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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 in 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 synthezited lactones and the natural product and the spectroscopic data of its acetylated derivative 26a, let 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 species1 producing a grey powdery mould on the plants. The major phytotoxic metabolites of B. cinerea are a family of sesquiterpenes with the botryane skeleton2 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 lactones5 and the relative thermodynamic instability of 11-membered lactones has made their synthesis and that of their derivatives difficult even using Mitsunobu lactonization6 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 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.

Fig. 1. Structure of compound 1

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 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°C9 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 C23 and C24 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 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 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-OPr)_4. In this occasion only Z isomer could 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.

The aldehyde 11a was treated (Scheme 5) with the appropriate oxazolidinone by the procedure reported by Evans 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 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-OPr)_4. In this occasion only Z isomer could 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 (S)-21 with 3-bromo-2-methylprop-1-ene which proceeded as described in literature, 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 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% of yield and 86% de. Conversion of this compound into aldehyde 11b was carried out following a similar synthetic strategy that described in Scheme 4.

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

Condensation of the aldehyde 11b with the appropriate oxazolidinone (Scheme 7) by the procedure reported by Evans,16 afforded via methanolsysis 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 by using SmI2,17 were unsuccessful. Finally a RCM reaction catalyzed by the ruthenium complex A in refluxing CH2Cl2 in the presence of a catalytic amount of Ti(i2OPr)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.

Scheme 6. Stereoselective synthesis of aldehyde 11b

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 BF3·Et2O/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 stagnolid G, a 10-membered lactone with a free hydroxyl group at the C-4 position.18 However we only we obtained an untreatable reaction mixture. Additional deprotection experiments with ZnBr2/PrSH19 again yielded a complex reaction mixture.

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

<table>
<thead>
<tr>
<th>Comp./Position</th>
<th>1</th>
<th>3</th>
<th>(Z)-8</th>
<th>(E)-8</th>
<th>20a</th>
<th>20b</th>
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<td>4.29</td>
<td>4.42</td>
<td>4.33</td>
<td>4.12</td>
</tr>
<tr>
<td>H-10′</td>
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<td>4.68</td>
<td>4.80</td>
<td>4.66</td>
<td>4.75</td>
<td>5.07</td>
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</table>
In the course of our research work with the phytopathogen fungus *B. cinerea*, we studied the mutant bcb04, which overproduced polyketides metabolites, yielding 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-butyro lactone structure 26 for the natural product (Fig. 2). The γ-butylactone would be thermodynamically more stable than the 11-membered lactone. In the literature there are a number of precedents for the corrections to the structures of medium-sized lactones.

**Fig. 2. Compound 26 and 26a.**

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 δH 4.12 and 4.17 ppm in 26 to δH 4.55 ppm in 26a. This signal was correlated in the HMBC with the signal assigned to the carbonyl group of the acetate at δC 170.1 ppm indicating that an acetyl group was on hydroxyl group on C-10 what is incompatible with the original structure 1. The other acetate group was situated on hydroxyl group on C-3 for the HMBC correlations observed between the signals at δH 4.97 ppm (H-3) and the signal at δC 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-butylactone and acetate esters. Although compound 1 itself had IR absorption at 1748 cm⁻¹ which is rather low for a γ-butylactone, this might be affected by hydrogen bonding from the hydroxyl group at C-3.

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

**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 the four compounds 3, (Z)-8, (E)-8 and 20a. The results showed that the increase in conformational restrictions imposed by the substituents have a high influence in 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. Based in 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, let 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(3H)-one (26). Works are 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 CaH₂ and tetrahydrofuran was dried over sodium and benzophenone and freshly distilled before use. Air- and moisture-sensitive reactions were performed under argon atmosphere. Purification by semipreparative and analytical HPLC was performed with a Hitachi/Merck L-6270 apparatus equipped with a differential refractometer detector (RI-7490). A LiChrospher® Si 60 (5µm) LiChroCart® (250 mm × 4 mm) column and a LiChrospher® Si 60 (10µm) LiChroCart® (250 mm × 10 mm) were used in isolation experiments. Silica gel (Merck) was used for column chromatography. TLC was performed on Merck Kieselgel 60 F₂₅₄₅, 0.25 mm thick. Optical rotations were determined with a digital polarimeter. Infrared spectra were recorded on a FT-IR spectrophotometer and reported as wave number (cm⁻¹). ¹H and 13C NMR measurements were recorded on Varian Unity 400 MHz, Agilent 500 MHz and Varian Inova 600 MHz spectrometers with SiMe₄ as the internal reference. Chemical shifts are reported in parts per million (ppm) and were referenced to CDCl₃ (δH 7.25, δC 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=quartet, quint=quintuplet; sext=sextuplet; m=multiplet, br=broad. High-Resolution Mass Spectroscopy (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**

(2R,3R,4E)-allyl 3-hydroxy-2,4,8-trimethylmona-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.

