633, 3513, 3080, 2961, 2931, 2824, 2290, 2004, 1846, 1736, 1638, 1543, 1463, 1417, 1386, 1369, 1259, 1216, 1150, 1101, 1040, 1008, 918; $[\alpha]_D^{20}$=+73.6 (c=0.7, EtOAc).

3.1.4. Methanesulfonic acid {(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-methyl ester (8). To a cold (0 °C), stirred solution of alcohol **7** (505 mg, 1.63 mmol), in CH_2Cl_2 (12.5 mL), was added Et_3N (680 μL, 4.88 mmol) followed by MsCl (189 μL, 2.44 mmol). After stirring at room temperature for 15 h, the solvent was evaporated under reduced pressure. Purification of the crude by filtration through a plug of silica gel (eluting with CH_2Cl_2) afforded mesylate **8** (634 mg, quant.) as a colourless oil. R_f=0.72 (CH_2Cl_2/EtOAc, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.94–5.74 (m, 1H), 5.33 (br, 1H), 5.18–5.03 (m, 2H), 4.75 (d, 1H, J=7.0 Hz), 4.70 (d, 1H, J=7.0 Hz), 4.30 (dd, 1H, J_1=9.9 Hz, J_2=7.2 Hz), 4.07 (dd, 1H, J_1=9.9 Hz, J_2=8.6 Hz), 3.70–3.58 (m, 1H), 3.43 (s, 3H), 3.03 (s, 3H), 2.63 (br, 1H), 2.39 (br, 1H), 2.26–2.07 (m, 1H), 1.96 (br, 2H), 1.75–1.20 (m, 7H), 1.05 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.7 Hz), 0.87 (d, 3H, J=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3, 136.2, 120.8, 115.3, 96.7, 80.1, 69.2, 55.9, 41.0, 38.0, 37.3, 36.7, 33.9, 30.1,

27.2, 23.9, 22.1, 20.8, 17.8, 13.1; FT-IR (CCl_4): ν 2962, 2930, 2291, 2003, 1845, 1734, 1555, 1370, 1344, 1259, 1216, 1177, 1098, 1009; $[\alpha]_D^{20}=+21.0$ ($c=1.4$, EtOAc); HRMS (ESI): m/z: calculated for $C_{20}H_{37}NO_5S$: 406.2627 $[M+NH_4]^+$; found: 406.2622 (resolution 10,000).

3.1.5. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetonitrile (9). To a stirred solution of mesylate **8** (634 mg, 1.63 mmol), in CH_3CN (16.9 mL), was added 18-crown-6 (1.29 g, 4.89 mmol) followed by KCN (319 mg, 4.89 mmol). After stirring for 8 h at 80 °C, the solvent was evaporated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **9** (473 mg, 91%) as a colourless oil. $R_f=0.52$ (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85–5.76 (m, 1H), 5.35 (br, 1H), 5.21–5.05 (m, 2H), 4.73 (s, 2H), 3.58 (dt, 1H, $J_1=9.6$ Hz, $J_2=1.6$ Hz), 3.42 (s, 3H), 2.70 (br, 1H), 2.46–1.90 (m, 6H), 1.77–1.52 (m, 6H), 1.26 (ddd, 1H, $J_1=14.8$ Hz, $J_2=8.8$ Hz, $J_3=2.8$ Hz), 1.08 (d, 3H, $J=7.2$ Hz), 0.95 (d, 3H, $J=6.8$ Hz), 0.89 (d, 3H, $J=6.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.1, 135.1, 121.0, 119.8, 115.7, 96.9, 80.2, 55.9, 41.0, 39.5, 34.9, 34.7, 29.6, 27.3, 23.6, 22.1, 20.6, 18.9, 17.3, 13.2; FT-IR (CCl_4): ν 3081, 2963, 2892, 2847, 2823, 2290, 2247, 2004, 1847, 1638, 1558, 1463, 1426, 1388, 1372, 1257, 1217, 1151, 1101, 1041, 1006, 980, 920; $[\alpha]_D^{20}=+48.2$ ($c=1.33$, EtOAc); HRMS (ESI): m/z: calculated for $C_{20}H_{33}NaNO_2$: 342.2409 $[M+Na]^+$; found: 342.2419 (resolution 10,000).

3.1.6. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetaldehyde (10). To a cold (−78 °C), stirred solution of compound **9** (295 mg, 0.92 mmol), in toluene/*n*-hexane (15.0 mL, v/v: 1/2), was slowly added DIBAL-H (1.5 M in toluene, 6.1 mL, 9.20 mmol). After 45 min the reaction mixture was treated with EtOAc (7.5 mL) and an aqueous tartaric acid solution (1.0 M, 7.5 mL), and warmed to room temperature. After 1 h the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (5×10 mL). The organic extracts were washed with saturated $NaHCO_3$ aqueous solution (2×10 mL). The solvent was evaporated under reduced pressure to afford aldehyde **10** (296 mg, quant.) as a colourless oil, which was used without further purification. $R_f=0.2$ (CH_2Cl_2).

3.1.7. (*R*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (11) and (*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (12). To a cold (0 °C), stirred solution of ^{d}Ipc$_2$BOMe[13c] (1.0 M in THF, 2.4 mL, 2.42 mmol) was slowly added AllMgBr (1.0 M in Et_2O, 2.1 mL, 2.14 mmol). After stirring for 1 h at room temperature, the reaction mixture was cooled to −78 °C and aldehyde **10** (230 mg, 0.71 mmol) in Et_2O (2.8 mL) was added. After stirring for 15 h, the reaction mixture was warmed gradually to −20 °C during 8 h, and treated with an aqueous NaOH solution (6.0 M, 3.5 mL) and H_2O_2 (35%, 2.8 mL). After stirring for 16 h at room temperature, the organic phase was separated and the aqueous layer was extracted with iPr_2O (3×10 mL). A first flash chromatography (*n*-hexane/EtOAc, 9/1) afforded combined alcohols **11** and **12** as a mixture (48%). A second flash chromatography (CH_2Cl_2/iPr_2O, 95/5) afforded **11** (94 mg, 36%) and **12** (31 mg, 12%) as colourless oils (**11**/**12**=3:1).

Compound **11**. $R_f=0.32$ (CH_2Cl_2/iPr_2O, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.98–5.68 (m, 2H), 5.31 (br, 1H), 5.27–4.98 (m, 4H), 4.69 (s, 2H), 3.89–3.68 (m, 1H), 3.60–3.33 (m, 4H), 2.67 (br, 1H), 2.40–1.18 (m, 16H), 1.06 (d, 3H, $J=6.9$ Hz), 0.91 (d, 3H, $J=6.8$ Hz), 0.82 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3, 137.0, 134.8, 121.0, 118.3, 115.2, 96.5, 80.7, 68.2, 55.8, 42.3, 41.1, 38.4, 35.1, 34.7, 34.5, 30.5, 27.0, 24.1, 22.7, 21.0, 17.4, 14.0; FT-IR (CCl_4): ν 3623, 3590, 3079, 2961, 2823, 2290, 1839, 1742, 1640, 1559, 1440, 1415, 1373, 1262, 1151, 1019, 918; $[\alpha]_D^{20}=+40.9$ ($c=0.98$, EtOAc); HRMS (ESI): m/z: calculated for $C_{23}H_{41}O_3$: 365.3056 $[M+H]^+$; found: 365.3065 (resolution 10,000).

