DOI: 10.1002/ejoc.201201526

Stereoselective Synthesis and Absolute Configuration Determination of Xylariolide A

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Keywords: Natural products / Total synthesis / Asymmetric synthesis / Configuration determination / Medicinal chemistry / Lactones

The asymmetric synthesis of the antibacterial and antitumoral natural compound xylariolide A (**1**) and five stereoisomers has been achieved. The strategy is based on the one-pot epoxidation/lactonisation or dihydroxylation/lactonisation of the hypothetical biosynthetic intermediate xylarioic A acid (**8**). The absolute configuration of xylariolide A was thus determined to be 3*R*,4*S*,5*R*,1′*R*,2′*R* after the synthesis of **1**, two epimers, i.e., 1′-*epi*-xylariolide A (**3**) and 2′-*epi*-xylariolide A (**4**), and three more diastereoisomers **5**–**7**.

Introduction

Trisubstituted γ-butyrolactones are widely distributed in nature, and they display various biological activities.[1] Fungi from the *Xylaria* genus are an abundant source of natural products from different structural classes, including terpenoids,[2] cyclopeptides,[3] xanthones,[4] and polyketides.[5] The study of the metabolites produced by an endophytic fungal strain of *Xylaria* sp. NCY2, isolated from the medicinal plant *Torreya jackii* Chun, an evergreen shrub from the Taxaceae family,[6] led to the isolation of a polyketide γ-lactone named xylariolide A (**1**; Figure 1). Xylariolide A (**1**) is structurally related to the tetraketide acid moiety of 1-(xylarenone A) xylariate A (**2**), another metabolite isolated from the *Xylaria* sp. NCY2 strain.

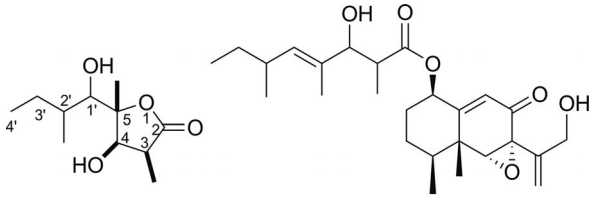

Figure 1. Structures of xylariolide A (**1**) and 1-(xylarenone A) xylariate A (**2**).

Xylariolide A (**1**) inhibits the growth of the pathogenic bacteria *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus*, and shows moderate antitumoral activity against HepG2 and HeLa cells.[6] Spectroscopic analysis of isolated **1** led to the proposal that the relative stereochemistry of compound **1** was 3*R**,4*S**,5*R**, on the basis of nOe correlations; no stereochemical assignments for carbons C-1′ and C-2′ were established in the original report.

As a part of an ongoing program of research into the chemical biology of fungal polyketides, including structural elucidation, biosynthetic, and synthetic studies,[7] our attention has been drawn to tetraketides such as xylariolide A (**1**). The stereoselective preparation of compound **1** would allow the determination of its absolute stereochemistry, and would provide material for its biological evaluation. In this paper, we report the first stereoselective total synthesis of xylariolide A (**1**) and related stereoisomers (3*R*,4*S*,5*R*,1′*S*,2′*R*)-**3** (1′-*epi*-xylariolide A), (3*R*,4*S*,5*R*,1′*R*,2′*S*)-**4** (2′-*epi*-xylariolide A), (3*R*,4*S*,5*R*,1′*S*,2′*S*)-**5**, (3*R*,4*S*,5*S*,1′*R*,2′*S*)-**6**, and (3*R*,4*S*,5*S*,1′*R*,2′*R*)-**7**. We also report the stereoselective preparation of xylarioic acid A (**8**), i.e., the acid moiety of compound **2**, and the assignment of the absolute stereochemistry of compound **1** as 3*R*,4*S*,5*R*,1′*R*,2′*R*.