(2R,3R,4S,5R)-allyl 4,5-epoxy-3-hydroxy-2,4,8-trimethylmonon-8-enoate (6). VO(acac)₂ (vanadyl acetylacetonate, 17.9 mg, 0.06 mmol) was added a solution cooled at -20°C of (2R,3R,4E)-allyl 3-hydroxy-2,4,8-trimethylmona-4,8-dienoate (4) (180.0 mg, 0.71 mmol) in dry CH₂Cl₂ (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 Na₂SO₃ (3 mL) was added and then allowed to warm to room temperature stirring for 30 min. The aqueous layer was extracted three times with diethyl ether (15 mL) and the organic layers 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:Et₂O (75:25) yielded the compound 6 as a single isomer (123.3 mg, 64%). Colourless oil; [α]D²⁰⁺17.5° (c 0.65 in CHCl₃); IR (film) νmax/cm⁻¹: 3480 (OH), 3079, 2940, 1739 (CO), 1650, 1456, 1376, 1246, 1186, 1041, 996, 889; ¹H NMR (400 MHz, CDCl₃)
CHCl$_3$), 1.74 (3H, s, 4'2Me), 1.69 (1H, dddd, J = 14.4, 8.8, 6.2 Hz, 3'a2H), 2.12 (1H, dt, J = 14.4, 7.6 Hz, 3'b); 1.85 (1H, ddd, J = 14.1, 8.8, 7.6, 2.0 Hz, 2'a-H), 1.74 (3H, s, 4'-Me), 1.69 (1H, ddd, 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$_3$) $\delta$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): calculated for C$_{19}$H$_{28}$O$_2$ [M+H]$^+$ 329.2114, found 329.2110.

RCM of ester 6.  (1,3-Bis(2,6-trimethylphenyl)-2-imidazolidinylidene)dichlorophenylmethyltricyclo[3.2.2.0$^3$-6]octylphenyloxiph/ospheniruthenium (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 degaseated and dry CH$_2$Cl$_2$ (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 ether:Et$_2$O (90:10) yielded a mixture 3:1 of (Z)-8 (23.8 mg, 26%) and (E)-8 (7.9 mg, 9%).

(2R,3R,4S,5R,8E)-4,5-epoxy-3-hydroxy-2,4,8-trimethyldec-8-enolide (Z)-(8): Colourless oil; [?]$_D^20$ +14.9° (c 0.77 in CHCl$_3$); IR (film) $\nu$max/cm$^{-1}$ 3434 (OH), 2928, 1737 (CO), 1456, 1383, 1205, 1081, 935, 904; $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$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, dd, 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$_3$) $\delta$C 172.8, 143.8, 120.9, 54.2, 59.4, 59.1, 44.3, 28.2, 23.9, 22.1, 16.7, 15.8; HRMS (CI): calculated for C$_{19}$H$_{28}$O$_2$ [M+H]$^+$ 329.2114, found 329.2116.

Epoxidation of lactone (E)-3.  (2R,3R,4E,8E)-3-hydroxy-2,4,8-trimethyldec-8-enolide (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.

(2S,3S)-2,3-epoxy-2,6-dimethylhept-6-en-1-ol (13a). Ti(OPr)$_2$ (4.3 mL, 14.7 mmol) was added at -20°C to a solution of (+)-DIT ((+)-disopropyl L-lactate, 3.8 mL, 17.7 mmol) in dry CH$_2$Cl$_2$ (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$_2$Cl$_2$ (45 mL) was added slowly 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 (3h), diethyl ether (15 mL) and a saturated Na$_2$SO$_4$ solution (15 mL) were added and the mixture was allowed to warm to room temperature, stirred for an additional hour, filtered with Et$_2$O 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 2h 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$_2$O 80:20 yielded the alcohol (13a) (2778 mg, 90%). Colourless oil; $[\alpha]_D^20$ -6.4° (c 0.65 in CHCl$_3$); IR (film) $\nu$max/cm$^{-1}$ 3438 (OH), 3052, 2939, 1650, 1452, 1369, 1068, 1051, 892; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$H 4.72 (1H, br s, 7b-H), 4.71 (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, OH), 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),
portions of ethyl acetate (40 mL). The combined organic
petroleum ether:Et$_2$O purified by silica gel column chromatography. Elution with