Compound **12**. $R_f=0.44$ (CH_2Cl_2/iPr_2O, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.95–5.72 (m, 2H), 5.29 (br, 1H), 5.23–5.01 (m, 4H), 4.74 (s, 2H), 3.83–3.60 (m, 2H), 3.42 (s, 3H), 2.75–2.60 (m, 1H), 2.40–1.85 (m, 6H), 1.75–1.53 (m, 6H), 1.45–1.21 (m, 4H), 1.07 (d, 3H, $J=6.8$ Hz), 0.92 (d, 3H, $J=6.7$ Hz), 0.87 (d, 3H, $J=6.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.7, 136.3, 134.9, 120.8, 118.1, 115.0, 97.0, 80.2, 68.0, 55.9, 42.8, 41.2, 39.3, 34.2, 34.1, 32.5, 29.5, 27.4, 24.1, 22.3, 20.8, 19.9, 13.2; FT-IR (CCl_4): ν 3622, 3590, 3080, 2960, 2823, 2291, 2004, 1847, 1741, 1639, 1559, 1463, 1439, 1415, 1386, 1376, 1252, 1218, 1152, 1102, 1043, 1006, 980; $[\alpha]_D^{20}=+19.6$ ($c=0.87$, EtOAc); HRMS (ESI): m/z: calculated for $C_{23}H_{41}O_3$: 365.3056 $[M+H]^+$; found: 365.3061 (resolution 10,000).

Following the same procedure described above and using ^{l}Ipc$_2$BOMe[13c] as chiral auxiliary, the 2 epimeric alcohols were obtained in 54% yield and in a ratio **11**/**12**=1:6.

3.1.8. Acetic acid (*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl}-but-3-enyl ester (13). To a cold (0 °C), stirred solution of alcohol **11** (87 mg, 0.24 mmol), in CH_2Cl_2 (1.6 mL), was added Et_3N (66 μL, 0.48 mmol), followed by DMAP (2.9 mg, 0.024 mmol) and Ac_2O (34 μL, 0.36 mmol). After stirring for 30 min, the reaction mixture was warmed to room temperature and stirred for further 1 h. The reaction mixture was treated with a $NaHCO_3$ saturated aqueous solution (3 mL) and stirred for 15 min. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **13** (89 mg, 91%) as a colourless oil. $R_f=0.65$ (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.90–5.73 (m, 2H), 5.29 (br, 1H), 5.21–4.97 (m, 5H), 4.70 (s, 2H), 3.58–3.35 (m, 4H), 2.62 (br, 1H), 2.41–1.20 (m, 18H), 1.06 (d, 3H, $J=6.9$ Hz), 0.90 (d, 3H, $J=6.7$ Hz), 0.81 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 140.3, 136.9, 133.8, 120.9, 117.7, 115.3, 96.5, 80.4, 71.4, 55.9, 41.1, 39.0, 38.4, 34.8, 34.4, 31.3, 30.4, 27.0, 24.0, 22.6, 21.2, 20.9, 17.6, 14.0; FT-IR (CCl_4): ν 3079, 2961, 2823, 2290, 2003, 1837, 1739, 1641, 1553, 1440, 1418, 1371, 1242, 1150, 1098, 1044, 918; $[\alpha]_D^{20}=+50.6$ ($c=1.03$, EtOAc); HRMS (ESI): m/z: calculated for

$C_{25}H_{46}NO_4$: 424.3421 $[M+NH_4]^+$; found: 424.3434 (resolution 10,000).

3.1.9. Acetic acid (*R*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl}-but-3-enyl ester (14). To a cold (0 °C), stirred solution of alcohol **12** (92 mg, 0.25 mmol), in CH_2Cl_2 (1.7 mL) was added Et_3N (70 μL, 0.50 mmol) followed by DMAP (3.1 mg, 0.025 mmol) and Ac_2O (36 μL, 0.38 mmol). After stirring for 30 min at 0 °C, the reaction was warmed to room temperature. After further 1 h, the reaction mixtures was filtered through a plug of silica gel (eluting with CH_2Cl_2). Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **14** (81 mg, 80%) as a colourless oil. R_f=0.50 (*n*-hexane/EtOAc, 9/1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.93–5.64 (m, 2H), 5.27 (br, 1H), 5.20–4.94 (m, 5H), 4.73 (s, 2H), 3.64 (dt, 2H, J_1=10.2 Hz, J_2=2.8 Hz), 3.41 (s, 3H), 2.75 (br, 1H), 2.42–2.20 (m, 3H), 2.06–1.20 (m, 15H), 1.09 (d, 3H, J=6.8 Hz), 0.87 (d, 3H, J=6.3 Hz), 0.84 (d, 3H, J=5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 140.6, 135.6, 133.6, 120.7, 117.7, 114.9, 97.3, 80.1, 71.0, 55.8, 41.3, 39.7, 39.5, 33.1, 31.3, 30.6, 29.1, 27.4, 23.9, 22.8, 22.1, 21.1, 20.6, 12.7; FT-IR (CCl_4): ν 3080, 2962, 2823, 2290, 2008, 1836, 1739, 1641, 1558, 1462, 1439, 1417, 1373, 1242, 1151, 1130, 1101, 1044, 940; $[\alpha]_D^{20}$=+9.6 (c=0.83, EtOAc); HRMS (ESI): *m/z*: calculated for $C_{25}H_{43}O_4$: 424.3421 $[M+H]^+$; found: 424.3439 (resolution 10,000).

3.1.10. Acetic acid (*Z*)-[(4*R*,4a*R*,6*S*,10*R*,11*S*,12a*R*)-4-isopropyl-11-methoxymethoxy-1,10-dimethyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (16). To a stirred solution of diene **13** (35 mg, 0.086 mmol), in degassed CH_2Cl_2 (8.0 mL), was added a solution of Grubbs catalyst **15** (4.4 mg, 5.2 μmol) in degassed CH_2Cl_2 (650 μL). After stirring for 15 h at room temperature, the reaction mixture was heated at 40 °C for 7 h. The reaction mixture was treated with DMSO (31 μL) and stirred for 15 h at room temperature under argon atmosphere. Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **16** (25 mg, 78%) as a colourless oil. R_f=0.77 (*n*-hexane/EtOAc, 9/1, TLC runs twice); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (dt, 1H, J_1=10.8 Hz, J_2=5.0 Hz), 5.52 (dd, 1H, J_1=10.8 Hz, J_2=10.3 Hz), 5.30 (br, 1H), 5.13–5.05 (m, 1H), 4.73 (d, 1H, J=6.9 Hz), 4.61 (d, 1H, J=6.9 Hz), 3.79–3.72 (m, 1H), 3.42 (s, 3H), 2.94–2.84 (m, 1H), 2.70 (ddd, 1H, J_1=14.8 Hz, J_2=10.3 Hz, J_3=4.0 Hz), 2.24 (dt, 1H, J_1=14.8 Hz, J_2=4.3 Hz), 2.09–1.50 (m, 15H), 1.38 (br, 1H), 1.15 (d, 3H, J=6.6 Hz), 0.88 (d, 3H, J=6.8 Hz), 0.77 (d, 3H, J=6.7 Hz); ^{13}C NMR (50. MHz, $CDCl_3$): δ 170.4, 138.1, 134.1, 124.5, 120.8, 95.9, 81.6, 74.5, 55.8, 38.0, 37.4, 36.6, 34.3, 34.1, 32.1, 29.2, 27.1, 24.5, 24.0, 21.4, 21.0, 18.3, 15.5; FT-IR (CCl_4): ν 2961, 2931, 2290, 2004, 1847, 1735, 1558, 1464, 1370, 1245, 1218, 1150, 1099, 1042, 1008, 980; $[\alpha]_D^{20}$=+102.0 (c=0.83, EtOAc); HRMS (ESI): *m/z*: calculated for $C_{23}H_{38}NaO_4$: 401.2662 $[M+Na]^+$; found: 401.2659 (resolution 10,000).