Results and Discussion

The occurrence of xylarioic A acid (**8**) as a substructure of compound **2** suggests that **8** is a biosynthetic precursor of xylariolides **A**, **B**, and **C**. Based on this, we proposed a metabolite-inspired retrosynthetic analysis for a stereoselective synthesis of xylariolide A (**1**), as shown in Scheme 1. According to the data from the original report where the relative stereochemistry for the γ-lactone substituents was described, a total of eight possible stereoisomers of xylariolide A (**1**) have to be considered (Figure 2). Therefore, a syn-

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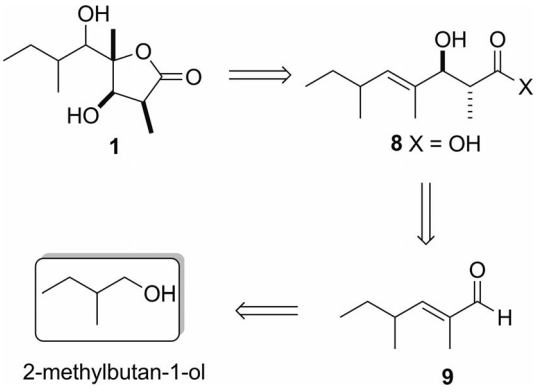
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201526.

thetic plan should consider the synthesis of diastereomers arising from all four possible configurations at the 1′ and 2′ positions. The stereochemistry at the other chiral centres should be either 3*R*,4*S*,5*R* or 3*S*,4*R*,5*S*, consistent with the assignment of the relative configuration of the natural product in which a *cis* relationship between the C-3 methyl, the C-5 methyl, and the C-4 hydroxy groups was determined by an nOe experiment.[6]



Scheme 1. Retrosynthetic analysis for the synthesis of xylariolide A.

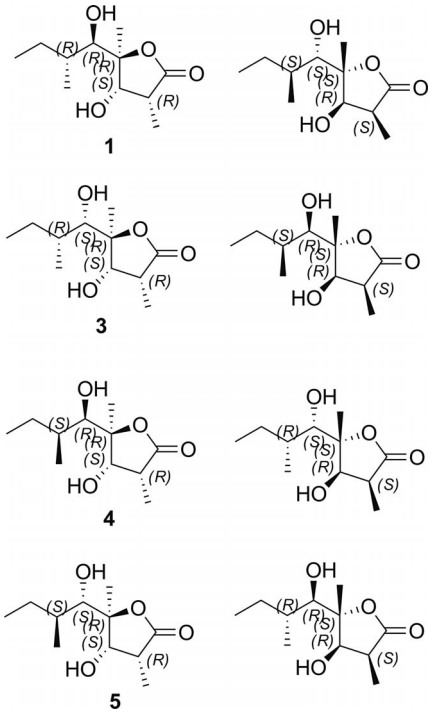
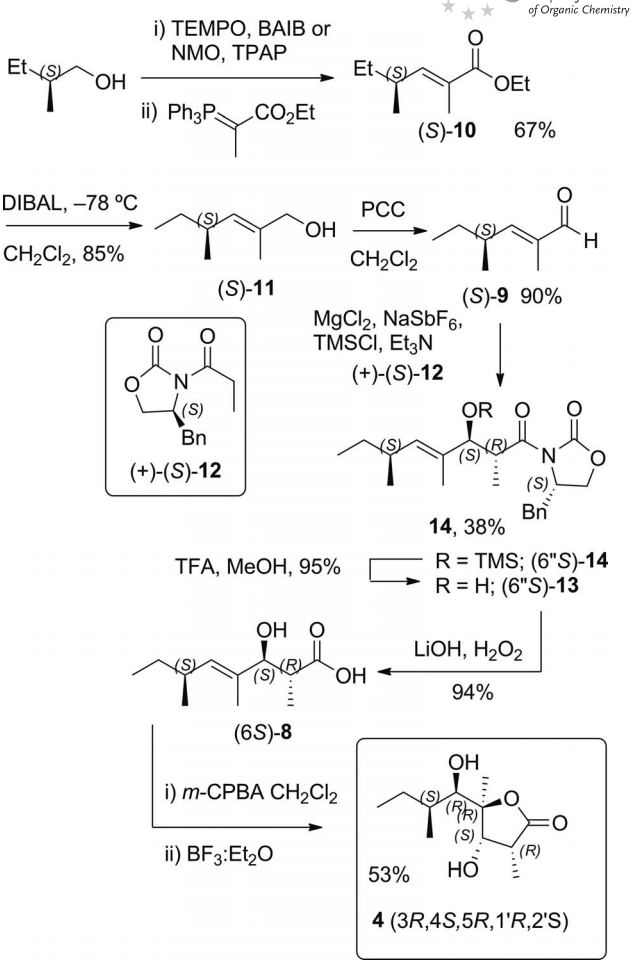


Figure 2. Stereochemical possibilities for xylariolide A (**1**).

