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The synthesis of 3-hydroxy-2,4,8-trimethyldec-8-enolides and an approach to 3,4-dihydroxy-2,4,6,8-tetramethyldec-8-enolide†

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The synthesis of several derivatives of 3-hydroxy-2,4,8-trimethyldec-8-enolide and attempts at the synthesis of 3,4-dihydroxy-2,4,6,8-tetramethyldec-8-enolide (**1**), a structure which has been assigned to a metabolite of the phytopathogenic fungus, *Botrytis cinerea*, gave products whose spectroscopic data had significant differences from those reported for the natural product **1**. The rare 11-membered lactone rings were constructed by ring-closing metathesis reactions. The increase in conformational restrictions imposed by the substituents has a high influence on the stereochemistry of the ring-closing metathesis reaction and gives rise to a decrease in the yield for the synthesis of 11-membered lactones. The predominant alkene which was obtained was the (*Z*)-isomer. The observed spectroscopic differences between the synthesized lactones and the natural product and the spectroscopic data of its acetylated derivative **26a** allowed us to revise the structure **1** to that of the γ-butyrolactone **26**.

Introduction

Botrytis cinerea is an aggressive phytopathogenic fungus that affects more than 200 plant species[1] producing a grey powdery mould on the plants. The major phytotoxic metabolites of *B. cinerea* are a family of sesquiterpenes with the botryane skeleton[2] and two families of polyketide lactones with a common biosynthetic origin. These are the botrylactones, and the botcinic and botcineric acids with their cyclic relatives, the botcinins.[3]

The structure, 3,4-dihydroxy-2,4,6,8-tetramethyldec-8-enolide (**1**), has been assigned to a metabolite which was isolated from a mutant strain of *B. cinerea*. This structure (Fig. 1) was assigned on the basis of NMR data using COSY, HSQC, HMBC and nOe-1D experiments.[4] However there are only a few examples of naturally occurring 11-membered lactones[5] and the relative thermodynamic instability of 11-membered lactones has made their synthesis and that of their derivatives difficult even using Mitsunobu lactonization[6] or an intramolecular Reformatsky reaction.[7] Compound **1** was isolated in a very small amount so its possible biological activity could not be determined. In the context of our interest in the metabolites of *B. cinerea*, we have attempted to verify the structure **1** by means of a total synthesis which would not only provide information about the chemistry of this interesting family but also allow us to study its biological activity. Recently we have carried out the enantioselective synthesis of **3**,[8] a close analogue of the structure assigned to the natural product. We examined the use of a 'mutasynthetic' biotransformation in order to achieve the chemo- and stereoselective functionalization of C-4. However no such functionalization was detected and so we have resorted to chemical methods to achieve this target. In this paper we describe the synthesis of several 3-hydroxy-2,4,8-trimethyldec-8-enolides and an approach to the synthesis of the reported structure **1** for the natural product.

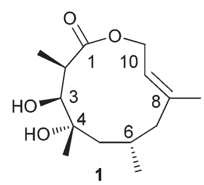

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Fig. 1 Structure of compound **1**.

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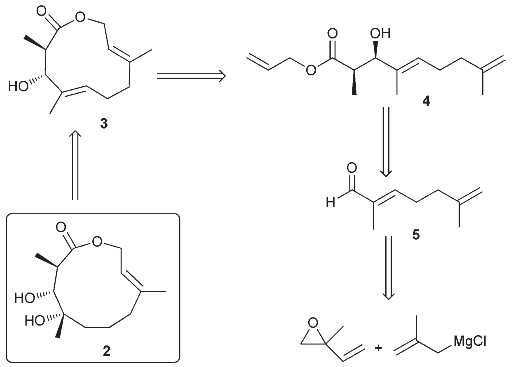
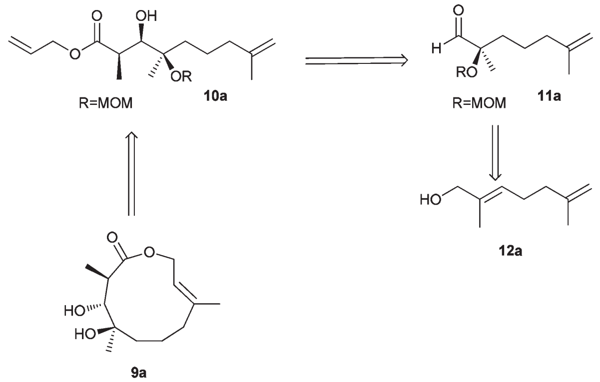
† Electronic supplementary information (ESI) available: Copies of the ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final products. See DOI: 10.1039/c4ob01792g

Results and discussion

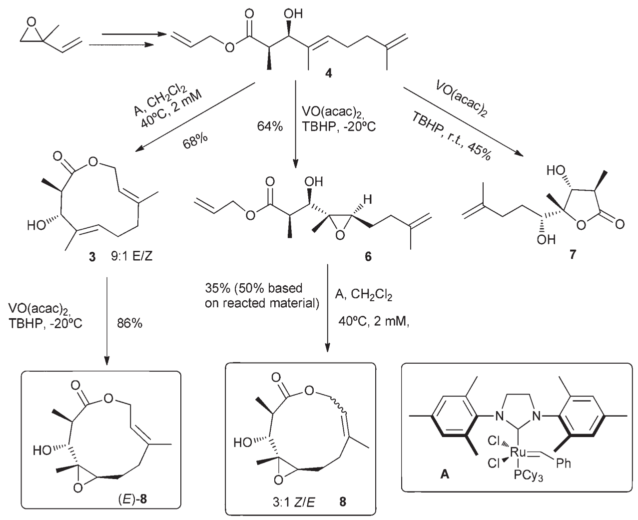
We examined the synthesis of the analogous simpler lactone **2** with the aim of establishing a route to the introduction of the



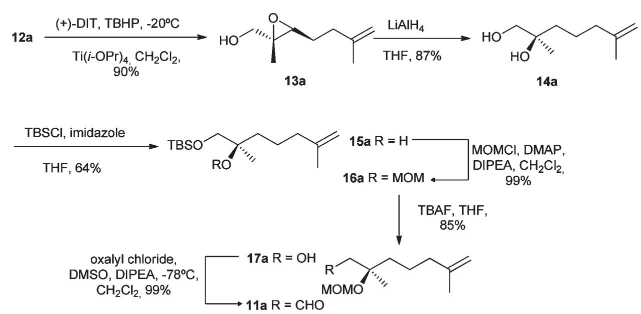
Scheme 1 Retrosynthetic analysis of lactone **2**.



Scheme 3 Retrosynthetic analysis of **9a**.



Scheme 2 Synthesis of lactones **3** and **8**.



Scheme 4 Stereoselective synthesis of aldehyde **11a**.

functionality at the C-4 position. The retrosynthetic analysis of **2** is shown in Scheme 1 in which a ring-closing metathesis (RCM) and an aldol condensation play key roles.

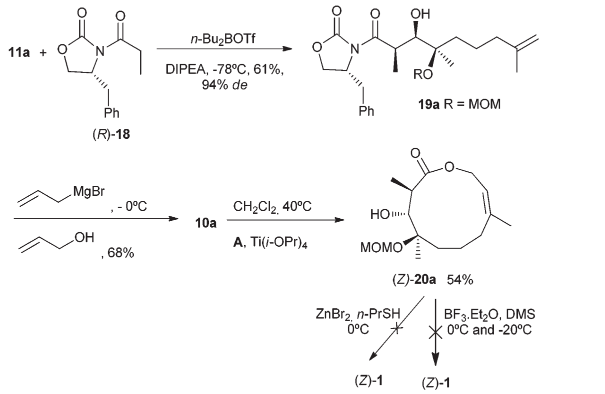
The ester **4** was prepared using our previously described procedure.[8] Stereoselective epoxidation with $VO(acac)_2$ and 1.3 eq. of TBHP at −20 °C[9] afforded the *erythro* epoxide **6** (Scheme 2). In addition the γ-butyrolactone **7** was obtained when the reaction was performed at room temperature and 2.0 eq. of THBP were used. The RCM of **6** led to a *Z*/*E* mixture of the lactones **8** in low yield and in which the *Z* isomer predominated. Alternatively the RCM of the ester **4** afforded the lactone (*E*)-**3** in 68% yield as a 9 : 1 *E*/*Z* mixture.

Epoxidation with $VO(acac)_2$ and TBHP afforded the lactone (*E*)-**8**. However the reductive cleavage of the epoxide was unsuccessful under all the conditions that were examined.

At this stage we decided to adopt an alternative synthetic route in which the 4-position was functionalized previously to the RCM. With this aim, we chose compound **9a** as a model because it has the *anti* disposition between both C-3 and C-4 hydroxyl groups found in compound **1**. Furthermore it could be synthesized in good yield through a *syn* aldol reaction of the aldehyde **11a**, obtained from the known alcohol **12a**, followed by exocyclic cleavage of the corresponding oxazolidinone with allyl alcohol and RCM of the obtained ester **10a** (Scheme 3). In addition to the preparation of the compound **9a** was achieved as a part of our ongoing program in increasing the structural diversity of the 11-membered lactone by RCM.[8]

The synthesis of **9a** began (Scheme 4) with a Sharpless asymmetric epoxidation of the alcohol **12a** with (+)-DIT[10] which afforded the epoxide **13a** in 90% yield. Reductive cleavage of **13a** with $LiAlH_4$ gave the diol **14a** whose sequential protection of primary and tertiary hydroxyl groups with TBS and MOM respectively, followed by desilylation and Swern oxidation under mild conditions, afforded the aldehyde **11a** in good overall yield.