3.1.11. Acetic acid (*Z*)-[(4*R*,4a*R*,6*R*,10*R*,11*S*,12a*R*)-4-isopropyl-11-methoxymethoxy-1,10-dimethyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (17). To a stirred solution of diene **14** (20 mg, 0.049 mmol), in degassed CH_2Cl_2 (4.6 mL), was slowly added a solution Grubbs catalyst **15** (2.5 mg, 3.0 μmol) in degassed CH_2Cl_2 (370 μL). The reaction mixture was stirred for 15 h at room temperature, then for 7 h at 40 °C and then for 15 h at room temperature. Further Grubbs catalyst **15** (1 mg) was added and then heated at 40 °C for 7 h. The reaction mixture was treated with DMSO (20 μL) and stirred for 15 h at room temperature under argon atmosphere. Purification by flash chromatography (*n*-hexane to *n*-hexane/EtOAc, 95/5) afforded compound **17** (13.1 mg, 71%) as a colourless oil. R_f=0.77 (*n*-hexane/EtOAc, 9/1, TLC runs twice); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46–5.40 (m, 2H), 5.33 (br, 1H), 5.24–5.15 (m, 1H), 4.72 (d, 1H, J=6.9 Hz), 4.60 (d, 1H J=6.9 Hz), 3.89–3.82 (m, 1H), 3.42 (s, 3H), 3.02–2.93 (m, 1H), 2.81–2.71 (m, 1H), 2.34–2.21 (m, 2H), 2.06 (s, 3H), 2.00–1.75 (m, 6H), 1.71–1.50 (m, 4H), 1.46–1.37 (m, 1H), 1.13 (d, 3H J=6.6 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.67 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 138.7, 133.6, 124.9, 120.9, 95.8, 81.4, 72.7, 55.8, 37.5, 37.0, 35.1, 34.5, 33.6, 32.4, 26.9, 26.4, 24.5, 24.4, 21.2, 21.0, 18.0, 14.7; FT-IR (CCl_4): ν 2961, 2930, 2290, 2003, 1847, 1740, 1558, 1458, 1369, 1246, 1149, 1098, 1042, 1008, 930; $[\alpha]_D^{20}$=+86.4 (c=0.56, EtOAc); HRMS (ESI): *m/z*: calculated for $C_{23}H_{38}NaO_4$: 401.2662 $[M+Na]^+$; found: 401.2657 (resolution 10,000).

3.1.12. Acetic acid (*Z*)-[(4*R*,4a*R*,6*S*,10*R*,11*S*,12a*R*)-11-hydroxy-4-isopropyl-1,10-dimethyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (18). To a stirred solution of compound **16** (6.4 mg, 0.017 mmol), in acetone (390 μL), was added *p*-TSA monohydrate (8.0 mg, 0.042 mmol). After stirring for 90 h at room temperature, the reaction mixture was filtered through a plug of silica gel (eluting with CH_2Cl_2). Purification by flash chromatography (*n*-hexane/EtOAc, 85/15) afforded alcohol **18** (4.4 mg, 78%) as an amorphous white solid. R_f=0.38 (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (dt, 1H, J_1=11.0 Hz, J_2=4.8 Hz), 5.52 (dd, 1H, J_1=J_2=11.0 Hz), 5.31 (br, 1H), 5.11–5.04 (m, 1H), 3.92–3.84 (m, 1H), 2.84 (br, 1H), 2.76–2.67 (m, 1H), 2.29–2.22 (m, 1H), 2.07 (s, 3H), 2.03–1.93 (m, 1H), 1.88–1.48 (m, 11H), 1.39 (br, 1H), 1.17 (d, 3H, J=6.7 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 138.4, 133.3, 125.6, 121.3, 76.3, 75.0, 38.4, 38.0, 37.8, 37.0, 35.0, 32.6, 29.7, 27.6, 24.9, 24.4, 21.9, 21.4, 18.5, 15.9; FT-IR (CCl_4): ν 3631, 3455, 3015, 2961, 2931, 2847, 2290, 2003, 1847, 1734, 1558, 1452, 1370, 1245, 1218, 1102, 1010; $[\alpha]_D^{20}$=+88.4 (c=0.74, $CHCl_3$).

3.1.13. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid (*Z*)-[(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-acetoxy-1-isopropyl-4,7-dimethyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (20). To the mixed anhydride **19** (prepared according to Ref. 6b; 155 mg, 0.66 mmol) were added a solution of alcohol **18** (7.4 mg, 0.022 mmol) in $(CH_2Cl)_2$ (1.3 mL), followed by Et_3N (40 mg, 55 μL, 0.40 mmol) and DMAP (2.7 mg, 0.022 mmol). After stirring for 48 h at room temperature, the solvent was evaporated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc, 2/8) afforded compound **20** (5.6 mg, 54%) as a colourless oil. R_f=0.35 (*n*-hexane/

EtOAc, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, J=15.6 Hz), 7.47 (s, 1H), 7.09 (s, 1H), 6.58 (d, 1H, J=15.6 Hz), 5.67 (dt, 1H, J_1=10.8 Hz, J_2=5.0 Hz), 5.59 (dd, 1H, J_1=J_2=10.8 Hz), 5.31 (br, 1H), 5.21 (dt, 1H, J_1=11.5 Hz, J_2=3.0 Hz), 5.15–5.08 (m, 1H), 3.72 (s, 3H), 3.05–2.95 (m, 1H), 2.73 (ddd, 1H, J_1=14.6 Hz, J_2=10.8 Hz, J_3=4.0 Hz), 2.28 (dt, 1H, J_1=14.6 Hz, J_2=4.5 Hz), 2.14–1.25 (m, 16H) 1.06 (d, 3H, J=6.6 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 167.2, 138.6, 137.6, 135.9, 133.6, 125.1, 122.4, 120.8, 116.3, 77.7, 74.3, 37.7, 37.5, 36.5, 33.7, 33.6, 32.0, 27.1, 24.5, 23.9, 22.7, 21.5, 21.0, 17.8, 14.1; FT-IR (CCl_4): ν 3016, 2961, 2929, 2873, 2856, 2291, 2003, 1847, 1734, 1708, 1645, 1548, 1458, 1387, 1370, 1297, 1245, 1218, 1162, 1103, 1008, 933; $[\alpha]_D^{20}$=+28.9 (c=0.56, EtOAc); HRMS (ESI): m/z: calculated for $C_{28}H_{41}N_2O_4$: 469.3061 $[M+H]^+$; found: 469.3070 (resolution 10,000).