Our strategy involved the stereoselective synthesis of intermediate **8** by the one-pot oxidation/olefination of 2-methylbutan-1-ol, followed by an *anti* asymmetric aldol reaction using an oxazolidinone chiral auxiliary. Starting from either racemic 2-methylbutan-1-ol or from (2*S*)-2-methylbutan-1-ol, the two epimers of (3*R*,4*S*,5*R*,1′*R*)-xylariolide at C-2′ were obtained following the stereoselective synthetic route proposed in Scheme 2.



Scheme 2. Stereoselective synthesis of lactone **4** (TFA = trifluoroacetic acid; TMS = trimethylsilyl).

Enantiomerically pure acid (6*S*)-**8** was prepared following the synthetic sequence showed in Scheme 2. Thus, (*S*)-2-methylbutan-1-ol was subjected to a one-pot oxidation/olefination using *N*-methylmorpholine *N*-oxide (NMO; 1.0 equiv.) in the presence of tetrapropylammonium perruthenate (TPAP; 0.03 equiv.), in order to suppress the racemisation of the aldehyde intermediate, to produce (2*E*,4*S*)-ethyl 2,4-dimethylhex-2-enoate [(*S*)-**10**] in 67% yield.[8] Reduction of (*S*)-**10** with DIBAL (diisobutylaluminum hydride) gave alcohol (*S*)-**11**, whose subsequent oxidation with PCC (pyridinium chlorochromate) produced the corresponding aldehyde [i.e., (*S*)-**9**].[8] This aldehyde was treated with oxazolidin-2-one (+)-(*S*)-**12** and catalytic amounts of $MgCl_2$ and $NaSbF_6$[9] to give *anti* aldol product (6′′*S*)-**14** in 38% yield and with 88% *dr*.[10] The configurations of C-2 and C-3 in the aldol product (i.e., **14**) were confirmed by comparison of the NMR spectroscopic data and optical rotation of (6′′*S*)-**13**, obtained by methanolysis of (6′′*S*)-**14**, with those reported for the product of the aldol reaction between (*S*)-**12** and 2-methylcinnamaldehyde, whose stereochemistry was unequivocally established by Evans et al.[9]

Oxidative hydrolysis[11] of the chiral auxiliary in (6′′*S*)-**13** gave (2*R*,3*S*,4*E*,6*S*)-3-hydroxy-2,4,6-trimethyloct-4-enoic

acid [(6*S*)-**8**], whose structure was confirmed by a combination of spectrometric and spectroscopic studies, with particular importance given to 1D and 2D NMR analysis. The constitution of compound (6*S*)-**8** is the same as that of the side-chain of 1-(xylarenone A)xylariate A (**2**). The ^{1}H NMR spectroscopic data of (6*S*)-**8** were very similar to those described for the xylarioyl A moiety of compound **2**,[6] although some variations were observed in their ^{13}C NMR spectra, which could be due to stereochemical differences.

Acid (6*S*)-**8** was subjected to a one-pot stereoselective epoxidation with *m*-CPBA (*m*-chloroperbenzoic acid), and a lactonisation catalysed by $BF_3{\cdot}Et_2O$[12] to give γ-butyrolactone **4**. A series of nOe effects between the signals at δ_H = 3.07, 4.58, and 3.64 ppm (due to H-3, H-4, and H-1′, respectively; Figure 3), consistent with a *cis*-*cis* relative configuration for the methyl and hydroxy groups in the lactone ring, supported the assignment of the stereochemistry of compound **4** as 3*R*,4*S*,5*R*,1′*R*,2′*S*.