The aldehyde **11a** was treated (Scheme 5) with an appropriate oxazolidinone by the procedure reported by Evans[11] to afford the *syn*-aldol product **19a** in 61% yield and 94% de. Exocyclic cleavage of the oxazolidinone **19a** with allyl alcohol and 4 eq. of allylmagnesium bromide at −20 °C generated the ester **10a** with a yield of 68%. Finally a RCM reaction of **10a** under high dilution conditions catalyzed by the second generation ruthenium complex **A**[12] in dry, degassed, refluxing dichloromethane produced the 11-membered lactone **20a** in only 18% yield. However lactone **20a** was obtained in 54% yield when the reaction was carried out in the presence of a catalytic amount of $Ti(i\text{-}OPr)_4$.[13] In this occasion only *Z* isomer could



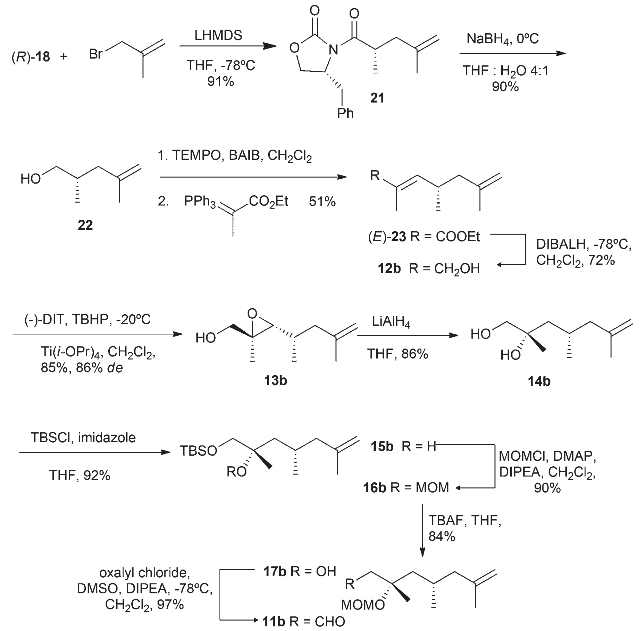
Scheme 5 Stereoselective synthesis of (Z)-20a.

be detected showing again a high influence of the nature of substituents on C-4 and C-5 in the stereochemistry of the RCM reaction.

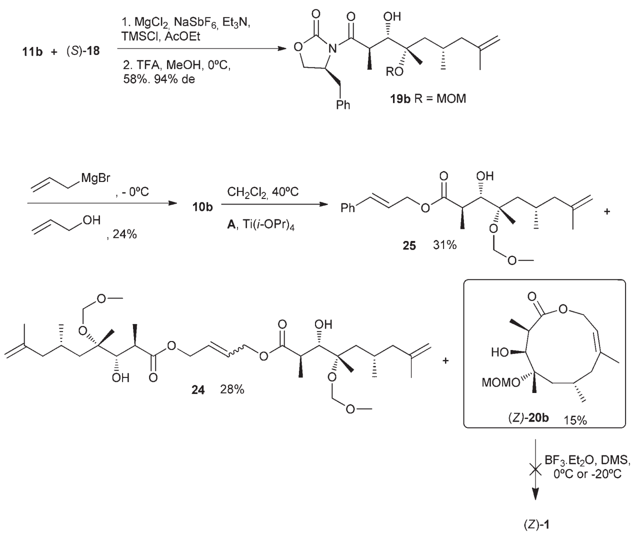
Given that the geometry of the alkene obtained by RCM could not be easily predicted, we decided to try the total synthesis of **1** following a similar synthetic strategy to that described in Scheme 3. Firstly we performed the enantioselective alkylation of the oxazolidinone (−)-(*R*)-**18** with 3-bromo-2-methylprop-1-ene which proceeded as described in the literature,[14] to give the adduct **21**. This had the required stereochemistry of the methyl group at C6 of **1**. Reductive cleavage of the auxiliary with $NaBH_4$ gave the alcohol **22** in 90% yield. A one-pot oxidation/olefination using the TEMPO-BAIB system followed by reaction with (carbethoxyethylidene)-triphenyl phosphorane[15] produced the ester (*E*)-**23** stereoselectively and in 51% yield.‡ Reduction of (*E*)-**23** with DIBALH and subsequent Sharpless asymmetric epoxidation with (−)-DIT afforded the epoxide **13b** in 85% yield and 86% de (Scheme 6). Conversion of this compound into aldehyde **11b** was carried out following a similar synthetic strategy that is described in Scheme 4.

Condensation of the aldehyde **11b** with the appropriate oxazolidinone (Scheme 7) by the procedure reported by Evans[16] afforded *via* methanolysis of the silyloxy derivative the *anti*-aldol product **19b** in 58% yield and 94% de. Unexpectedly the conversion of **19b** into the ester **10b** with allyl alcohol/allylmagnesium bromide at 0 °C only proceeded with a 23% yield. Attempts to improve this yield by varying the temperature and reagent stoichiometry or using SmI_2[17] were unsuccessful. Finally a RCM reaction catalyzed by the ruthenium complex **A** in refluxing CH_2Cl_2 in the presence of a catalytic amount of $Ti(i\text{-}OPr)_4$,[13] afforded a complex mixture from which the lactone **20b** was isolated in only 15% yield. This lactone was the (*Z*)-isomer, protected as its MOM ether, of the target structure **1**.

Unfortunately, all attempts to remove the MOM protecting group from both compounds **20a** and **b** were fruitless. So, several attempts at the deprotection were carried out using



Scheme 6 Stereoselective synthesis of aldehyde 11b.



Scheme 7 Stereoselective synthesis of (Z)-20a.

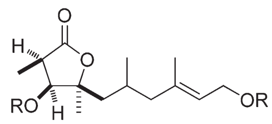
$BF_3 \cdot Et_2O$/DMS at different temperatures. This method has been successfully used by Marco *et al.* for the removal of a MOM protecting group in the last step of the synthesis of stagnolide G, a 10-membered lactone with a free hydroxyl group at the C-4 position.[18] However we only obtained an untreatable reaction mixture. Additional deprotection experiments with $ZnBr_2$–PrSH[19] again yielded a complex reaction mixture.

The NMR data for all synthetic lactones (**3**, **8** and **20a–b**) together with those obtained in the previous mutasynthetic experiments,[8] when compared with those that had been

‡ *Z*-isomer could not detected by ^1H NMR.

Table 1 Comparison of δ_H of H-10 and H-10′ protons for compounds **1**, **3**, (*Z*)-**8**, (*E*)-**8** and **20a–b** (δ_H values in ppm)

Comp./position	**1**	**3**	(*Z*)-**8**	(*E*)-**8**	**20a**	**20b**
H-10	4.12	4.33	4.29	4.42	4.33	4.12
H-10′	4.17	4.68	4.80	4.66	4.75	5.07



26 R=H
26a R=Ac

Fig. 2 Compounds **26** and **26a**.

reported for the natural product **1**, showed significant differences in the features that were common to all of them. Firstly the proton signals which were assigned to H-10 in the natural product appeared within a narrow range of chemical shifts between δ_H 4.17 and δ_H 4.12 ppm typical of a freely rotating system. In both the (*Z*)- and (*E*)-isomers of the synthetic lactones, these proton resonances are clearly distinct, one of them appearing at a higher chemical shift (δ_H 4.66–5.07 ppm) (Table 1). Furthermore the synthetic lactones showed a correlation in the HMBC experiment between the carbonyl of the lactone and the H-10 signals which was not observed in the corresponding experiment for the natural product. All the differences revealed by the NMR data point to a possible error in the structure assigned to the natural product. Consequently the proposed 11-membered ring structure for **1** is doubtful and a re-examination of this structure **1** was necessary.

In the course of our research work with the phytopathogen fungus *B. cinerea*, we studied the mutant bcbot4,[20] which overproduced polyketide metabolites, yielding a sufficient amount of compounds **1**, to revise the structure. The carbon framework of **1** was unequivocally established on the basis of HSQC and HMBC heteronuclear correlations. However in the light of our synthetic work with the compounds **3**, (*Z*)-**8**, (*E*)-**8**, **20a** and **20b**, a significant observation was the absence of a three-bond through-oxygen HMBC correlation for the O=C–O–C–H system in the natural product **1**. This led us to consider an alternative γ-butyrolactone structure **26** for the natural product (Fig. 2). The γ-butyrolactone would be thermodynamically more stable than the 11-membered lactone. In the literature there are a number of precedents for the corrections[21,22] to the structures of medium-sized lactones.

Acetylation of **26**, under standard conditions, quantitatively afforded a diacetate **26a** whose NMR spectra showed the incorporation of two acetate units. The resonances assigned to H-10 had shifted from δ_H 4.12 and 4.17 ppm in **26** to δ_H 4.58 ppm in **26a**. This signal was correlated in the HMBC with the signal assigned to the carbonyl group of the acetate at δ_C 170.1 ppm indicating that an acetyl group was on the hydroxyl group on C-10 what is incompatible with the original structure **1**. The other acetate group was situated on the hydroxyl group on C-3 for the HMBC correlations observed between the signals at δ_H 4.97 ppm (H-3) and the signal at δ_C 169.2 ppm. The IR spectrum of the diacetate **26a** had carbonyl absorption at 1775 and 1740 cm^{-1} corresponding to the presence of a γ-butyrolactone and acetate esters. Although compound **1** itself had IR absorption at 1748 cm^{-1} which is rather low for a γ-butyrolactone, this might be affected by hydrogen bonding from the hydroxyl group at C-3.[23]

The nOe observed interaction between H-2, H-3 and methyl at C-4 supported a relative configuration of the ring as 2*R**,3*S**,4*S**.

Conclusions

In summary we have examined several strategies for the enantioselective synthesis of structures that are analogues of that reported for the fungal metabolite **1** using the ring-closing metathesis as a key-step. These included the (*Z*)-isomer **20b** containing a MOM protecting group, and four compounds **3**, (*Z*)-**8**, (*E*)-**8** and **20a**. The results showed that the increase in conformational restrictions imposed by the substituents has a high influence on the stereochemistry of the ring-closing metathesis reaction and gives rise to a decrease in the yield for the synthesis of 11-membered lactones. The predominant alkene obtained was the (*Z*)-isomer. The observed spectroscopic differences between the synthetized lactones **3**, (*Z*)-**8**, (*E*)-**8**, **20a** and **20b** and the natural product **1** and spectroscopic data of its acetylated derivative **26a** allowed us to revise the structure **1** to that of 4-hydroxy-5-(6-hydroxy-2,4-dimethylhex-4-enyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (**26**). Work is in progress in order to determine its absolute configuration.