3.1.14. (2*S*,3*R*)-1-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-3-(4-methoxy-phenoxy)-pent-4-en-2-ol (28). To a cold (−60 °C), stirred solution of 1-allyloxy-4-methoxy-benzene[36] (575.5 mg, 3.5 mmol) in THF (27.9 mL), was added *sec*-butyllithium (2.5 mL, 3.5 mmol, 1.3 M in cyclohexane). After stirring for 1.5 h, the resulting orange solution (colour is important) was transferred, via cannula, to a cold (−78 °C) suspension of (*S*,*S*)-**4**[11] (3.5 mmol, based on the amount of $CpTiCl_3$) in Et_2O (25.0 mL). The reaction mixture was stirred for 3 h (colour changed from yellow to orange and finally dark brown), and then was treated with a solution of aldehyde **3** (495 mg, 1.95 mmol) in THF (5.0 mL). After 16 h, the reaction mixture was warmed to 0 °C and then stirred for 8 h. The mixture was then treated with a NH_4F aqueous solution (45%, 100 mL) and stirred for further 16 h. After filtration through a pad of Celite® the organic phase was separated and the aqueous layer was extracted with iPr$_2$O (3×50 mL). Purification of the crude by flash chromatography on silica gel (petroleum ether/EtOAc, 9/1) gave a white foam (2.0 g) which was subjected to crystallization of Taddol from CCl_4. The solid was accurately washed and the mother liquors combined and concentrated, affording compound **28** (809 mg, impure of Taddol). A second purification by flash chromatography on basic alumina (toluene/CH_2Cl_2, 95/5) finally afforded pure **28** (598 mg, 73%) as colourless oil. R_f=0.40 (basic alumina plate, toluene/CH_2Cl_2, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.94–6.75 (m, 4H), 6.04–5.79 (m, 1H), 5.44–5.21 (m, 3H), 4.50–4.36 (m, 2H), 4.28–4.03 (m, 1H), 3.75 (s, 3H), 3.35 (s, 6H), 2.88 (d, 1H, J=4.5 Hz), 2.61–2.47 (m, 1H), 2.17–1.49 (m, 10H), 0.93 (d, 3H, J=6.3 Hz), 0.84 (d, 3H, J=6.3 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 153.9, 152.3, 136.4, 134.6, 121.4, 118.5, 117.4, 114.4, 106.9, 83.9, 70.5, 55.6, 55.3, 39.9, 36.0, 34.4, 32.4, 27.0, 24.4, 22.1, 21.0, 17.2; FT-IR (CCl_4): ν 3602, 3468, 2960, 2834, 2289, 1848, 1730, 1558, 1504, 1465, 1386, 1227, 1111, 929; $[\alpha]_D^{20}$=+51.8 (c=0.48, EtOAc); HRMS (ESI): calculated for $C_{25}H_{42}NO_5$: 436.3063 $[M+NH_4]^+$; found: 436.3066 (resolution 10,000).

3.1.15. 1-{(*R*)-1-[(*S*)-2-((1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl)-1-methoxy-methoxy-ethyl]-allyloxy}-4-methoxy-benzene (29). To a stirred solution of alcohol **28** (598 mg, 1.43 mmol) in CH_2Cl_2 (4.0 mL), was added DIPEA (1.5 mL, 8.58 mmol), TBAI (106 mg, 0.29 mmol) and MOMCl (543 μL, 7.15 mmol). After stirring for 7 h, the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (10 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **29** (628 mg, 95%) as a colourless oil. R_f=0.28 (basic alumina plate, iPr$_2$O/toluene, 5/95); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92–6.75 (m, 4H), 5.91 (ddd, 1H, J_1=17.1 Hz, J_2=10.7 Hz, J_3=6.3 Hz), 5.34–5.22 (m, 3H), 4.86 (s, 3H), 4.67 (br, 1H), 4.33 (d, 1H, J=5.3 Hz), 4.22–4.15 (m, 1H), 3.75 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 2.43 (br, 1H), 2.05–1.52 (m, 9H), 0.91 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 152.6, 137.9, 135.1, 120.3, 117.9, 117.3, 114.3, 107.0, 97.8, 83.3, 79.5, 55.6, 55.3, 54.3, 40.3, 36.3, 34.0, 31.8, 26.9, 24.4, 22.2, 21.2, 17.3; FT-IR (CCl_4): ν 2932, 2833, 2289, 2007, 1848, 1742, 1544, 1510, 1466, 1442, 1369, 1230, 1153, 1040, 926; $[\alpha]_D^{20}$=+59.7 (c=0.47, EtOAc); HRMS (ESI): calculated for $C_{27}H_{46}NO_6$: 480.3325 $[M+NH_4]^+$; found: 480.3318 (resolution 10,000).

3.1.16. (1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxy-methoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enecarbaldehyde (30). To a stirred solution of compound **29** (602 mg, 1.30 mmol) in CH_3CN/H_2O (7.6 mL, v/v: 98/2), was added $LiBF_4$ (122 mg, 1.30 mmol). After stirring for 6 h, the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (15 mL) and CH_2Cl_2 (10 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL) to give crude **30** (540 mg), which was used without further purification. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1), for analytical purposes, afforded pure **30** as a colourless oil. R_f=0.47 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.81 (d, 1H, J=3.9 Hz), 6.92–6.70 (m, 4H), 5.90–5.70 (m, 1H), 5.49–5.19 (m, 3H), 4.85–4.62 (m, 3H), 3.75 (s, 3H), 3.65 (dt, 1H, J_1=9.5 Hz, J_2=3.8 Hz), 3.31 (s, 3H), 2.72–2.45 (m, 2H) 2.15–1.65 (m, 9H), 0.94 (d, 3H, J=6.4 Hz), 0.84 (d, 3H, J=6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 206.9, 135.7, 134.4, 121.5, 118.8, 117.0, 114.4, 97.4, 81.9, 79.0, 55.6, 51.8, 37.5, 34.0, 30.1, 28.1, 24.2, 21.7, 20.7, 18.2; FT-IR (CCl_4): ν 2962, 2290, 1719, 1558, 1508, 1261, 1225, 1103, 1008, 980, 823; $[\alpha]_D^{20}$=+36.6 (c=0.13, EtOAc); HRMS (ESI): calculated for $C_{25}H_{40}NO_5$: 434.2906 $[M+NH_4]^+$; found: 434.2914 (resolution 10,000).

3.1.17. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxy-methoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-methanol (31). To a stirred solution of crude **30**, in EtOH (13.6 mL), was added $NaBH_4$ (74 mg, 1.95 mmol). After stirring for 20 min, the reaction mixture was treated with solid NH_4Cl (696 mg, 13.0 mmol), stirred for further 30 min, diluted with iPr$_2$O and dried over Na_2SO_4. Purification by flash chromatography (petroleum ether/EtOAc, 8/2) afforded compound **31** (408 mg, 75%, over two steps) as a colourless oil. R_f=0.15 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88–6.75 (m,

4H), 5.91 (ddd, 1H, $J_1=16.8$ Hz, $J_2=10.2$ Hz, $J_3=6.3$ Hz), 5.33–5.27 (m, 3H), 4.88 (d, 1H, $J=6.8$ Hz), 4.76 (d, 1H, $J=6.8$ Hz), 4.67–4.61 (m, 1H), 3.93 (dt, 1H, $J_1=9.6$ Hz, $J_2=3.3$ Hz), 3.82–3.71 (m, 4H), 3.63–3.54 (m, 1H), 3.39 (s, 3H), 2.43 (br, 1H), 2.07 (br, 1H), 2.00–1.47 (m, 10H), 0.91 (d, 3H, $J=6.8$ Hz), 0.84 (d, 3H, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 152.1, 137.1, 134.8, 121.0, 118.8, 117.2, 114.4, 97.6, 82.7, 79.8, 62.0, 56.0, 55.6, 41.3, 36.3, 34.2, 30.9, 27.0, 24.2, 22.2, 21.0, 16.6; FT-IR (CCl_4): ν 3514, 2961, 2933, 2896, 2290, 2003, 1857, 1544, 1507, 1259, 1228, 1105, 1041, 1008, 930; $[\alpha]_D^{20}=+61.2$ ($c=0.57$, EtOAc); HRMS (ESI): calculated for $C_{25}H_{42}NO_5$: 436.3063 $[M+NH_4]^+$; found: 436.3060 (resolution 10,000).