calcd for C$_{14}$H$_{20}$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$_2$O (31.9 mmol)) was added slowly at
0ºC to a solution of (2S,3S)-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 (3h), the mixture was recolored at 0ºC and water (20 mL)
and 1N HCl was 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. [a]$^2_0$ +2.9º (c 4.7 in CHC1$_3$); IR (film) $\nu$cm$^{-1}$ 3300 (OH), 3074, 2924, 1650, 1456, 1374, 1134, 1055, 886; 1H NMR (400 MHz, CDCl$_3$) $\delta$ 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); 13C NMR (100 MHz, CDCl$_3$) $\delta$ 145.5, 110.0, 72.9, 38.13, 38.10, 23.1, 22.2, 21.6; HRMS (CI$^+$): calcd for C$_{14}$H$_{20}$O$_2$ [M-H$_2$O] $^+$ 140.1201, found 140.1208.

(R)-1-(tert-butyldimethylsilyloxy)-2,6-dimethylhept-6-en-2-ol (15a). A solution of tert-butyldichloromethylsilane (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-en-1,2-diol (14a). (379 mg, 2.4 mmol) in dry THF (3.4 mL) at
0ºC under an argon atmosphere. The mixture was allowed to warm to room temperature and when TLC showed that the reaction was complete (6h) 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 to give a crude product which was purified by silica gel column chromatography. Elution with petroleum ether:Et$_2$O 70:30 yielded the alcohol 17a (201 mg, 85%). Colourless oil; [a]$^2_0$ +2.9º (c 0.15 in CHCl$_3$); IR (film) $\nu$cm$^{-1}$ 3458 (OH), 2932, 1650, 1442, 1374, 1238, 1144, 1028, 888; 1H NMR (400 MHz, CDCl$_3$) $\delta$ 4.66 (1H, d, $J$ 7.2 Hz, CH$_2$OMe), 4.65 (1H, br s, 7b-H), 4.63 (1H, d, $J$ 7.2 Hz, CH$_2$OMe), 4.62 (1H, br s, 7a-H), 3.41 (1H, d, $J$ 13.6, 6.8 Hz, 1b-H), 3.36 (3H, s, OMe), 3.31 (1H, d, $J$ 13.6, 6.8 Hz, 1a-H), 1.96 (2H, t, $J$ 6.8 Hz, 5-H), 1.69 (3H, s, 6-Me), 1.48-1.42 (4H, m, 3-H and 4-H), 1.14 (3H, s, 2-Me); 13C NMR (100 MHz, CDCl$_3$) $\delta$ 145.5, 110.9, 72.8, 39.10, 38.19, 23.1, 22.2, 21.6. HRMS (CI$^+$): calcd for C$_{17}$H$_{23}$O$_2$Si [M-H$_2$O] $^+$ 271.2093, found 271.2097.

(R)-1-(tert-butyldimethylsilyloxy)-2-(methoxymethoxy)-2,6-
dimethylhept-6-ene (16a). Anhydrous dimethylsulfoxide (DMSO, 0.25 mL, 4.4 mmol) in dry CH$_2$Cl$_2$ (3.4 mL) was added over 5 min dropwise to a solution of freshly distilled oxaly chloride (0.15 mL, 1.76 mmol) in dry CH$_2$Cl$_2$ (5.1 mL) at –60ºC in a bath of acetone/N$_2$ under an argon atmosphere. The resultant 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$_2$Cl$_2$ (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 –60ºC. Then N,N'-disopropylethylenimine (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, which was used immediately in the next step. [α]_D^{20} = +1.6° (c 1.2 in CHCl₃); IR (film) ν_max/cm⁻¹ 3074, 2924, 1734 (CO), 1651, 1453, 1376, 1144, 1119, 1084, 919, 889; ¹H NMR (400 MHz, CDCl₃) δ_H 9.48 (1H, s, 1-H), 4.71 (1H, d, J 7.2 Hz, CH/HOME), 4.66 (1H, br, s, 7b-H), 4.62 (1H, br, s, 7a-H), 4.61 (1H, d, J 7.2 Hz, CH/HOME), 3.35 (3H, s, OMe), 1.96 (2H, t, J 7.2 Hz, 5-H), 1.64 (2H, s, 6-Me), 1.62-1.39 (4H, m, 3a-H, 3b-H and 4-H); ¹³C NMR (100 MHz, CDCl₃) δ_C 203.5, 145.0, 110.4, 92.0, 82.2, 55.8, 37.8, 34.8, 32.2, 22.0, 16.7; HRMS (ESI⁺): calcd for C₁₄H₂₀O₂Na [M+H]⁺ 434.2543, found 434.2559.