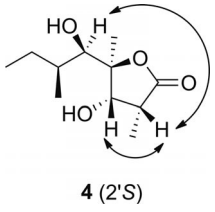
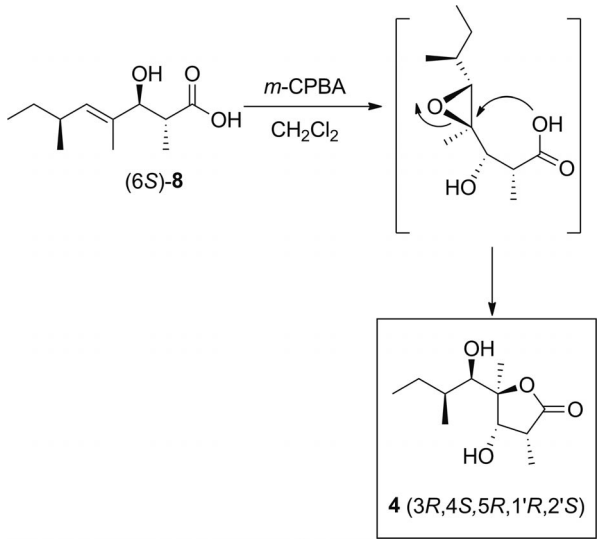


Figure 3. Selected nOe correlations for compound **4**.

This outcome is consistent with the reaction mechanism outlined in Scheme 3 in which the hydroxy-directed epoxidation of (6*S*)-**8** is predicted to give a *threo*-epoxide.[13] This then undergoes an epoxide ring opening by intramolecular nucleophilic attack of the carboxylic acid fragment with inversion of configuration at C-4, to give the lactone ring with a 3*R*,4*S*,5*R*,1′*R* configuration.

Comparison of the spectroscopic data of compound **4** with those reported for xylariolide A showed significant differences in both the ^{1}H and the ^{13}C NMR data, especially in those signals corresponding to the side-chain (see Tables 1 and 2). With the aim of examining whether these differences were due to the alternative stereochemistry at C-1′, we prepared diastereoisomers of compound **4**, with the same absolute stereochemistry at C-3, C-4, and C-5. Dihydroxylation of acid (6*S*)-**8** catalysed by OsO_4[14] gave a 1:1 mixture of the two triols resulting from *syn*-dihydroxylation on each of the faces of the olefin, and this was followed by in situ lactonisation to give lactones **5** and **6** (Scheme 4).



Scheme 3. Stereoselective epoxidation of acid (6*S*)-**8** gave lactone **4**.

Table 1. Comparison of ^{13}C NMR data of **1**, **3**–**5**, and xylariolide A.[a]

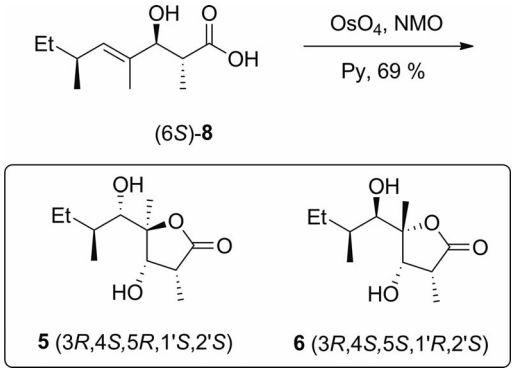
Carbon	**1**	**3**	**4**	**5**	Xylariolide A[6]
C-2	178.4	178.7	178.7	178.4	178.6
C-3	40.2	40.2	40.8	40.1	40.2
C-4	9.3	9.3	9.2	9.2	9.3
C-5	72.4	73.8	71.5	73.7	72.7
C-1′	90.4	90.6	91.3	90.7	90.3
C-2′	16.6	17.0	17.5	16.6	16.6
C-3′	79.7	77.4	78.0	79.4	79.8
C-4′	36.5	35.7	35.9	36.2	36.6
C-3-Me	16.9	13.0	13.5	17.5	16.9
C-5-Me	24.1	28.3	28.1	22.8	24.1
C-1′-Me	11.2	11.9	11.6	11.7	11.2

[a] Chemical shift values, δ, are in ppm.