Experimental

General procedures

Unless otherwise noted, materials and reagents were obtained from commercial suppliers and were used without further purification. Dichloromethane, ethyl acetate and triethylamine were freshly distilled from CaH_2 and tetrahydrofuran was dried over sodium and benzophenone and freshly distilled before use. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Purification by semipreparative and analytical HPLC was performed with Hitachi/Merck L-6270 apparatus equipped with a differential refractometer detector (RI-7490). A LiChrospher® Si 60 (5 μm) LiChroCart® (250 mm × 4 mm) column and a LiChrospher® Si 60 (10 μm) LiChroCart® (250 mm × 10 mm) were used in isolation experiments. Silica gel (Merck) was used for column chromatography. TLC was performed on Merck Kiesegel 60 F_{254}, 0.25 mm thick. Optical rotations were determined with a digital polarimeter. Infrared spectra were recorded on a FT-IR spectrophotometer and reported as wavenumber (cm^{-1}). ^1H and ^{13}C NMR measurements were recorded on Varian Unity 400 MHz, Agilent 500 MHz and Varian Inova 600 MHz spectrometers with $SiMe_4$ as the internal reference. Chemical shifts are reported in parts per million (ppm) and were referenced to $CDCl_3$ (δ_H 7.25, δ_C 77.0). NMR assignments were made using a combination of 1D and 2D techniques. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quarter; quint = quintuplet; sext = sextuplet; m = multiplet, br = broad. High-Resolution Mass Spectra (HRMS) was recorded with a double-focusing magnetic sector mass spectrometer in the positive ion mode or with a QTOF mass spectrometer in positive ion electrospray mode at 20 V cone voltage or in positive ion APCI mode.

Synthesis of the substrates

(2*R*,3*R*,4*E*)-Allyl 3-hydroxy-2,4,8-trimethylnona-4,8-dienoate (4). This compound was obtained by means of the procedure described in the literature and its spectroscopic data were identical to those described in the literature.[8]

(2*R*,3*R*,4*S*,5*R*)-Allyl 4,5-epoxy-3-hydroxy-2,4,8-trimethyl-non-8-enoate (6). VO(acac)$_2$ (vanadyl acetylacetonate, 17.9 mg, 0.06 mmol) was added to a solution cooled at −20 °C of (2*R*,3*R*,4*E*)-allyl 3-hydroxy-2,4,8-trimethylnona-4,8-dienoate (**4**) (180.0 mg, 0.71 mmol) in dry CH_2Cl_2 (1.8 mL) under an argon atmosphere. The mixture was stirred for 10 min and then TBHP (0.18 mL of a solution 5.0–6.0 M in nonane, 0.93 mmol) was added. The mixture was stirred for 3 h and a saturated solution of Na_2SO_3 (3 mL) was added and then allowed to warm to room temperature with stirring for 30 min. The aqueous layer was extracted three times with diethyl ether (15 mL) and the organic layer was washed with brine, dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent gave a crude product that was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O (75 : 25) yielded the compound **6** as a single isomer (123.3 mg, 64%). Colourless oil; $[\alpha]_D^{20}$ +17.5° (*c* 0.65 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3480 (OH), 3079, 2940, 1739 (CO), 1650, 1456, 1376, 1246, 1186, 1041, 996, 889; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.92 (1H, ddt, *J* 17.2, 10.6, 5.6 Hz, 2′-H), 5.32 (1H, ddd, *J* 17.2, 2.8, 1.4 Hz, 3′a-H), 5.23 (1H, ddd, *J* 10.6, 2.8, 1.4 Hz, 3′b-H), 4.74 (br s, 1H, 9a-H), 4.71 (br s, 1H, 9b-H), 4.61 (2H, d, *J* 5.6 Hz, 1′-H), 4.11 (1H, d, *J* 4.0 Hz, 3-H), 3.11 (1H, t, *J* 6.2 Hz, 5-H), 2.68 (1H, dq, *J* 7.2, 4.0 Hz, 2-H), 2.28 (O*H*, s), 2.16 (2H, m, 7-H), 1.73 (3H, s, 8-Me), 1.70 (2H, m, 6-H), 1.29 (3H, s, 4-Me), 1.15 (3H, d, *J* 7.2 Hz, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.8, 144.5, 132.0, 118.3, 110.5, 72.7, 65.4, 61.3, 58.8, 41.5, 34.3, 26.3, 22.4, 14.8, 10.2; HRMS (CI$^+$): calcd for $C_{15}H_{25}O_4$ $[M + H]^+$ 269.1753, found 269.1745.

(2*R*,3*R*,4*R*,5*R*,1′*R*)-4-Hydroxy-5-(1-hydroxy-4-methylpent-4-enyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (7). VO(acac)$_2$ (vanadyl acetylacetonate, 5.0 mg, 0.02 mmol) was added to a solution of (2*R*,3*R*,4*E*)-allyl 3-hydroxy-2,4,8-trimethylnona-4,8-dienoate (**4**) (50.0 mg, 0.2 mmol) in dry CH_2Cl_2 (0.3 mL) under an argon atmosphere at room temperature. The mixture was stirred for 10 min before the addition of TBHP (0.07 mL of a solution 5.0–6.0 M in nonane, 0.4 mmol). The mixture was stirred for 18 h and then quenched with a saturated solution of Na_2SO_3 (1 mL) and was stirred for an additional 30 min. The aqueous layer was extracted three times with diethyl ether (10 mL) and the organic layer was washed with brine, dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent gave a crude product that was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O (70 : 30) yielded the compound **7** (19.0 mg, 45%). Colourless oil; $[\alpha]_D^{20}$ +13.7° (*c* 1.8 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3412 (OH), 3075, 2934, 1780 (CO), 1455, 1380, 1217, 1096, 1047, 949, 887; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.76 (1H, br s, 5′a-H), 4.74 (1H, br s, 5′b-H), 3.97 (1H, dd, *J* 6.8, 5.5 Hz, 4-H), 3.95 (1H, dd, *J* 10.5, 3.8, 2.0 Hz, 1′-H), 3.36 (O*H*, d, *J* 5.5 Hz), 2.85 (O*H*, d, *J* 3.8 Hz), 2.77 (1H, q, *J* 6.8 Hz, 3-H), 2.26 (1H, ddd, *J* 14.4, 8.8, 6.2 Hz, 3′a-H), 2.12 (1H, dt, *J* 14.4, 7.6 Hz, 3′b-H), 1.85 (1H, dddd, *J* 14.1, 8.8, 7.6, 2.0 Hz, 2′a-H), 1.74 (3H, s, 4′-Me), 1.69 (1H, dddd, *J* 14.1, 10.5, 7.6, 6.2 Hz, 2′b-H), 1.43 (3H, s, 5-Me), 1.35 (3H, d, *J* 6.8 Hz, 3-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 176.6, 145.5, 111.0, 85.3, 82.9, 73.7, 43.6, 34.5, 28.6, 22.3, 20.3, 14.2; HRMS (CI$^+$): calcd for $C_{12}H_{18}O_3$ $[M - H_2O]^+$ 210.1256, found 210.1266.

RCM of ester 6. (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)tricyclohexylphosphine) ruthenium (2nd generation Grubbs ruthenium catalyst, 93.7 mg, 0.11 mmol) was added to a refluxing stirred solution of ester **6** (101.0 mg, 0.38 mmol) in deoxygenated and dry CH_2Cl_2 (316 mL) under an argon atmosphere. The reaction mixture was stirred until consumption of the starting material (18 h). The crude product was filtered over a pad of silica gel, and washed with ethyl acetate (400 mL). The solvent was removed under reduced pressure to give a crude product that was purified by silica gel column chromatography. Elution with ether petroleum–Et_2O (90 : 10) yielded a mixture 3 : 1 of (*Z*)-**8** (23.8 mg, 26%) and (*E*)-**8** (7.9 mg, 8%).§

(2*R*,3*R*,4*S*,5*R*,8*Z*)-4,5-Epoxy-3-hydroxy-2,4,8-trimethyldec-8-enolide (*Z*)-(8). Colourless oil; $[\alpha]_D^{20}$ −14.9° (*c* 0.77 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3434 (OH), 2928, 1737 (CO), 1456, 1383, 1205, 1081, 935, 904; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.73 (1H, dt, *J* 7.0, 1.2 Hz, 9-H), 4.80 (1H, dd, *J* 12.0, 7.0 Hz, 10a-H), 4.29 (1H, dd, *J* 12.0, 7.0 Hz, 10b-H), 3.70 (1H, d, *J* 4.4 Hz, 3-H), 3.08 (1H, dd, *J* 11.2, 2.8 Hz, 5-H), 2.71 (1H, dq, *J* 7.2, 4.4 Hz, 2-H), 2.38–2.30 (1H, m, 7a-H), 2.22–2.16 (1H, m, 7b-H), 1.77 (3H, s, 8-Me), 1.48–1.39 (2H, m, 6-H), 1.32 (3H, s, 4-Me), 1.31 (3H, d, *J* 7.2 Hz, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 172.8, 143.8, 120.9, 75.4, 62.3, 59.4, 59.1, 44.3, 28.2, 23.9, 22.1, 16.7, 15.8; HRMS (CI$^+$): calcd for $C_{13}H_{21}O_4$ $[M + H]^+$ 241.1440, found 241.1442.

(2*R*,3*R*,4*S*,5*R*,8*E*)-4,5-Epoxy-3-hydroxy-2,4,8-trimethyldec-8-enolide (*E*)-(8). Colourless oil; $[\alpha]_D^{20}$ +30.3° (*c* 0.1 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3430 (OH), 2929, 1735 (CO), 1456, 1384, 1205, 1083, 997, 941; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.79 (1H, dd, *J* 8.8, 6.6 Hz, 9-H), 4.66 (1H, dd, *J* 10.9, 6.6 Hz, 10a-H), 4.42 (1H, dd, *J* 10.9, 8.8 Hz, 10b-H), 3.01 (1H, d, *J* 10.5 Hz, 3-H), 2.69 (1H, dd, *J* 10.6, 1.7 Hz, 5-H), 2.53 (1H, dq, *J* 10.5, 6.6 Hz, 2-H), 2.26–2.18 (1H, m, 7a-H), 1.99 (1H, ddd, *J* 14.5, 4.2,

§ 50% based on the reacted material.

1.6 Hz, 7b-H), 1.77 (3H, d, *J* 1.6 Hz, 8-Me), 1.63–1.54 (2H, m, 6-H), 1.30 (3H, s, 4-Me), 1.24 (3H, d, *J* 6.6 Hz, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.5, 143.8, 121.6, 80.4, 64.7, 64.4, 60.8, 42.0, 36.2, 25.6, 15.9, 14.4, 10.9; HRMS (CI^+): calcd for $C_{13}H_{21}O_4$ $[M + H]^+$ 241.1440, found 241.1444.