3.1.18. Methanesulfonic acid (1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl ester (32). To a cold (0 °C), stirred solution of alcohol **31** (367 mg, 0.88 mmol) in CH_2Cl_2 (7.0 mL), was added TEA (367 μL, 2.63 mmol) followed by MsCl (102 μL, 1.30 mmol). After 1 h, the reaction mixture was warmed to room temperature and stirred for 2 h. The solution was concentrated under reduced pressure and filtered through a plug of silica gel. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 8/2) afforded mesylate **32** (414 mg, 95%) as a colourless oil. $R_f=0.20$ (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89–6.76 (m, 4H), 5.87 (ddd, 1H, $J_1=16.2$ Hz, $J_2=10.4$ Hz, $J_3=5.8$ Hz), 5.37–5.29 (m, 3H), 4.85 (d, 1H, $J=6.9$ Hz), 4.78–4.70 (m, 2H), 4.34–4.13 (m, 2H), 3.85 (dt, $J_1=10.4$ Hz, $J_2=2.6$ Hz, 1H), 3.75 (s, 3H), 3.33 (s, 3H), 3.01 (s, 3H), 2.47 (br, 1H), 2.27–2.13 (m, 1H), 2.07–1.50 (m, 9H), 0.92 (d, 3H, $J=6.9$ Hz), 0.89 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 152.2, 135.8, 134.8, 120.9, 118.7, 117.1 (2C), 114.4 (2C), 97.5, 82.2, 79.1, 69.4, 55.8, 55.6, 37.7, 37.3, 37.1, 33.8, 30.0, 27.2, 23.9, 22.0, 20.7, 18.1; FT-IR (CCl_4): ν 2962, 2898, 2291, 2004, 1857, 1742, 1544, 1507, 1370, 1345, 1229, 1178, 1106, 1041, 1007, 979; $[\alpha]_D^{20}=+64.0$ ($c=0.48$, EtOAc); HRMS (ESI): calculated for $C_{26}H_{44}NO_7S$: 514.2839 $[M+NH_4]^+$; found: 514.2831 (resolution 10,000).

3.1.19. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetonitrile (33). To a stirred solution of mesylate **32** (410 mg, 0.83 mmol) in CH_3CN (8.0 mL), was added 18-crown-6 (1.09 g, 4.13 mmol) and KCN (269 mg, 4.13 mmol). After stirring for 2.5 h at 80 °C, the red solution was diluted with CH_2Cl_2 and filtered through a plug of silica gel. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **33** (353 mg, quant.) as a colourless oil. $R_f=0.31$ (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.92–6.75 (m, 4H), 5.87 (ddd, 1H, $J_1=16.3$ Hz, $J_2=10.4$ Hz, $J_3=5.9$ Hz), 5.43–5.30 (m, 3H), 4.88–4.75 (m, 3H), 3.80–3.69 (m, 4H), 3.32 (s, 3H), 2.53 (br, 1H), 2.41–2.30 (m, 2H), 2.30–2.12 (m, 1H), 2.12–1.88 (m, 3H), 1.77–1.40 (m, 6H), 0.93 (d, 3H, $J=6.3$ Hz), 0.89 (d, 3H, $J=6.3$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.9, 152.0, 134.8, 134.7, 121.0, 119.8, 119.0, 117.0, 114.4, 97.7, 81.7, 79.2, 55.8, 55.6, 39.7, 34.4, 29.4, 27.3, 26.5, 23.6, 22.0, 20.5, 19.2, 17.3; FT-IR (CCl_4): ν 2961, 2934, 2896, 2847, 2834, 2290, 2003, 1857, 1558, 1507, 1465, 1441, 1427, 1388, 1370, 1250, 1228, 1182, 1152, 1106, 1066, 1041, 1006, 980; $[\alpha]_D^{20}=+23.9$ ($c=1.02$, EtOAc); HRMS (ESI): calculated for $C_{26}H_{38}NO_4$: 428.2801 $[M+H]^+$; found: 428.2811 (resolution 10,000).

3.1.20. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetaldehyde (34). To a cold (−78 °C), stirred solution of compound **33** (67 mg, 0.16 mmol) in toluene/*n*-hexane (2.55 mL, v/v: 1/2), was added DIBAL-H (1.5 M in toluene, 1.1 mL, 1.56 mmol). After stirring for 1 h, the reaction mixture was treated with EtOAc (1.3 mL) and an aqueous tartaric acid solution (1.0 M, 1.3 mL), then warmed to room temperature and stirred for further 1 h. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (5×5 mL). The organic extracts were washed with a saturated $NaHCO_3$ aqueous solution (2×5 mL) to give crude **34** (68 mg), which was used without further purification. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 14/1), for analytical purposes, afforded pure **34** (67 mg, quant.) as a colourless oil. $R_f=0.39$ (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, 1H, $J=2.2$ Hz), 6.89–6.74 (m, 4H), 5.87 (ddd, 1H, $J_1=17.1$ Hz, $J_2=10.7$ Hz, $J_3=6.0$ Hz), 5.38–5.24 (m, 3H), 4.86–4.70 (m, 3H), 3.80–3.67 (m, 4H), 3.31 (s, 3H), 2.53–2.29 (m, 4H), 2.07–1.85 (m, 3H), 1.73–1.60 (m, 4H), 1.60–1.46 (m, 1H), 1.35–1.23 (m, 1H), 0.95 (d, 3H, $J=6.7$ Hz), 0.84 (d, 3H, $J=6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 154.0, 152.2, 135.8, 134.9, 121.0, 118.7, 117.1, 114.4, 99.6, 82.1, 79.3, 55.8, 55.6, 43.3, 40.1, 34.7, 32.5, 29.8, 27.5, 23.9, 22.1, 20.8, 19.0; FT-IR (CCl_4): ν 2961, 2910, 2834, 2713, 2003, 1857, 1727, 1559, 1507, 1466, 1442, 1388, 1370, 1259, 1226, 1152, 1105, 1068, 1042, 1008, 980; $[\alpha]_D^{20}=+27.6$ ($c=0.46$, EtOAc); HRMS (ESI): calculated for $C_{26}H_{38}O_5$: 448.3063 $[M+NH_4]^+$; found: 448.3048 (resolution 10,000).