(4R,2'R,3'R,4'R)-4-benzyl-3-[3-hydroxy-4-(methoxy-methoxy)-2,4,8-trimethyln-8-enyl]oxazolidin-2-one (19a). n-Dibutylboron triflate (1.1 mL of a 1.0 M solution in CH₂Cl₂, 1.1 mmol) was added dropwise at 0°C to a stirred solution of (4R)-4-benzyl-3-propionyloxazolidin-2-one (1.0 M solution in THF) was added slowly to a solution of allylmagnesium bromide (0.3 mL of a 1.0 M solution in Et₂O, 0.3 mmol) in dry CH₂Cl₂ (1.3 mL under an argon atmosphere. The mixture was stirred for 5 min and then N,N′-dipropylethylamine 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)-2,6-dimethylhept-6-enal (11a) (176 mg, 0.88 mmol) was added dropwise in dry CH₂Cl₂ (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 of 2.1 M MeOH·H₂O, 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 re-dissolved 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, filtered and the solvent was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. Elution with petroleum ether: ethyl acetate (75:25) yielded the compound mmol) in allylic alcohol (0.2 mL) was slowly added. When TLC monitoring indicated the completion of the reaction (3h), a saturated ammonium chloride solution (4 mL) was added and then 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: ethyl acetate (90:10) yielded the compound (20 µg) as a colourless oil; [α]_D^{20} +8.0° (c 0.68 in CHCl₃); IR (film) ν_max/cm⁻¹ 3444 (OH), 2950, 1732 (CO), 1645, 1457, 1377, 1153, 1030, 919, 887; ¹H NMR (400 MHz, CDCl₃) δ_H 5.90 (1H, ddt, J 1.8, 7.2 Hz, 7a-H, CH/HOME), 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 (3H, d, 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); ¹³C NMR (100 MHz, CDCl₃) δ_C 175.7, 145.5, 132.0, 118.3, 110.1, 91.0, 81.6, 75.1, 65.2, 55.7, 41.1, 35.7, 22.3, 21.5, 19.7, 13.6; HRMS (ESI⁺): calcd for C₁₇H₃₈O₈Na [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 CH₂Cl₂ (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 CH₂Cl₂ (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 ether:ethyl acetate (20:2:1) yielded the lactone (Z)-20a (9.2 mg, 54%).

(2R,3R,4R,Z)-3-hydroxy-4-(methoxy-methoxy)-2,4,8-trimethyldec-8-enolide ((Z)-20a): Colourless oil; [α]_D^{20} +27.7° (c 0.17 in CHCl₃); IR (film) ν_max/cm⁻¹ 3508 (OH), 2921, 2850, 1728 (CO), 1454, 1377, 1252, 1142, 1036, 914, 827; ¹H NMR (500 MHz, CDCl₃) 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, CH/HOME), 4.65 (1H, d, J 7.6 Hz, CH/HOME), 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, dd, 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 Hz, 2-Me), 1.25 (1H, m, 5a-H), 1.21 (3H, s, 4-Me); ¹³C NMR (125 MHz, CDCl₃) 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 (ESI⁺): calcd for C₂₉H₅₀O₁₀ [M+H]⁺ 434.2543, found 434.2559.

(2R,3R,4R)-Allyl 3-hydroxy-4-(methoxy-methoxy)-2,4,8-trimethyln-8-enate (10a). Allylmagnesium bromide (0.3 mL of a 1.0 M solution in THF) was added slowly to a solution of (4R)-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/N₂. 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 phases 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 the compound 21 as an only isomer (358 mg, 91%). Spectroscopic data of compound 21 were identical to those described in the literature for its enantiomer. Colourless oil; [α]D20 -6.0º (c 0.83 in CHCl3); IR (film) νmax/cm−1 3314 (OH), 3072, 2958, 1651, 1455, 1374, 1011, 885; 1H NMR (400 MHz, CDCl3) δH 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, d, 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); 13C NMR (100 MHz, CDCl3) δC 144.2, 133.2, 132.1, 111.3, 68.6, 45.6, 30.0, 22.3, 20.3, 13.5; HRMS (CI): calecd for C15H17 [M+H2O]2+ 137.1330, found 137.1315.