RCM of ester 4. Ester **4** (36.0 mg, 0.14 mmol) was converted to an inseparable mixture 9 : 1 of (*E*)-**3** (19.5 mg, 61%) and (*Z*)-**3** (2.1 mg, 7%) following the methodology described above for the RCM of ester **6**. Spectroscopic data of both compounds were identical to those described in the literature.[8]

Epoxidation of lactone (*E*)-3. (2*R*,3*R*,4*E*,8*E*)-3-hydroxy-2,4,8-trimethyldeca-4,8-dienolide ((*E*)-**3**) (13.0 mg, 0.06 mmol) was converted to a single product, whose spectroscopic data were identical to those described for (*E*)-**8** (12.0 mg, 86%), following the methodology described above for the epoxidation of the ester **4**.

(*E*)-2,6-Dimethylhepta-2,6-dien-1-ol (12a). This compound was obtained by means of the procedure described in the literature and its spectroscopic data were identical to those described in the literature.[8]

(2*S*,3*S*)-2,3-Epoxy-2,6-dimethylhept-6-en-1-ol (13a). Ti(i-OPr)$_4$ (4.3 mL, 14.7 mmol) was added at −20 °C to a solution of (+)-DIT ((+)-diisopropyl *L*-tartrate, 3.8 mL, 17.7 mmol) in dry CH_2Cl_2 (113 mL) under an argon atmosphere. The mixture was stirred for 20 min, and then a solution of (*E*)-2,6-dimethylhepta-2,6-dien-1-ol (**12a**) (2756 mg, 19.7 mmol) in dry CH_2Cl_2 (45 mL) was added slowly with stirring for 20 min. Finally, TBHP (7.1 mL of a solution 5.0–6.0 M in nonane, 39.4 mmol) was added slowly. When TLC showed that the reaction was complete (3 h), diethyl ether (15 mL) and a saturated Na_2SO_4 solution (15 mL) were added and the mixture was allowed to warm to room temperature, stirred for an additional hour, filtered with Et_2O through Celite and the solvent evaporated. The crude was redissolved in diethyl ether (40 mL) and a solution of NaOH (1.25 g) in 40 mL of brine was added at 0 °C. The mixture was stirred vigorously for 2 h and the aqueous layer was separated and extracted with three portions of diethyl ether (40 mL). The combined organic solution was washed with brine (80 mL), dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent gave a crude product that was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O 80 : 20 yielded the alcohol **13a** (2778 mg, 90%). Colourless oil; $[\alpha]_D^{20}$ −6.4° (*c* 0.65 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3438 (OH), 3052, 2939, 1650, 1452, 1369, 1068, 1051, 892; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.75 (1H, br s, 7b-H), 4.72 (1H, br s, 7a-H), 3.67 (1H, dd, *J* 12.0, 4.6 Hz, 1b-H), 3.55 (1H, dd, *J* 12.0, 8.4 Hz, 1a-H), 3.04 (1H, t, *J* 6.2 Hz, 3-H), 2.22 (dd, *J* 8.4, 4.6 Hz, O*H*), 2.19 (1H, dd, *J* 14.4, 7.2 Hz, 5b-H), 2.11 (1H, dd, *J* 14.4, 7.6 Hz, 5a-H), 1.74 (3H, s, 6-Me), 1.73–1.70 (2H, m, 4-H), 1.29 (3H, s, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.6, 110.5, 65.4, 61.1, 59.8, 34.4, 26.3, 22.3, 14.1; HRMS (CI^+): calcd for $C_9H_{17}O_2$ $[M + H]^+$ 157.1229, found 157.1230.

(*R*)-2,6-Dimethylhept-6-ene-1,2-diol (14a). $LiAlH_4$ (31.9 mL of a 1.0 M solution in Et_2O, 31.9 mmol) was added slowly at 0 °C to a solution of (2*S*,3*S*)-2,3-epoxy-2,6-dimethylhept-6-en-1-ol (**13a**) (2264 mg, 14.5 mmol) in THF (92 mL) under an argon atmosphere. The mixture was allowed to warm to room temperature and when TLC showed that the reaction was complete (3 h), the mixture was re-cooled at 0 °C and water (20 mL) and 1 N HCl were added slowly until pH 3. The layers were separated and the aqueous layer was extracted with two portions of ethyl acetate (40 mL). The combined organic solution was washed with brine (80 mL), dried over anhydrous sodium sulphate, filtered and the solvent was evaporated under reduced pressure to give diol **14a** (2000 mg, 87%) as a colourless oil, which was used in the next step without further purification. $[\alpha]_D^{20}$ +2.5° (*c* 4.7 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3300 (OH), 3074, 2942, 1650, 1456, 1374, 1134, 1055, 886; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.68 (1H, br s, 7b-H), 4.65 (1H, br s, 7a-H), 3.44 (1H, d, *J* 10.8 Hz, 1b-H), 3.38 (1H, d, *J* 10.8 Hz, 1a-H), 2.00 (2H, t, *J* 6.8 Hz, 5-H), 1.69 (3H, s, 6-Me), 1.48–1.41 (4H, m, 3-H and 4-H), 1.14 (3H, s, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.5, 110.0, 72.9, 69.7, 38.13, 38.10, 23.1, 22.2, 21.6; HRMS (CI^+): calcd for $C_9H_{16}O$ $[M - H_2O]^+$ 140.1201, found 140.1208.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylhept-6-en-2-ol (15a). A solution of *tert*-butylchlorodimethylsilane (517 mg, 3.36 mmol) in dry THF (1.8 mL) was added to a solution of imidazole (1307 mg, 19.2 mmol) and (*R*)-2,6-dimethylhept-6-ene-1,2-diol (**14a**). (379 mg, 2.4 mmol) in dry THF (3.4 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature and when TLC showed that the reaction was complete (6 h) diethyl ether was added (20 mL). The organic layer was washed three times with brine (80 mL), dried over anhydrous sodium sulphate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O 90 : 10 yielded compound **15a** (406 mg, 64%). Colourless oil; $[\alpha]_D^{20}$ +2.3° (*c* 2.9 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3460 (OH), 3074, 2930, 2857, 1651, 1463, 1374, 1254, 1093, 885, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.63 (1H, br s, 7b-H), 4.61 (1H, br s, 7a-H), 3.36 (1H, d, *J* 9.4 Hz, 1b-H), 3.31 (1H, d, *J* 9.4 Hz, 1a-H), 1.95 (2H, t, *J* 7.2 Hz, 5-H), 1.65 (3H, s, 6-Me), 1.48–1.33 (4H, m, 3-H and 4-H), 1.05 (3H, s, 2-Me), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.7, 109.9, 72.2, 70.1, 38.3, 38.1, 25.8 (3C), 23.1, 22.3, 21.7, 18.2, −5.5 (2C); HRMS (CI^+): calcd for $C_{15}H_{31}O_2Si$ $[M - H]^+$ 271.2093, found 271.2079.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)-2,6-dimethylhept-6-ene (16a). Chloromethyl methyl ether (MOMCl) (0.41 mL, 4.93 mmol) was added slowly to a stirred mixture of (*R*)-1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-6-en-2-ol (**15a**) (384 mg, 1.41 mmol), *N*,*N*′-diisopropylethylamine (1.2 mL, 7.05 mmol), *N*,*N*′-dimethylaminepyridine (34 mg, 0.28 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C under an argon atmosphere and the mixture was allowed to warm to room temperature with stirring for 16 h. Then, saturated ammonium chloride solution (40 mL) and diethyl ether (50 mL) were added, the layers were separated and the aqueous layer was extracted twice with Et_2O (50 mL). The combined organic solution was washed with 0.1 N HCl (80 mL), saturated sodium bicarbonate (80 mL), twice with brine (80 mL), dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under reduced pressure to give compound **16a** (427 mg, 99%) as a yellow oil, which was used in the next step without further purification. $[\alpha]_D^{20}$ −2.8° (*c* 0.32 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3073, 2930, 1649, 1463, 1374, 1255, 1146, 1104, 1040, 886, 837, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.72 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.70 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.66 (1H, br s, 7b-H), 4.64 (1H, br s, 7a-H), 3.49 (1H, d, *J* 10.0 Hz, 1b-H), 3.43 (1H, d, *J* 10.0 Hz, 1a-H), 3.33 (3H, s, OMe), 1.97 (2H, dd, *J* 7.6, 6.0 Hz, 5-H), 1.68 (3H, s, 6-Me), 1.48–1.42 (4H, m, 3-H and 4-H), 1.16 (3H, s, 2-Me), 0.86 (9H, s, $SiC(CH_3)_3$), 0.01 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.8, 109.8, 91.2, 78.5, 68.4, 55.1, 38.2, 36.1, 25.8 (3C), 22.2, 21.3, 21.1, 18.1, −5.6 (2C); HRMS (CI^+): calcd for $C_{11}H_{25}O_3Si$ $[M - C_6H_{11}]^+$ 233.1573, found 233.1570.

(*R*)-2-(Methoxymethoxy)-2,6-dimethylhept-6-en-1-ol (17a). Tetrabutylammonium fluoride (TBAF, 1.7 mL of a 1.0 M solution, 1.7 mmol) was added slowly to a stirred solution of (*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)-2,6-dimethylhept-6-ene (**16a**) (371 mg, 1.18 mmol) in dry tetrahydrofuran (12 mL) under an argon atmosphere. When TLC showed that the reaction was complete (3 h), the mixture was washed three times with brine (6 mL), dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under reduced pressure to give a crude product which was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O 70 : 30 yielded the alcohol **17a** (201 mg, 85%). Colourless oil; $[\alpha]_D^{20}$ −2.9° (*c* 0.15 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3458 (OH), 2932, 1650, 1442, 1374, 1238, 1144, 1028, 888; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.66 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.65 (1H, br s, 7b-H), 4.63 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.62 (1H, br s, 7a-H), 3.41 (1H, dd, *J* 13.6, 6.8 Hz, 1b-H), 3.36 (3H, s, OMe), 3.31 (1H, dd, *J* 13.6, 6.8 Hz, 1a-H), 1.96 (2H, t, *J* 6.8 Hz, 5-H), 1.65 (3H, s, 6-Me), 1.54–1.36 (4H, m, 3-H and 4-H), 1.12 (3H, s, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.4, 110.0, 90.7, 79.3, 68.2, 55.3, 38.0, 35.6, 22.2, 21.2, 20.0; HRMS (CI^+): calcd for $C_{11}H_{22}O_3$ $[M]^+$ 202.1569, found 202.1564.