3.1.21. (*S*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (35). To a cold (0 °C), stirred solution of AllMgBr (1.0 M in Et_2O, 3.8 mL, 3.80 mmol) was added ^{d}Ipc$_2$BOMe[13c] (1.0 M in THF, 4.2 mL, 4.18 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h, cooled to −78 °C and treated with a solution of aldehyde **34** (545 mg, 1.27 mmol) in THF (10.0 mL). After stirring for 48 h, the reaction mixture was warmed to 0 °C and treated with a NaOH aqueous solution (6.0 M, 6.4 mL) and H_2O_2 (35%, 4.4 mL). After 3 h at room temperature, the mixture was heated to 50 °C and stirred for further 2 h. The organic phase was separated and the aqueous layer was extracted with EtOAc (3×10 mL). Purification of the crude by flash chromatography (petroleum ether/EtOAc, 85/15) afforded compound **35** (420 mg, 70%) as a colourless oil. For characterization and analytical data, see below.

3.1.22. (*S*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (35). To a cold (0 °C), stirred suspension of (*R*,*R*)-**4**[11] (0.53 mmol, based on the amount of $CpTiCl_3$) in Et_2O (6.0 mL), was added a solution of AllMgBr (1.0 M in Et_2O, 444 μL, 0.44 mmol). After stirring the brown-green solution for 1.5 h, the reaction mixture was cooled to −78 °C. To this solution

was added, via cannula, a solution of aldehyde **34** (96 mg, 0.22 mmol) in Et_2O (2.0 mL). The reaction mixture was stirred for 3 h, treated with a NH_4F aqueous solution (45%, 5 mL) and stirred for further 15 h at room temperature. The organic phase was separated and the aqueous layer was extracted with iPr_2O (3×10 mL). Purification of the crude by flash chromatography (petroleum ether/EtOAc, 85/15) afforded compound **35** (92 mg, 87%) as a colourless oil. R_f=0.38 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90–6.78 (m, 4H), 5.96–5.79 (m, 2H), 5.39–5.30 (m, 3H), 5.20–5.11 (m, 2H), 4.87 (d, 1H, J=6.8 Hz), 4.77 (d, 1H, J=6.8 Hz), 4.75–4.70 (m, 1H), 3.89–3.73 (m, 5H), 3.36 (s, 3H), 2.42–2.25 (m, 2H), 2.17–1.99 (m, 2H), 1.99–1.67 (m, 7H), 1.67–1.48 (m, 3H), 1.43–1.25 (m, 2H), 0.93 (d, 3H, J=6.7 Hz), 0.85 (d, 3H, J=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.9, 152.2, 136.5, 134.9, 134.7, 121.0, 118.7, 118.4, 117.2, 114.4, 97.4, 82.5, 79.4, 68.3, 55.8, 55.6, 42.2, 38.8, 34.7, 34.3, 34.1, 30.4, 27.2, 24.2, 22.5, 20.9, 18.0; FT-IR (CCl_4): ν 3585, 3403, 3028, 2961, 2290, 2004, 1855, 1548, 1506, 1465, 1441, 1386, 1368, 1260, 1227, 1150, 1103, 1010, 927; $[\alpha]_D^{20}$=+77.0 (c=1.04, EtOAc); HRMS (ESI): calculated for $C_{29}H_{44}NaO_5$: 495.30809 [M+Na]$^+$; found: 495.30596 (resolution 23,400).

3.1.23. *tert*-Butyl-((*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl}-but-3-enyloxy)-diphenyl-silane (36). To a stirred solution of alcohol **35** (500 mg, 1.06 mmol) in CH_2Cl_2 (12.0 mL), was added imidazole (360 mg, 5.29 mmol) followed by TBDPSCl (581 mg, 2.11 mmol). After stirring for 16 h at room temperature, the solvent was removed under reduced pressure and the crude was purified by flash chromatography (petroleum ether/EtOAc, 25/1) to give compound **36** (677 mg, 90%) as a colourless oil. R_f=0.59 (petroleum ether/EtOAc, 8/2); HRMS (ESI): calculated for $C_{45}H_{66}NO_5Si$: 728.4710 [M+NH_4]$^+$; found: 728.4700 (resolution 10,000).

3.1.24. (2*S*,3*R*)-1-{(1*R*,5*R*,6*R*)-6-[(*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-5-isopropyl-2-methyl-cyclohex-2-enyl}-3-(4-methoxy-phenoxy)-pent-4-en-2-ol (37). To a cold (−20 °C), stirred solution of compound **36** (520 mg, 0.73 mmol) in CH_2Cl_2 (22.0 mL), was added Me_2S (209 mg, 3.36 mmol) and $BF_3\cdot OEt_2$ (550 mg, 3.88 mmol).[37] After 30 min (time control is essential), the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (4.0 mL) and warmed to room temperature under vigorous stirring. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). Purification of the crude by flash chromatography (toluene/iPr_2O, 8/2) afforded compound **37** (219 mg, 45%) as a colourless oil. R_f=0.31 (toluene/iPr_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.69 (m, 4H), 7.47–7.35 (m, 6H), 6.91–6.81 (m, 4H), 5.94–5.81 (m, 2H), 5.39–5.29 (m, 2H), 5.17 (br, 1H), 5.01–4.94 (m, 2H), 4.38 (dd, 1H, J_1=6.7 Hz, J_2=4.1 Hz), 3.92–3.78 (m, 5H), 2.33–2.24 (m, 2H), 2.20–2.12 (m, 1H), 2.01–1.84 (m, 2H), 1.70–1.32 (m, 9H), 1.07 (s, 9H), 0.88 (d, 3H, J=6.7 Hz), 0.80 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 152.0, 136.0, 135.6, 135.3, 135.0, 134.6, 134.3, 129.5, 127.5, 121.1, 119.5, 117.4, 117.1, 114.5, 83.8, 70.9, 70.6, 55.7, 40.9, 38.8, 34.2, 33.4, 32.3, 31.2, 27.3, 27.0, 23.9, 22.3, 20.7, 19.4; FT-IR (CCl_4): ν 3400, 3072, 2963, 2905, 2290, 2001, 1854, 1558, 1442, 1413, 1296, 1219, 1018, 823; $[\alpha]_D^{20}$=+30.1 (c=0.77, EtOAc).

3.1.25. 2,2-Dimethyl-propionic acid (1*S*,2*R*)-1-{(1*R*,5*R*,6*R*)-6-[(*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-5-isopropyl-2-methyl-cyclohex-2-enylmethyl}-2-(4-methoxy-benzyl)-but-3-enyl ester (38). To a stirred solution of compound **37** (87 mg, 0.13 mmol), pyridine (1.0 mL) and DMAP (3.2 mg, 0.026 mmol) in CH_2Cl_2 (2.0 mL), was added PivCl (32 μL, 0.26 mmol). After stirring for 16 h at 40 °C, the reaction mixture was treated with a saturated NH_4Cl aqueous solution (5.0 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with water and brine. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **38** (65 mg, 66%) as a colourless oil. R_f=0.45 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.64 (m, 4H), 7.48–7.31 (m, 6H), 6.90–6.76 (m, 4H), 6.08–5.96 (m, 1H), 5.85 (ddd, 1H, J_1=17.1 Hz, J_2=10.6 Hz, J_3=6.4 Hz), 5.41–5.32 (m, 2H), 5.19–5.03 (m, 3H), 4.56 (dd, 1H, J_1=J_2=5.3 Hz), 3.94 (br, 1H), 3.77 (s, 3H), 2.37–2.27 (m, 1H), 2.21–2.11 (m, 1H), 2.06–1.97 (m, 1H), 1.96–1.84 (m, 1H), 1.75–1.41 (m, 6H), 1.41–1.26 (m, 3H), 1.13 (s, 9H), 1.07 (s, 9H), 0.79 (d, 3H, J=7.1 Hz), 0.77 (d, 3H, J=6.8 Hz); $[\alpha]_D^{20}$=+6.0 (c=0.95, EtOAc); HRMS (ESI): calculated for $C_{48}H_{67}O_5Si$: 751.4758 [M+H]$^+$; found: 751.4761 (resolution 12,000).