(2R,3R,4S)-2,3-epoxy-2,4,6-trimethylhepta-6-en-1-ol (13b). (2R,3R,4S)-2,4,6-trimethylhepta-2,6-dien-1-ol (12b) (826.1 mg, 5.36 mmol) was converted to (2R,3R,4S)-2,3-epoxy-2,4,6-trimethylhepta-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; [α]D25 +1.9º (c 0.88 in CHCl3); IR (film) νmax/cm−1 3418 (OH), 3074, 2927, 1646, 1455, 1378, 1035, 891; 1H NMR (400 MHz, CDCl3) δH 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, dd, J 13.2, 7.0, 0.8 Hz, 5a-H), 1.95 (1H, dd, J 13.2, 7.0, 0.8 Hz, 5b-H), 1.69 (3H, s, 6-Me), 1.63 (1H, d, J 9.4, 7.0 Hz, 4-Me), 1.26 (3H, s, 2-Me), 1.06 (3H, d, J 7.0 Hz, 4-Me); 13C NMR (100 MHz, CDCl3) δC 142.9, 112.3, 65.49, 65.46, 62.1, 42.3, 30.7, 22.3, 17.6, 14.5; HRMS (ESI): calecd for C10H18O4Na [M+Na]+ 193.1204, found 193.1199.

(2R,4S,5S)-2,4,6-trimethylhept-6-ene-1,2-diol (14b). (2R,3R,4S)-2,4,6-trimethylhept-6-en-1-ol (13b) (773.9 mg, 4.55 mmol) was converted to (2R,4S,5S)-2,4,6-trimethylhept-6-ene-1,2-diol (14b) (993.6 mg, 88%) following the methodology described above for the synthesis of 14a. Colourless oil; [α]D20 +24.2º (c 0.22 in CHCl3); IR (film) νmax/cm−1 3378 (OH), 3073, 2928, 1649, 1458, 1376, 1038, 888; 1H NMR (500 MHz, CDCl3) δH 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, d, J 14.4, 7.2 Hz, 3a-H), 1.28 (1H, d, J 14.4, 7.6 Hz, 3b-H), 1.17 (3H, s, 2-Me), 0.96 (3H, d, J 6.4 Hz, 4-Me); 13C NMR (125 MHz, CDCl3) δC 144.5, 111.9, 73.4, 70.5, 47.7, 44.7, 26.5, 23.3, 21.2, 18.1; HRMS (CI): calecd for C9H16O2Na [M+H]+ 173.1542, found 173.1542.

(2R,4S,5R)-1-((tert-butyldimethylsilyloxy)-2,4,6-trimethylhept-6-en-2-ol (15b). (2R,4S,5R)-2,4,6-trimethylhept-6-ene-1,2-diol (14b) (675.3 mg, 3.92 mmol) was converted to (2R,4S,5R)-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; [α]D20 +3.8º (c 0.13 in CHCl3); IR (film) νmax/cm−1 3475 (OH), 3074, 2954, 2858, 1648, 1463, 1376, 1255, 1094, 836, 776; 1H NMR (400 MHz, CDCl3) δH 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 (OH, 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, d, 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, Si(CH3)3). 0.06 (6H, s,}
(2S,4S)-1-(tert-butyldimethylsilyl)oxy-2-(methoxy)methoxy-2,4,6-trimethylhept-6-en-1-ol (16b). (2S,4S)-1-(tert-butyldimethylsilyl)oxy-2,4,6-trimethylhept-6-en-2-ol (15b) (486.8 mg, 1.70 mmol) was converted to (2S,4S)-1-(tert-butyldimethylsilyl)oxy-2-(methoxy)methoxy-2,4,6-trimethylhept-6-en-1-ol (16b) (506.0 mg, 90%) following the methodology described above for the synthesis of 16a. Colourless oil; [α]D<sub>20</sub>+4.4° (c 0.14 in CHCl<sub>3</sub>); IR (film) ν<sub>max</sub>/cm<sup>-1</sup> 3072, 2929, 1648, 1460, 1374, 1256, 1101, 1037, 837, 776; 1<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>β</sub> 4.74 (1H, d, J<sub>11,6</sub> 7.4 Hz, CH/JOme), 4.73 (1H, br s, 7a-H), 4.71 (1H, d, J<sub>7,4</sub> 7.4 Hz, CH/JOme), 4.64 (1H, br s, 7b-H), 3.49 (1H, d, J<sub>10,0</sub> 10.0 Hz, 1a-H), 3.46 (1H, d, J<sub>10,0</sub> 10.0 Hz, 1b-H), 3.35 (3H, s, OMe), 2.07 (1H, dd, J<sub>17,6,9.6</sub> 7.4 Hz, 5a-H), 1.85-1.79 (2H, m, 4-H and 5b-H), 1.68 (3H, s, 6-Me), 1.51 (1H, m, 6b-H), 1.46 (1H, d, J<sub>14.6</sub> 7.3 Hz, 5b-H), 1.30 (2H, s, 2-Me), 0.91 (3H, d, J<sub>6,0</sub> 6.4 Hz, 1-Me), 0.88-0.60 (6H, s, Si(CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ<sub>β</sub> 144.8, 111.6, 91.2, 79.1, 69.0, 55.3, 47.7, 42.8, 28.1, 25.8 (3C), 22.1, 21.4, 18.3, 13.2 (2C); HRMS (Cl<sup>+</sup>): calcd for C<sub>21</sub>H<sub>37</sub>OSi [M+H]<sup>+</sup> 327.2406, found 327.2397.