(*R*)-2-(Methoxymethoxy)-2,6-dimethylhept-6-enal (11a). Anhydrous dimethylsulfoxide (DMSO, 0.25 mL, 4.4 mmol) in dry CH_2Cl_2 (3.4 mL) was added over 5 min dropwise to a solution of freshly distilled oxalyl chloride (0.15 mL, 1.76 mmol) in dry CH_2Cl_2 (5.1 mL) at – 60 °C in a bath of acetone/N_2 under an argon atmosphere. The resulting clear solution was stirred for an additional 10 min, and then a solution of (*R*)-2-(methoxymethoxy)-2,6-dimethylhept-6-en-1-ol (**17a**) (178.3 mg, 0.88 mmol) in CH_2Cl_2 (3.4 mL) was added dropwise over 5 min. During this time the solution acquired a white appearance and stirring was continued for an additional 30 min at −60 °C. Then *N*,*N*′-diisopropylethylamine (1.5 mL, 8.8 mmol) was added dropwise over 5 min and stirring was continued for an additional 15 min. The reaction flask was removed from the cold bath and allowed to warm gradually to room temperature with stirring over 30 min. This was followed by the addition of water (10 mL). The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (15 mL). The combined organic solution was washed with 0.1 N HCl (30 mL), saturated sodium bicarbonate (30 mL), water (30 mL), twice with brine (30 mL), dried over anhydrous sodium sulphate and filtered. The solvent was concentrated under reduced pressure at 0 °C to yield quantitatively the aldehyde **11a** (176 mg, 100%) as a yellow oil that was used immediately in the next step. $[\alpha]_D^{20}$ +1.6° (*c* 1.2 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3074, 2924, 1734 (CO), 1651, 1453, 1376, 1144, 1119, 1084, 1049, 918, 889; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.48 (1H, s, 1-H), 4.71 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.66 (1H, br s, 7b-H), 4.62 (1H, br s, 7a-H), 4.61 (1H, d, *J* 7.2 Hz, CH*H*OMe), 3.35 (3H, s, OMe), 1.96 (2H, t, *J* 7.2 Hz, 5-H), 1.64 (3H, s, 6-Me), 1.62–1.39 (4H, m, 3a-H, 3b-H and 4-H), 1.24 (3H, s, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 203.5, 145.0, 110.4, 92.0, 82.2, 55.8, 37.8, 34.8, 22.2, 20.6, 17.6; HRMS (ESI^+): calcd for $C_{11}H_{22}O_4Na$ $[M + H_2O + Na]^+$ 241.1410, found 241.1405.

(4*R*,2″*R*,3″*R*,4″*R*)-4-Benzyl-3-[3-hydroxy-4-(methoxy-methoxy)-2,4,8-trimethylnon-8-enoyl]oxazolidin-2-one (19a). *n*-Dibutylboron triflate (1.1 mL of a 1.0 M solution in CH_2Cl_2, 1.1 mmol) was added dropwise at 0 °C to a stirred solution of (−)-(4*R*)-4-benzyl-3-propionyloxazolidin-2-one ((−)-(*R*)-**18**) (206.1 m, 0.88 mmol) in dry CH_2Cl_2 (1.3 mL) under an argon atmosphere. The mixture was stirred for 5 min and then *N*,*N*′-diisopropylethylamine was added dropwise (0.2 mL, 1.2 mmol). After complete addition, the mixture was stirred at 0 °C for 15 min. The yellow solution was re-cooled to −78 °C and a solution of (*R*)-2-(methoxymethoxy)-2,6-dimethylhept-6-enal (**11a**) (176 mg, 0.88 mmol) was added dropwise in dry CH_2Cl_2 (0.5 mL). The mixture was stirred at −78 °C and was then allowed to warm to 0 °C and stirred for an additional hour. The reaction was quenched with a mixture of phosphate buffer (1 mL of a 1.0 M solution at pH 7) and MeOH (3 mL) at 0 °C and the mixture was stirred for 5 min. Finally, a solution 2.4 : 1 MeOH–H_2O_2 30% (3 mL) was added slowly at 0 °C and was stirred for an additional hour. The solvent was concentrated under reduced pressure and the residue was redissolved in diethyl ether. The aqueous layer was extracted three times with diethyl ether (10 mL). Combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulphate, and then filtered. The solvent was evaporated under reduced pressure to give a crude product which was purified by silica gel column chromatography. Elution with petroleum ether–ethyl acetate (75 : 25) yielded compound **19a** (115.3 mg, 61%, 94% de). Colourless oil; $[\alpha]_D^{20}$ −24.8° (*c* 6.1 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3505 (OH), 3064, 2937, 1743 (CO), 1694 (CO), 1455, 1350, 1210, 1106, 1028, 971, 920, 890; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 (2H, m, *H*arom), 7.23 (1H, m, *H*arom), 7.19 (2H, m, *H*arom), 4.73 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.69 (1H, br s, 9′b-H), 4.67 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.66–4.62 (2H, m, 4-H and 9′a-H), 4.18 (2H, m, 5-H), 4.11 (1H, quint, *J* 6.8 Hz, 2′-H), 3.97 (1H, t, *J* 6.8 Hz, 3′-H), 3.40 (3H, s, OMe), 3.28 (1H, dd, *J* 13.2, 3.6 Hz, C*H*HPh), 3.21 (d, *J* 6.8 Hz, CHO*H*), 2.76 (1H, dd, *J* = 13.2, 9.6 Hz, CH*H*Ph), 2.00 (2H, t, *J* 7.2 Hz, 7′-H), 1.69 (3H, s, 8′-Me), 1.66–1.48 (2H, m, 5′-H), 1.47–1.35 (2H, m, 6′-H), 1.29 (3H, d, *J* 6.8 Hz, 2′-Me), 1.19 (3H, s, 4′-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.4, 152.9, 145.5, 135.2, 129.4, 128.9, 127.3, 110.1, 91.0, 81.4, 74.4, 66.0, 55.7, 55.5, 38.9, 38.1, 37.7, 35.6, 22.2, 21.7, 20.4, 13.5; HRMS (CI^+): calcd for $C_{24}H_{36}NO_6$ $[M + H]^+$ 434.2543, found 434.2559.

(2*R*,3*R*,4*R*)-Allyl 3-hydroxy-4-(methoxymethoxy)-2,4,8-trimethylnon-8-enoate (10a). Allylmagnesium bromide (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol) was added at 0 °C to the alcohol (0.9 mL) under an argon atmosphere in a Schlenk flask. The allylic mixture was stirred for 10 min and re-cooled at − 20 °C. Then, a solution of **19a** (63.2 mg, 0.15 mmol) in allylic alcohol (0.2 mL) was slowly added. When TLC monitoring indicated the completion of the reaction (3 h), a saturated ammonium chloride solution (4 mL) was added and then the reaction mixture was allowed to warm to room temperature. The aqueous layer was extracted three times with diethyl ether (10 mL). Combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and the solvent was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O (90 : 10) yielded the ester **10a** (33.8 mg, 68%) as a colourless oil; $[\alpha]_D^{20}$ +8.0° (*c* 0.68 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3444 (OH), 2950, 1732 (CO), 1645, 1456, 1377, 1153, 1030, 919, 887; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.90 (1H, ddt, *J* 17.2, 10.4, 5.8 Hz, 2′-H), 5.31 (1H, ddd, *J* 17.2, 2.8, 1.4 Hz, 3′a-H), 5.22 (1H, ddd, *J* 10.4, 2.8, 1.4 Hz, 3′b-H), 4.70 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.69 (1H, br s, 9b-H), 4.66 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.65 (1H, br s, 9a-H), 4.56 (2H, dt, *J* 5.8, 1.4 Hz, 1′-H), 3.89 (1H, t, *J* 7.0 Hz, 3-H), 3.37 (3H, s, OMe), 3.14 (d, *J* 7.0 Hz, O*H*), 2.70 (1H, quint, *J* 7.0 Hz, 2-H), 1.98 (2H, t, *J* 6.8 Hz, 7-H), 1.68 (3H, s, 8-Me), 1.60–1.40 (4H, m, 5a-H, 5b-H and 6-H), 1.25 (3H, d, *J* 7.0 Hz, 2-Me), 1.18 (3H, s, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.7, 145.5, 132.0, 118.3, 110.1, 91.0, 81.6, 75.1, 65.2, 55.7, 41.1, 38.1, 35.7, 22.3, 21.5, 19.7, 13.6; HRMS (ESI^+): calcd for $C_{17}H_{30}O_5Na$ $[M + H]^+$ 337.1985, found 337.1990.

RCM of 10a. A solution of ester **10a** (18.6 mg, 0.06 mmol) and freshly distilled Ti(i-OPr)$_4$ (6 μL, 0.02 mmol) in deoxygenated and dry CH_2Cl_2 (60 mL) was refluxed for 2 h under an argon atmosphere. Then, a solution of catalyst **A** (10.0 mg, 0.01 mmol) in deoxygenated and dry CH_2Cl_2 (60 mL) was added to the mixture and the whole was refluxed for 24 h. The crude was filtered over a pad of silica gel, and washed with ethyl acetate. The solvent was removed under reduced pressure to give a crude that was purified by silica gel column chromatography. Elution with ether petroleum–ethyl acetate 90 : 10 yielded the lactone (*Z*)-**20a** (9.2 mg, 54%).

(2*R*,3*R*,4*R*,8*Z*)-3-Hydroxy-4-(methoxymethoxy)-2,4,8-trimethyldec-8-enolide ((*Z*)-20a). Colourless oil; $[\alpha]_D^{20}$ −27.7° (*c* 0.17 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3508 (OH), 2921, 2850, 1728 (CO), 1454, 1377, 1252, 1142, 1036, 914, 827; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.54 (1H, t, *J* 6.2 Hz, 9-H), 4.75 (1H, dd, *J* 12.8, 6.2 Hz, 10b-H), 4.74 (1H, d, *J* 7.6 Hz, C*H*HOMe), 4.65 (1H, d, *J* 7.6 Hz, CH*H*OMe), 4.33 (1H, dd, *J* 12.8, 6.2 Hz, 10a-H), 3.82 (1H, d, *J* 10.2 Hz, 3-H), 3.38 (3H, s, OMe), 2.46 (1H, dq, *J* 10.2, 6.8 Hz, 2-H), 2.33 (1H, ddd, *J* 13.4, 9.2, 7.2 Hz, 7b-H), 1.84–1.80 (1H, m, 7a-H), 1.75–1.72 (1H, m, 5b-H), 1.70 (3H, s, 8-Me), 1.69–1.60 (2H, m, 6a-H and 6b-H), 1.33 (3H, d, *J* 6.8 2-Me), 1.25 (1H, m, 5a-H), 1.21 (3H, s, 4-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.0, 146.2, 118.7, 90.6, 81.8, 74.4, 60.8, 55.8, 43.0, 33.2, 32.1, 23.8, 20.4, 18.1, 16.4; HRMS (CI^+): calcd for $C_9H_{15}O$ 139.1123, found 139.1122.