3.1.26. 2,2-Dimethyl-propionic acid (1*S*,2*R*)-1-((1*R*,5*R*,6*R*)-6-[(*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-5-isopropyl-2-methyl-cyclohex-2-enylmethyl)-2-hydroxy-but-3-enyl ester (39). To a cold (0 °C), stirred solution of compound **38** (20 mg, 0.03 mmol) in CH_3CN/H_2O (328 μL, v/v: 4/1), was added ceric ammonium nitrate (36 mg, 0.07 mmol).[38] After stirring for 1 h, the reaction mixture was filtered through a plug of silica (eluting with EtOAc). Purification of the crude by flash chromatography (toluene/iPr_2O, 95/5) afforded **39** (11 mg, 67%) as a colourless oil. R_f=0.31 (toluene/iPr_2O, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74–7.65 (m, 4H), 7.47–7.32 (m, 6H), 6.07–5.72 (m, 2H), 5.38–4.84 (m, 6H), 4.14 (br, 1H), 3.88 (br, 1H), 2.40–1.80 (m, 4H), 1.73–1.05 (m, 29H), 0.78 (d, 3H, J=6.7 Hz), 0.76 (d, 3H, J=6.5 Hz).

3.1.27. 2,2-Dimethyl-propionic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenylsilanyloxy)-7-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (40). To a stirred solution of diene **39** (11 mg, 0.017 mmol) in degassed CH_2Cl_2 (2.1 mL), was slowly added a solution of Grubbs catalyst **15** (1.5 mg, 0.002 mmol) in CH_2Cl_2 (166 μL) and stirred for 24 h. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded **40** (2.2 mg, 21%) as a colourless oil. For characterization and analytical data, see below.

3.1.28. 2,2-Dimethyl-propionic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (41). To stirred a solution of diene **38** (50 mg, 0.066 mmol) in

CH_2Cl_2 (5.5 mL), was added, via syringe pump (during 45 min), a freshly prepared solution of Grubbs catalyst **15** (5.7 mg, 0.0066 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 15 h, the reaction mixture was heated to 40 °C for 24 h. Purification of the crude by flash chromatography (petroleum ether/CH_2Cl_2, 4/6) afforded the starting material **38** (7.7 mg) and the RCM product **41** (25 mg, 52%; 62% considering the recovered starting material) as a colourless oil. R_f=0.50 (petroleum ether/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.63 (m, 4H), 7.51–7.33 (m, 6H), 6.80–6.63 (m, 4H), 6.12 (dt, 1H, J_1=11.0 Hz, J_2=5.3 Hz), 5.71 (dd, 1H, J_1=11.0 Hz, J_2=9.6 Hz), 5.44 (dt, 1H, J_1=10.6 Hz, J_2=3.5 Hz), 5.23 (br, 1H), 4.97 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 4.01 (br, 1H), 3.76 (s, 3H), 2.64–2.54 (m, 1H), 2.43–2.34 (m, 1H), 1.87–1.59 (m, 10H), 1.52–1.35 (m, 2H), 1.26 (s, 9H), 1.17–1.08 (m, 10H), 0.81 (d, 3H, J=6.8 Hz), 0.55 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 153.9, 151.6, 137.2, 135.9, 134.1, 133.9, 130.6, 129.7, 127.6, 121.0, 117.1, 114.4, 74.9, 74.1, 72.8, 55.6, 39.0, 37.6, 37.3, 36.2, 36.1, 33.2, 31.8, 27.2, 27.0, 26.9, 24.3, 23.8, 21.0, 19.2, 15.7; FT-IR (CCl_4): ν 3072, 2962, 2932, 2859, 2291, 2003, 1847, 1730, 1551, 1507, 1480, 1463, 1442, 1428, 1389, 1367, 1260, 1229, 1158, 1106, 1065, 1008, 980; $[\alpha]_D^{20}$=+137.7 (c=0.74, EtOAc); HRMS (ESI): calculated for $C_{39}H_{55}O_3Si$: 599.3921 [M-PMPOH+H]$^+$; found: 599.3918 (resolution 10,000).

3.1.29. 2,2-Dimethyl-propionic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenylsilanyloxy)-7-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (40). To a cold (0 °C), stirred solution of compound **41** (22 mg, 0.03 mmol) in CH_3CN/H_2O (1.0 mL, v/v: 4/1), was added ceric ammonium nitrate (35 mg, 0.064 mmol) in one portion.[38] After 15 min, the reaction mixture was diluted with CH_3CN and filtered through a plug of silica gel. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 8/2) afforded compound **40** (14.8 mg, 80%) as a colourless oil. R_f=0.45 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.61 (m, 4H), 7.49–7.35 (m, 6H), 6.01 (dt, 1H, J_1=11.1 Hz, J_2=5.2 Hz), 5.62 (dd, 1H, J_1=11.1 Hz, J_2=9.6 Hz), 5.27–5.17 (m, 2H), 4.60 (dd, 1H, J_1=9.6 Hz, J_2=2.9 Hz), 3.93 (br, 1H), 2.53–2.42 (m, 1H), 2.32–2.23 (m, 1H), 1.92–1.58 (m, 9H), 1.53–1.32 (m, 2H), 1.31–1.20 (m, 10H), 1.09 (s, 9H), 0.81 (d, 3H, J=6.8 Hz), 0.58 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 137.0, 135.9, 135.8, 134.3, 134.1, 129.6, 129.2, 129.1, 127.6, 127.5, 121.4, 76.6, 72.7, 68.5, 39.0, 37.9, 37.0, 35.9, 35.6, 32.9, 31.8, 27.2, 27.0, 24.3, 23.7, 21.0, 19.2, 16.2; FT-IR (CCl_4): ν 3448, 3072, 3051, 2962, 2931, 2859, 2291, 2003, 1847, 1731, 1558, 1480, 1462, 1428, 1389, 1368, 1262, 1218, 1156, 1104, 1009, 980; $[\alpha]_D^{20}$=+71.3 (c=0.94, EtOAc); HRMS (ESI): calculated for $C_{39}H_{56}NaO_4Si$: 639.38400 [M+Na]$^+$; found: 639.38421 (resolution 17,000).