(2R,3S,5S,6S)-Allyl 3-hydroxy-4-(methoxy)methoxy)-2,4,6,8-tetramethylnon-8-enoate (10b). Compound 10b (31.0 mg, 0.07 mmol) was converted to (2R,3S,5S,6S)-allyl 3-hydroxy-4-(methoxy)methoxy)-2,4,6,8-tetramethylnon-8-enoate (10b) (5.4 mg, 24%) following the methodology described above for the synthesis of 10a. Colourless oil; [α]<sub>D</sub>-2.6° (c 0.23 in CHCl<sub>3</sub>); IR (film) ν<sub>max</sub>/cm<sup>-1</sup> 3439 (OH), 2921, 1733 (CO), 1673, 1455, 1380, 1034, 746; 1<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>β</sub> 5.91 (1H, dtt, J<sub>17,2,10,4</sub> 1.8, 6.5 Hz, 2-H), 5.33 (1H, ddd, J<sub>17,2,10,4</sub> 1.8, 6.5 Hz, 2-H), 4.73 (1H, br s, 9a-H), 4.67 (1H, d, J<sub>7,2</sub> 7.2 Hz, CH/JOme), 4.64 (1H, d, J<sub>7,2</sub> 7.2 Hz, CH/JOme), 4.63 (1H, br s, 9b-H), 4.56 (2H, m, 1a-H), 3.72 (3H, s, OMe), 3.08 (1H, q, J<sub>7,2</sub> 7.2 Hz, 3-H), 2.88 (2H, m, 3b-H), 2.01 (1H, m, 5a-H), 1.89-1.80 (2H, m, 5b-H and 4-H), 1.68 (3H, t, J<sub>14,4</sub> 3.2 Hz, 3a-H), 1.38 (1H, d, J<sub>14,4</sub> 7.4, 6.3 Hz, 3b-H), 1.20 (3H, s, 2-Me), 0.91 (3H, d, J<sub>6,4</sub> 6.4 Hz, 1-Me); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ<sub>β</sub> 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 (Cl<sup>+</sup>): calcd for C<sub>23</sub>H<sub>37</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 470.2519, found 470.2520.

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 were further purified by analytical HPLC (Hexane: ethyl acetate 85:15, flow = 0.8
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 (3R,4S,5S,2'R,4'E)-4-acetoxy-5-(6-acetoxy-2,4-dimethylhex-4-enyl)-3,5-dimethyl-4,5-dihydrofuran-2(3H)-one (26a) (3.4 mg, 100%). Yellow oil: [α]D20 +20° (c 0.30, CHCl3); IR (film) νmax 3454, 1775, 1740, 1455, 1374, 1223, 1087, 1022, 990, 939 cm⁻¹; 1H NMR (400 MHz, CDCl3) 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 (dd, J = 6.8 Hz, 3H), 0.82 (s, 3H), 0.69 (d, J = 6.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 173.2, 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⁺): calculated for C18H18O2Na[M+Na⁺]363.1784, found 363.1795.

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Notes and references

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Z-isomer could not be detected by 1H NMR

Electronic Supplementary Information (ESI) available: [Copies of the 1H NMR and 13C NMR spectra for all key intermediates and final products]. See DOI: 10.1039/b000000x/


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