(4*R*,2″*S*)-4-Benzyl-3[2,4-dimethylpent-4-enoyl]oxazolidin-2-one (21). LHMDS (lithium bis(trimethylsilyl)amide, 2.5 mL of a 1.0 M solution in THF) was added slowly to a solution of (4*R*)-4-benzyl-3-propionyloxazolidin-2-one ((*R*)-**18**) (500 mg, 2.14 mmol) in dry THF (2.5 mL) under an argon atmosphere at − 78 °C in a bath of acetone/N_2. The mixture was stirred for 10 min and then a solution of 3-bromo-2-methylpropene (0.4 mL, 4.1 mmol) in dry THF (0.5 mL) was added and stirred for 1 h. The reaction mixture was allowed to warm to room temperature and was stirred for additional 3 h. Saturated ammonium chloride solution (10 mL) and ethyl acetate (15 mL) were added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate (15 mL). The combined organic phase was washed with brine (25 mL), dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under reduced pressure to obtain a crude product which was purified by silica gel column chromatography. Elution with petroleum ether–AcOEt (85 : 15) yielded compound **21** as an only isomer (558 mg, 91%). Spectroscopic data of compound **21** were identical to those described in the literature for its enantiomer[14b] Colourless oil; $[\alpha]_D^{20}$ −50.4° (*c* 0.1 in CH_2Cl_2).

(*S*)-2,4-Dimethylpent-4-en-1-ol (22). $NaBH_4$ (489.5 mg, 12.9 mmol) was added at 0 °C to a stirred solution of (4*R*,2″*S*)-4-benzyl-3-[2,4-dimethylpent-4-enoyl]oxazolidin-2-one (**21**) (1000 mg, 3.23 mmol) in a mixture 4 : 1 THF–H_2O (16.1 mL). When TLC showed that the reaction was complete (24 h), 1 N HCl was added until pH = 7. The layers were separated and the aqueous layer was extracted with two portions of Et_2O (15 mL). The combined organic solution was washed with brine (30 mL), dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under reduced pressure at 0 °C to give a crude product which was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O (65 : 35) yielded the alcohol **22** (332 mg, 90%). Colourless oil; $[\alpha]_D^{20}$ −4.8° (*c* 0.42 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3400 (OH), 3089, 2850, 1634, 719; ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.75 (1H, br s, 5a-H), 4.70 (1H, br s, 5b-H), 3.50 (1H, dd, *J* 10.6, 5.6 Hz, 1a-H), 3.44 (1H, dd, *J* 10.6, 5.6 Hz, 1b-H), 2.10 (1H, m, 3a-H), 1.89–1.82 (2H, m, 2-H and 3b-H), 1.72 (3H, s, 4-Me), 0.89 (3H, d, *J* 6.4 Hz, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 144.5, 111.7, 68.4, 42.4, 33.6, 22.2, 16.6; HRMS (CI^+): calcd for $C_7H_{15}O$ $[M + H]^+$ 115.1123, found 115.1125.

(2*E*,4*S*)-Ethyl 2,4,6-trimethylhepta-2,6-dienoate (23). TEMPO (462 mg, 2.9 mmol) and BAIB (10.3 g, 31.9 mmol) were added at 0 °C to a solution of (*S*)-2,4-dimethylpent-4-en-1-ol (**22**) (1653 mg, 14.5 mmol) in dry CH_2Cl_2 (32.2 mL) and the mixture was stirred for 4 h. Then, (carbethoxyethylidene)triphenylphosphorane (13.4 g, 36.2 mmol) was added and the solution was stirred for further 12 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography. Elution with petroleum ether–Et_2O (97 : 3) yielded the ester (*E*)-**23** (1455.0 mg, 51%). Yellow oil; $[\alpha]_D^{20}$ +21.8° (*c* 0.12 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2963, 1710 (CO), 1682, 1446, 1367, 1252, 1202, 1120, 1075, 890, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.54 (1H, dq, *J* = 10.0, 1.4 Hz, 3-H), 4.72 (1H, br s, 7a-H), 4.65 (1H, br s, 7b-H), 4.16 (2H, q, *J* 7.2 Hz, 1′-H), 2.68 (1H, dsext, *J* 10.0, 6.8 Hz, 4-H), 2.03 (2H, d, *J* 6.8 Hz, 5-H), 1.83 (3H, d, *J* 1.4 Hz, 2-Me), 1.68 (3H, s, 6-Me), 1.27 (3H, t, *J* 7.2 Hz, 2′-H), 0.98 (3H, d, *J* 6.8 Hz, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.4, 147.5, 143.4, 126.3, 112.0, 60.4, 44.9, 31.4, 22.3, 19.5, 14.3, 12.4; HRMS (CI$^+$): calcd for $C_{10}H_{15}O$ $[M - C_2H_5O]^+$ 151.1123, found 151.1122.

(2*E*,4*S*)-2,4,6-Trimethylhepta-2,6-dien-1-ol (12b). Diisobutylaluminum hydride (DIBAL) (16.3 mL of a 1.0 M solution in CH_2Cl_2, 16.3 mmol) was slowly added to a solution of (2*E*,4*S*)-ethyl 2,4,6-trimethylhepta-2,6-dienoate (**23**) (1455.0 mg, 7.42 mmol) in dry CH_2Cl_2 (23.3 mL) and cooled at −78 °C. When TLC showed that the reaction was complete (1 h), a saturated solution of Rochelle's salt (40 mL) was added and the mixture was allowed to warm to room temperature while maintaining vigorous stirring. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic solutions were washed, dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent rendered a crude product that was purified by silica gel column chromatography. Elution with petroleum ether–ethyl acetate (80 : 20) yielded (2*E*,4*S*)-2,4,6-trimethylhepta-2,6-dien-1-ol (**12b**) (826.1 mg, 72%). Colourless oil; $[\alpha]_D^{20}$ −6.0° (*c* 0.83 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3314 (OH), 3072, 2958, 1651, 1455, 1374, 1011, 885; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.18 (1H, dq, *J* 9.2, 1.2 Hz, 3-H), 4.70 (1H, br s, 7a-H), 4.62 (1H, br s, 7b-H), 3.98 (2H, br s, 1-H), 2.59 (1H, dsext, *J* 9.2, 6.8 Hz, 4-H), 1.97 (2H, dd, *J* 6.8, 1.2 Hz, 5-H), 1.69 (3H, t, *J* 1.2 Hz, 6-Me), 1.67 (3H, d, *J* 1.2 Hz, 2-Me), 0.92 (3H, d, *J* 6.8 Hz, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.2, 133.2, 132.1, 111.3, 68.6, 45.6, 30.0, 22.2, 20.3, 13.5; HRMS (CI$^+$): calcd for $C_{10}H_{17}$ $[M + H - H_2O]^+$ 137.1330, found 137.1315.

(2*R*,3*R*,4*S*)-2,3-Epoxy-2,4,6-trimethylhept-6-en-1-ol (13b). (2*E*,4*S*)-2,4,6-trimethylhepta-2,6-dien-1-ol (**12b**) (826.1 mg, 5.36 mmol) was converted to (2*R*,3*R*,4*S*)-2,3-epoxy-2,4,6-trimethylhept-6-en-1-ol (**13b**) (773.9 mg, 85% yield, 86% de) following the methodology described above for the Sharpless asymmetric epoxidation of compound **12a**. Orange oil; $[\alpha]_D^{20}$ +1.9° (*c* 0.88 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3418 (OH), 3074, 2927, 1646, 1455, 1378, 1070, 1035, 891; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.77 (1H, br s, 7a-H), 4.68 (1H, br s, 7b-H), 3.64 (1H, dd, *J* 12.2, 4.6 Hz, 1a-H), 3.54 (1H, dd, *J* 12.2, 7.8 Hz, 1b-H), 2.73 (1H, d, *J* 9.4 Hz, 3-H), 2.03 (1H, ddd, *J* 13.2, 7.0, 0.8 Hz, 5a-H), 1.95 (1H, ddd, *J* 13.2, 7.0, 0.8 Hz, 5b-H), 1.69 (3H, s, 6-Me), 1.63 (1H, dsext, *J* 9.4, 7.0 Hz, 4-H), 1.26 (3H, s, 2-Me), 1.06 (3H, d, *J* 7.0 Hz, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.9, 112.3, 65.49, 65.46, 62.1, 42.3, 30.7, 22.3, 17.6, 14.5; HRMS (ESI$^+$): calcd for $C_{10}H_{18}O_2Na$ $[M + Na]^+$ 193.1204, found 193.1199.

(2*S*,4*S*)-2,4,6-Trimethylhept-6-ene-1,2-diol (14b). (2*R*,3*R*,4*S*)-2,3-epoxy-2,4,6-trimethylhept-6-en-1-ol (**13b**) (773.9 mg, 4.55 mmol) was converted to (2*S*,4*S*)-2,4,6-trimethylhept-6-ene-1,2-diol (**14b**) (675.3 mg, 86%) following the methodology described above for the synthesis of **14a**. Colourless oil; $[\alpha]_D^{20}$ +4.2° (*c* 0.22 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3378 (OH), 3073, 2928, 1649, 1458, 1376, 1038, 888; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.74 (1H, br s, 7a-H), 4.64 (1H, br s, 7b-H), 3.42 (1H, d, *J* 10.8 Hz, 1a-H), 3.35 (1H, d, *J* 10.8 Hz, 1b-H), 1.98 (1H, dd, *J* 12.0, 5.6 Hz, 5a-H), 1.88–1.79 (2H, m, 5b-H and H-4), 1.68 (3H, s, 6-Me), 1.45 (1H, dd, *J* 14.4, 7.2 Hz, 3a-H), 1.28 (1H, dd, *J* 14.4, 7.6 Hz, 3b-H), 1.17 (3H, s, 2-Me), 0.96 (3H, d, *J* 6.4 Hz, 4-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 144.5, 111.9, 73.4, 70.5, 47.7, 44.7, 26.5, 23.3, 22.1, 21.8; HRMS (CI$^+$): calcd for $C_{10}H_{21}O_2$ $[M + H]^+$ 173.1542, found 173.1542.