3.1.30. (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-ol (42). To a stirred solution of compound **37** (12 mg, 0.018 mmol) in degassed benzene (1.66 mL), was added, via syringe pump (during 30 min), a freshly prepared solution of Grubbs catalyst **15** (1.5 mg, 0.0018 mmol) in benzene (0.14 mL). After 19 h at 80 °C, the reaction mixture was cooled at room temperature, treated with DMSO (5 μL) and stirred for 12 h. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **42** (9.2 mg, 80%) as a colourless oil. R_f=0.78 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.66 (m, 4H), 7.48–7.33 (m, 6H), 6.79 (s, 4H), 6.11 (dt, 1H, J_1=11.4 Hz, J_2=5.1 Hz), 5.74 (dd, 1H, J_1=11.4 Hz, J_2=9.9 Hz), 5.23 (br, 1H), 4.90 (dd, 1H, J_1=9.9 Hz, J_2=2.6 Hz), 4.32–4.21 (m, 1H), 4.04–3.96 (m, 1H), 3.78 (s, 3H), 2.75 (s, 1H), 2.60–2.50 (m, 1H), 2.41–2.29 (m, 1H), 1.92–1.73 (m, 3H), 1.73–1.53 (m, 8H), 1.42–1.31 (m, 1H), 1.21–1.03 (m, 10H), 0.80 (d, 3H, J=6.8 Hz), 0.57 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 151.3, 137.2, 135.9, 134.2, 134.1, 130.8, 129.6, 127.6, 127.5, 127.0, 121.1, 117.3, 114.6, 77.6, 73.5, 72.6, 55.6, 38.0, 37.0, 35.9, 35.7, 33.3, 33.0, 27.2, 27.0, 24.3, 23.9, 19.2, 16.5, 14.0; FT-IR (CCl_4): ν 3400, 3072, 2962, 2859, 2290, 2003, 1852, 1742, 1558, 1428, 1389, 1258, 1219, 1105, 1066, 1007, 980; $[\alpha]_D^{20}$=+94.0 (c=0.92, EtOAc); HRMS (ESI): calculated for $C_{41}H_{54}NaO_4Si$: 661.36835 [M+Na]$^+$; found: 661.36917 (resolution 17,600).

3.1.31. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (43). To a stirred suspension of the mixed anhydride **19** (prepared according to Ref. 6b, 102 mg, 0.43 mmol) and of alcohol **42** (9.2 mg, 0.014 mmol) in $(CH_2Cl)_2$ (0.9 mL), was added DMAP (1.8 mg, 0.014 mmol) followed by TEA (40 μL, 0.29 mmol). After stirring for 1 h, the suspension (slightly more soluble) was heated to 80 °C for 2 h, cooled to room temperature overnight and heated to 80 °C for further 4 h. Purification by flash chromatography (petroleum ether/EtOAc, 1/9) afforded compound **43** (9.2 mg, 82%) as a clear yellowish oil. R_f=0.3 (petroleum ether/EtOAc, 2/8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.64 (m, 4H), 7.58 (d, 1H, J=15.7 Hz), 7.52 (s, 1H), 7.48–7.32 (m, 6H), 7.10 (s, 1H), 6.78–6.67 (m, 4H), 6.61 (d, 1H, J=15.7 Hz), 6.14 (dt, 1H, J_1=11.1 Hz, J_2=5.1 Hz), 5.81 (dd, 1H, J_1=11.1 Hz, J_2=10.5 Hz), 5.62–5.52 (m, 1H), 5.22 (br, 1H), 5.05–4.96 (m, 1H), 4.01 (br, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.66–2.54 (m, 1H), 2.44–2.33 (m, 1H), 1.91–1.02 (m, 22H), 0.78 (d, 3H, J=6.7 Hz), 0.54 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.9, 154.1, 151.8, 138.6, 137.0, 136.0, 135.9, 134.2, 134.0, 130.4, 129.6, 127.7, 127.6, 127.5, 122.2, 121.0, 117.7, 116.5, 114.4, 75.4, 74.3, 72.7, 55.6, 37.9, 37.1, 36.1, 36.0, 33.6, 33.1, 32.0, 27.0, 26.5, 24.3, 23.7, 21.0, 19.3, 16.1; FT-IR (CCl_4): ν 2963, 2291, 2002, 1847, 1709, 1646, 1558, 1413, 1260, 1219, 1160, 1099, 1012; $[\alpha]_D^{20}$=+71.6 (c=0.92, EtOAc); HRMS (ESI): calculated for $C_{48}H_{61}N_2O_5Si$: 773.43443 [M+H]$^+$; found: 773.43474 (resolution 15,100); calculated for $C_{48}H_{60}N_2NaO_5Si$: 795.41637 [M+Na]$^+$; found: 795.41775 (resolution 15,100).

3.1.32. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-hydroxy-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (44). To a

stirred solution of compound **43** (10 mg, 0.013 mmol) in THF (0.5 mL), was added TBAF (1.0 M in THF, 52 μL, 0.057 mmol). After stirring for 19 h, the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 1/9) afforded compound **44** (5.9 mg, 85%) as a clear yellowish oil. R_f=0.15 (petroleum ether/EtOAc, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H, J=15.7 Hz), 7.48 (s, 1H), 7.10 (s, 1H), 6.84–6.74 (m, 4H), 6.62 (d, 1H, J=15.7 Hz), 6.01 (dt, 1H, J_1=11.4 Hz, J_2=4.9 Hz), 5.86 (dd, 1H, J_1=11.4 Hz, J_2=9.5 Hz), 5.71–5.64 (m, 1H), 5.33 (br, 1H), 5.17 (dd, 1H, J_1=9.5 Hz, J_2=2.7 Hz), 4.05 (br, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.83–2.74 (m, 1H), 2.54–2.44 (m, 1H), 2.17–1.26 (m, 14H), 0.88 (d, 3H, J=6.8 Hz), 0.79 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 154.3, 151.8, 138.9, 137.1, 136.1, 129.2, 128.4, 122.3, 121.1, 117.7, 116.4, 114.5, 75.4, 74.1, 71.7, 55.6, 37.9, 37.6, 36.2, 35.7, 33.6, 32.9, 32.3, 27.1, 24.5, 23.9, 21.0, 16.1; FT-IR (CCl_4): ν 3468, 2963, 2928, 2855, 2290, 2002, 1847, 1709, 1559, 1414, 1261, 1219, 1099, 1013; $[\alpha]_D^{20}$=+79.3 (c=0.30, EtOAc); HRMS (ESI): calculated for $C_{32}H_{43}N_2O_5$: 535.3166 $[M+H]^+$; found: 535.3165 (resolution 10,000).

3.1.33. Molecular mechanics and semi-empirical calculations. The potential energy surface of structures **A**–**F** (Z and E stereoisomers, Fig. 2) was searched using Monte Carlo[27b] conformational searches with MacroModel (v8.5)[27a] running on a 3.0 GHz Intel Pentium 4 with LINUX Red Hat 9 operating system. The calculations were performed with the MM2* force field using the GB/SA continuum solvent model for $CHCl_3$.[27c] Interconversion of ring structures was enabled using the ring-opening method of Still.[39] Ring closure bonds were defined for both the six and ten-membered rings present in structures **A**–**F**. Each search was run in blocks of 15,000 steps until convergence was reached, that is, no new structures were found and the global minimum energy remained constant throughout the search. Typically, 50,000–60,000 steps were enough to ensure convergence. Each new cycle used as input the results of the previous cycle and different ring-closure bond choices were used. During the search, structures with energy 20 kJ mol^{-1} higher than the current global minimum were discarded. Structures were fully minimized for up to 5000 steps until the gradient was less than 0.05 kJ Å mol^{-1} using the Polak Ribiere conjugate gradient method.[40] Redundant conformations were removed after heavy atom superimposition (RMSD cutoff=0.25 Å). The lowest energy conformers obtained with MacroModel for the Z and the corresponding E stereoisomers of structures **A**–**F** (using a 20.0 kJ mol^{-1} energy window from the global minima) were optimized at the PM3 level[24] using the Gaussian 03 package.[28]

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