(2*S*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylhept-6-en-2-ol (15b). (2*S*,4*S*)-2,4,6-trimethylhept-6-ene-1,2-diol (**14b**) (675.3 mg, 3.92 mmol) was converted to (2*S*,4*S*)-1-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylhept-6-en-2-ol (**15b**) (1027.4 mg, 92%) following the methodology described above for the synthesis of **15a**. Colourless oil; $[\alpha]_D^{20}$ +3.8° (*c* 0.13 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3475 (OH), 3074, 2954, 2858, 1648, 1463, 1376, 1255, 1094, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.72 (1H, br s, 7a-H), 4.64 (1H, br s, 7b-H), 3.38 (1H, d, *J* 9.2 Hz, 1a-H), 3.33 (1H, d, *J* 9.2 Hz, 1b-H), 2.23 (O*H*, br s), 1.98 (1H, m, 5a-H), 1.88–1.79 (2H, m, 5b-H and 4-H), 1.68 (3H, s, 6-Me), 1.40 (1H, dd, *J* 14.4, 3.4 Hz, 3a-H), 1.26 (1H, dd, *J* 14.4, 7.6 Hz, 3b-H), 1.13 (3H, s, 2-Me), 0.98 (3H, d, *J* 6.0 Hz, 4-Me), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.6, 111.7, 72.7, 70.9, 47.8, 44.6, 26.5, 25.9 (3C), 23.4, 22.1, 21.6, 18.3, −5.5 (2C); HRMS (CI$^+$): calcd for $C_{16}H_{35}O_2Si$ $[M + H]^+$ 287.2406, found 287.2397.

(2*S*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)-2,4,6-trimethylhept-6-ene (16b). (2*S*,4*S*)-1-(*tert*-butyl-dimethylsilyloxy)-2,4,6-trimethylhept-6-en-2-ol (**15b**) (486.8 mg, 1.70 mmol) was converted to (2*S*,4*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)-2,4,6-trimethyl-hept-6-ene (**16b**) (506.0 mg, 90%) following the methodology described above for the synthesis of **16a**. Colourless oil; $[\alpha]_D^{20}$ +4.4° (*c* 0.14 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3072, 2929, 1648, 1460, 1374, 1256, 1101, 1037, 837, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.74 (1H, d, *J* 7.4 Hz, CH*H*OMe), 4.73 (1H, br s, 7a-H), 4.71 (1H, d, *J* 7.4 Hz, C*H*HOMe), 4.64 (1H, br s, 7b-H), 3.49 (1H, d, *J* 10.0 Hz, 1a-H), 3.46 (1H, d, *J* 10.0 Hz, 1b-H), 3.35 (3H, s, OMe), 2.07 (1H, dd, *J* 17.2, 9.6 Hz, 5a-H), 1.85–1.79 (2H, m, 4-H and 5b-H), 1.68 (3H, s, 6-Me), 1.51 (1H, dd, *J* 14.6, 3.8 Hz, 3a-H), 1.35 (1H, dd, *J* 14.6, 7.0 Hz, 3b-H), 1.20 (3H, s, 2-Me), 0.91 (3H, d, *J* 6.0 Hz, 4-Me), 0.88 (9H, s, $SiC(CH_3)_3$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.8, 111.6, 91.2, 79.1, 69.0, 55.3, 47.7, 42.8, 26.1, 25.8 (3C), 22.1, 21.4, 21.3, 18.2, −5.6 (2C); HRMS (CI$^+$): calcd for $C_{12}H_{23}OSi$ $[M - HOMOM - C(CH_3)_3]^+$ 211.1518, found 211.1517.

(2*S*,4*S*)-2-(Methoxymethoxy)-2,4,6-trimethylhept-6-en-1-ol (17b). (2*S*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxy-methoxy)-2,4,6-trimethylhept-6-ene (**16b**) (506.8 mg, 1.53 mmol) was converted to (2*S*,4*S*)-2-(methoxymethoxy)-2,4,6-trimethylhept-6-en-1-ol (**17b**) (276.0 mg, 84%) following the methodology described above for the synthesis of **17a**. Colourless oil; $[\alpha]_D^{20}$ +5.6° (*c* 0.33 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3439 (OH), 2920, 1646, 1446, 1374, 1256, 1150, 1111, 1042, 886; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.74 (1H, br s, 7a-H), 4.70 (1H, d, *J* 7.4 Hz, CH*H*OMe), 4.68 (1H, d, *J* 7.4 Hz, C*H*HOMe), 4.64 (1H, br s, 7b-H), 3.46 (1H, dd, *J* 12.2, 6.2 Hz, 1a-H), 3.41 (3H, s, OMe), 3.36 (1H, dd, *J* 12.2, 8.0 Hz, 1b-H), 3.26 (O*H*, dd, *J* 8.0, 6.2 Hz), 2.01 (1H, m, 5a-H), 1.88–1.80 (2H, m, 5b-H and 4-H), 1.68 (3H, t, *J* 1.2 Hz, 6-Me), 1.42 (1H, dd, *J* 14.4, 3.2 Hz, 3a-H), 1.38 (1H, dd, *J* 14.4, 7.6 Hz, 3b-H), 1.20 (3H, s, 2-Me), 0.91 (3H, d, *J* 6.4 Hz, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.4, 111.9, 90.8, 80.0, 68.9, 55.4, 47.8, 42.2, 26.2, 22.1, 21.4, 20.3; HRMS (CI^+): calcd for $C_{12}H_{24}O_3$ $[M]^+$ 216.1725, found 216.1734.

(2*S*,4*S*)-2-(Methoxymethoxy)-2,4,6-trimethylhept-6-enal (11b). (2*S*,4*S*)-2-(Methoxymethoxy)-2,4,6-trimethylhept-6-en-1-ol (**17b**) (260.0 mg, 1.20 mmol) was converted to (2*S*,4*S*)-2-(methoxymethoxy)-2,4,6-trimethylhept-6-enal (**11b**) (250.0 mg, 97%) following the methodology described above for the synthesis of **11a.** Colourless oil; $[\alpha]_D^{20}$ −6.7° (*c* 0.17 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3072, 2929, 1735 (CO), 1648, 1457, 1376, 1145, 1032, 889; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.55 (1H, s, 1-H), 4.76 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.73 (1H, br s, 7a-H), 4.65 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.63 (1H; br s, 7b-H), 3.38 (3H, s, OMe), 1.96 (1H, dd, *J* 15.6, 9.6 Hz, 5a-H), 1.87–1.82 (2H, m, 5b-H and 4-H), 1.65 (3H, s, 6-Me), 1.63 (1H, dd, *J* 14.6, 3.6 Hz, 3a-H), 1.46 (1H, dd, *J* 14.6, 8.2 Hz, 3b-H), 1.29 (3H, s, 2-Me), 0.86 (3H, d, *J* 6.0 Hz, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 203.9, 143.9, 112.2, 91.9, 82.8, 55.7, 47.1, 42.5, 25.9, 22.0, 21.4, 18.6; HRMS (ESI^+): calcd for $C_{12}H_{24}O_4Na$ $[M + H_2O + Na]^+$ 255.1572, found 255.1563.

(4*S*,2″*R*,3″*S*,4″*S*,6″*S*)-4-Benzyl-3-[3-hydroxy-4-(methoxy-methoxy)-2,4,6,8-tetramethyl)non-8-enoyl]oxazolidin-2-one (19b). (+)-(4*S*)-4-Benzyl-3-propionyloxazolidin-2-one ((+)-(*S*)-**18**)) (244 mg, 1.05 mmol) was treated with $MgCl_2$ (10.4 mg, 0.11 mmol), $NaSbF_6$ (84.8 mg, 0.33 mmol), triethylamine (0.25 mL, 2.1 mL), aldehyde **11b** (260.0 mg, 1.21 mmol) and chlorotrimethylsilane (0.18 mL, 1.58 mmol) in ethyl acetate (2.6 mL) at 25 °C for 48 h. The orange slurry was pushed through a pad of silica with Et_2O (200 mL) and the solvent was removed under reduced pressure. The residue was dissolved in dry methanol (105 mL) and trifluoroacetic acid (0.1 mL, 1.30 mmol) was added at 0 °C. The mixture was stirred for 15 minutes and the solvent was evaporated under reduced pressure to obtain a crude product which was purified by silica gel column chromatography. Elution with petroleum ether–ethyl acetate (85 : 15) yielded compound **19b** (268.2 mg, 58%, 94% de). Colourless oil: $[\alpha]_D^{20}$ +12.4° (*c* 0.66 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3466 (OH), 2928, 1781 (CO), 1676 (CO), 1456, 1384, 1208, 1030, 918, 890; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31–7.28 (2H, m, *H*arom), 7.25–7.20 (3H, m, *H*arom), 4.69 (1H, br s, 7′a-H), 4.68 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.67 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.65–4.59 (2H, m, 4-H and 7′b-H), 4.36 (O*H*, d, *J* 9.4 Hz), 4.33 (1H, dq, *J* 7.2, 2.4 Hz, 2′-H), 4.10 (2H, m, 5-H), 3.57 (1H, dd, *J* 9.4, 2.4 Hz, 3′-H), 3.42 (1H, dd, *J* 13.2, 2.8 Hz, C*H*HPh), 3.27 (3H, s, OMe), 2.55 (1H, dd, *J* 13.2, 10.6 Hz, CH*H*Ph), 2.08 (1H, dd, *J* 12.0, 4.6 Hz, 7a′-H), 1.91 (1H, dd, *J* 13.6, 3.2 Hz, 5′a-H), 1.84 (1H, dd, *J* 12.0, 7.6 Hz, 7′b-H), 1.82–1.70 (1H, m, 6′-H), 1.66 (3H, s, 8′-Me), 1.38 (3H, d, *J* 7.2 Hz, 2′-Me), 1.35 (3H, s, 4′-Me), 1.33 (1H, dd, *J* 13.6, 6.5 Hz, 5′b-H), 0.90 (3H, d, *J* 6.4 Hz, 6′-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 178.3, 152.9, 144.6, 135.5, 129.3, 129.0, 127.3, 111.7, 90.9, 81.8, 81.0, 65.8, 55.6, 55.3, 47.8, 43.1, 38.0, 34.6, 26.6, 22.0, 21.42, 21.37, 17.9; HRMS (ESI^+): calcd for $C_{25}H_{37}NO_6Na$ $[M + Na]^+$ 470.2519, found 470.2520.

(2*R*,3*S*,4*S*,6*S*)-Allyl 3-hydroxy-4-(methoxymethoxy)-2,4,6,8-tetramethylnon-8-enoate (10b). Compound **19b** (31.0 mg, 0.07 mmol) was converted to (2*R*,3*S*,4*S*,6*S*)-allyl 3-hydroxy-4-(methoxymethoxy)-2,4,6,8-tetramethylnon-8-enoate (**10b**) (5.4 mg, 24%) following the methodology described above for the synthesis of **10a**. Colourless oil. $[\alpha]_D^{20}$ +2.6° (*c* 0.32 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3439 (OH), 2921, 1733 (CO), 1673, 1455, 1380, 1034, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.91 (1H, ddt, *J* 17.2, 10.4, 5.6 Hz, 2′-H), 5.33 (1H, ddd, *J* 17.2, 2.8, 1.6 Hz, 3′a-H), 5.24 (1H, ddd, *J* 10.4, 2.8, 1.6 Hz, 3′b-H), 4.73 (1H, br s, 9a-H), 4.67 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.64 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.63 (1H, br s, 9b-H), 4.56 (2H, m, 1′-H), 3.72 (O*H*, d, *J* 9.6 Hz), 3.46 (1H, dd, *J* 9.6, 2.8 Hz, 3-H), 3.32 (3H, s, OMe), 2.81 (1H, dq, *J* 7.2, 2.8 Hz, 2-H), 2.07 (1H, dd, *J* 13.2, 5.2 Hz, 7a-H), 1.86–1.78 (2H, m, 5a-H and 7b-H), 1.77–1.72 (1H, m, 6-H), 1.68 (3H, s, 8-Me), 1.34 (3H, d, *J* 7.2 Hz, 2-Me), 1.29 (3H, s, 4-Me), 1.28–1.24 (1H, m, 5b-H), 0.89 (3H, d, *J* 6.0 Hz, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.2, 144.5, 132.0, 118.5, 111.8, 91.0, 81.4, 79.2, 65.1, 55.6, 47.8, 42.9, 38.7, 26.6, 22.1, 21.3, 20.7, 17.1; HRMS (ESI^+): calcd for $C_{18}H_{32}O_5Na$ $[M + Na]^+$ 351.2147, found 351.2142.

RCM of ester 10b. Compound **10b** (8.2 mg, 8 μmol) was subjected to an RCM following the methodology described above for the synthesis of **10a**. Elution with ether petroleum–EtOAc (80 : 20) yielded a mixture of (*Z*)-**20b** (1.1 mg, 15%), **24** (2.2 mg, 28%) and **25** (3.1 mg, 31%), which was further purified by analytical HPLC (hexane–ethyl acetate 85 : 15, flow = 0.8 mL min^{-1}; t_R = 34 min for lactone (*Z*)-**20b**, t_R = 43 min for linear dimer **24** and t_R = 22 min for **25**).

(2*R*,3*S*,4*S*,6*S*,8*Z*)-3-Hydroxy-4-(methoxymethoxy)-2,4,6,8-tetramethyldec-8-enolide ((*Z*)-20b). Colourless oil; $[\alpha]_D^{20}$ +34.2° (*c* 0.1 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3390 (OH), 2925, 1732 (CO), 1458, 1376, 1260, 1028, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.50 (1H, ddd, *J* 7.2, 6.0, 1.5 Hz, 9-H), 5.07 (1H, dd, *J* 13.2, 6.0 Hz, 10a-H), 4.77 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.62 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.12 (1H, dd, *J* 13.2, 7.2 Hz, 10b-H), 3.72 (1H, d, *J* 9.6 Hz, 3-H), 3.39 (3H, s, OMe), 2.89 (1H, dq, *J* 9.6, 7.2 Hz, 2-H), 2.00 (1H, dd, *J* 13.2, 1.2 Hz, 7a-H), 1.87 (1H, dd, *J* 13.2, 7.8 Hz, 7b-H), 1.80 (3H, t, *J* 1.5 Hz, 8-Me), 1.72 (2H, m, 5a-H and 6-H), 1.42 (1H, dd, *J* 13.2, 7.2 Hz, 5b-H), 1.34 (3H, s, 4-Me), 1.28 (1H, d, *J* 7.2 Hz, 2-Me), 1.15 (3H, d, *J* 6.6 Hz, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.2, 147.1, 117.1, 90.8, 82.2, 75.0, 59.0, 55.5, 46.0, 42.7, 30.9, 25.5, 25.3, 20.8, 16.5; HRMS (ESI^+): calcd for $C_{16}H_{28}O_5Na$ $[M + Na]^+$ 323.1834, found 323.1839.

Linear dimer 24. Colourless oil; $[\alpha]_D^{20}$ −7.3° (*c* 0.14 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3454 (OH), 2918, 2850, 1731 (CO), 1646, 1463, 1377, 1163, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.87 (2H, m, 2′-H), 4.73 (2H, br s, 9a-H), 4.66 (2H, d, *J* 7.2 Hz, C*H*HOMe), 4.64 (2H, br s, 9b-H), 4.63 (2H, d, *J* 7.2 Hz, CH*H*OMe), 4.60–4.54 (4H, m, 1′-H), 3.67 (O*H*, d, *J* 9.2 Hz), 3.46 (2H, dd, *J* 9.2, 2.8 Hz, 3-H), 3.32 (6H, s, OMe), 2.79 (2H, dq, *J* 7.2, 2.8 Hz, 2-H), 2.07 (2H, dd, *J* 12.8, 5.6 Hz, 7a-H), 1.86–1.75 (6H, m, 5a-H, 6-H and 7b-H), 1.68 (6H, s, 8-Me), 1.35–1.30 (2H, m, 5b-H), 1.33 (6H, d, *J* 7.2 Hz, 2-Me), 1.28 (6H, s, 4-Me), 0.89 (6H, d, *J* 6.4 Hz, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.1 (2C), 144.5 (2C), 128.1 (2C), 111.8 (2C), 91.0 (2C), 81.4 (2C), 79.1 (2C), 63.9 (2C), 55.6 (2C), 47.8 (2C), 42.9 (2C), 38.9 (2C), 26.6 (2C), 22.1 (2C), 21.4 (2C), 20.6 (2C), 17.1 (2C). HRMS (ESI$^+$): calcd for $C_{34}H_{60}O_{10}Na$ [M + Na]$^+$ 651.4084, found 651.4087.

(2*R*,3*S*,4*S*,6*S*,2′*E*)-3-Phenylprop-2-enyl 3-hydroxy-4-(methoxymethoxy)-2,4,6,8-tetramethylnon-8-enoate (25). Colourless oil; $[\alpha]_D^{20}$ −6.1° (*c* 0.1 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3454 (OH), 2920, 2850, 1735 (CO), 1458, 1164, 1032, 966; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 (2H, m, *H*arom), 7.32 (2H, m, *H*arom), 7.25 (1H, m, *H*arom), 6.65 (1H, d, *J* 15.6 Hz, 3′-H), 6.28 (1H, dt, *J* 15.6, 6.6 Hz, 2′-H), 4.74–4.71 (3H, m, 1′-H), 4.66 (1H, d, *J* 7.2 Hz, C*H*HOMe), 4.64 (1H, d, *J* 7.2 Hz, CH*H*OMe), 4.62 (1H, br s, 9a-H), 3.75 (O*H*, d, *J* 9.2 Hz), 3.48 (1H, dd, *J* 9.2, 2.8 Hz, 3-H), 3.31 (3H, s, OMe), 2.82 (1H, dq, *J* 7.2, 2.8 Hz, 2-H), 2.06 (1H, dd, *J* 13.2, 6.0 Hz, 7a-H), 1.84–1.80 (2H, m, 7a-H and 5a-H), 1.78–1.73 (1H, m, 6-H), 1.67 (3H, s, 6-Me), 1.36 (3H, d, *J* 7.2 Hz, 2-Me), 1.30 (1H, dd, *J* 13.8, 7.8 Hz, 5b-H), 1.29 (3H, s, 4-Me), 0.88 (3H, d, *J* 6.0 Hz, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.3, 144.5, 134.4, 130.2, 128.6 (2C), 128.1, 126.6 (2C), 123.0, 111.8, 91.0, 81.4, 79.2, 65.1, 55.6, 47.8, 43.0, 38.8, 26.6, 22.1, 21.3, 20.7, 17.2; HRMS (CI$^+$): calcd for $C_{24}H_{37}O_5$ [M + H]$^+$ 405.2488, found 405.2497.

Acetylation of natural product 1/26. Pyridine (2 drops) was added to a solution of natural product **1** (3.0 mg, 0.01 mmol) in acetic anhydride (0.5 mL) at 0 °C and stirred at room temperature for 18 h. Then, cyclohexane was added (2 mL) and the solvent was evaporated under reduced pressure. This procedure was repeated three times to give quantitatively (3*R*,4*S*,5*S*,2′*R*,4′*E*)-4-acetoxy-5-(6-acetoxy-2,4-dimethylhex-4-enyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (**26a**) (3.4 mg, 100%). Yellow oil: $[\alpha]_D^{20}$ −10.3° (*c* 0.30, $CHCl_3$); IR (film) ν_{max} 2945, 1775, 1740, 1455, 1374, 1223, 1087, 1022, 990, 939 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 5.36 (t, *J* = 6.8 Hz, 1H), 4.97 (d, *J* = 5.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 2H), 2.32 (dq, *J* = 6.8, 5.8 Hz, 1H), 2.14 (m, 1H), 1.71 (s, 3H), 1.68–1.61 (m, 3H), 1.59 (s, 3H), 1.48 (s, 3H), 1.26 (dd, *J* = 14.0, 5.2 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.82 (s, 3H), 0.69 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 175.2, 170.1, 169.2, 140.2, 121.5, 85.0, 77.0, 61.0, 48.1, 41.0, 38.5, 26.5, 22.6, 21.1, 20.5, 19.8, 16.0, 8.8; HRMS (ESI$^+$): calcd for $C_{18}H_{28}O_6Na$ [M + Na]$^+$ 363.1784, found 363.1795.

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