Table 2. Comparison of ^{1}H NMR data of **1**, **3**–**5**, and xylariolide A.[a]

Proton	**1**	**3**	**4**	**5**	Xylariolide A[6]
H-3	3.01 (quint, 7.6)	3.11 (quint, 7.2)	3.07 (quint, 7.5)	3.08 (quint, 7.4)	3.03 (quint, 7.4)
C-3-Me	1.25 (d, 7.6)	1.24 (d, 7.2)	1.24 (d, 7.5)	1.25 (d, 7.4)	1.27 (d, 7.5)
H-4	4.55 (dd, 5.0, 7.6)	4.45 (dd, 4.2, 7.2)	4.58 (dd, 4.8, 7.5)	4.41 (d, 7.4)	4.57 (d, 7.4)
C-5-Me	1.38 (s)	1.37 (s)	1.37 (s)	1.38 (s)	1.39 (s)
H-1′	3.45 (t, 5.6)	3.55 (dd, 2.2, 7.0)	3.64 (dd, 3.2, 5.6)	3.45 (d, 3.6)	3.46 (d, 5.6)
H-2′	1.57–1.63 (m)	1.77 (dsext, 2.2, 7.2)	1.64–1.72 (m)	1.70–1.84 (m)	1.56–1.62 (m)
C-2′-Me	1.00 (d, 6.8)	0.95 (d, 7.2)	0.96 (d, 6.8)	1.01 (d, 7.2)	1.02 (d, 6.8)
H-3′a	1.19–1.28 (m)	1.29–1.36 (m)	1.28–1.37 (m)	1.05–1.16 (m)	1.19–1.21 (m)
H-3′b	1.64–1.71 (m)	1.38–1.44 (m)	1.40–1.49 (m)	1.70–1.84 (m)	1.56–1.62 (m)
H-4′	0.92 (t, 7.6)	0.92 (t, 7.2)	0.91 (t, 7.2)	0.91 (t, 7.2)	0.94 (t, 7.4)
C-4-OH	1.79 (d, 5.0)	1.71 (d, 4.2)	1.72 (d, 4.8)	–	–
C-1′-OH	1.86 (d, 5.6)	1.64 (d, 7.0)	1.84 (d, 5.6)	–	–

[a] Chemical shift values, δ, are in ppm, and coupling constants, *J*, are in Hz (in parentheses).



Scheme 4. Synthesis of lactones **5** and **6**.

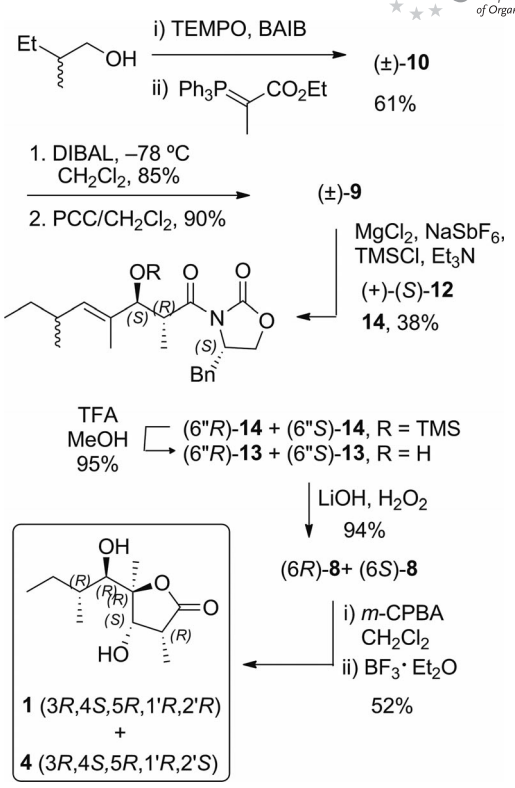
NOe correlations between protons H-3, H-4, and H-1′ in compound **5** were consistent with the relative configuration of the γ-butyrolactone moiety present in xylariolide A (**1**), but its observed physical and spectroscopic data turned out to be different from those reported for the natural product (see Tables 1 and 2). At this point, it seemed clear that natural xylariolide A or its enantiomer should have an alternative 2′*R* configuration. Therefore, our aim was to obtain the diastereomer of compound **4** that was epimeric at this position, which could be prepared stereoselectively following an identical synthetic sequence, starting from (*R*)-2-methylbutan-1-ol.[15,16]

Commercially available (±)-2-methylbutan-1-ol was subjected to one-pot oxidation/olefination using the TEMPO–BAIB [2,2,6,6-tetramethylpiperidin-1-oxyl and bis(acetoxy)-iodobenzene] system and (carbethoxyethylidene)triphenylphosphorane[17] to give (±)-(*E*)-ethyl 2,4-dimethylhex-2-enoate [(±)-**10**] in 61% yield.[18] Reduction of (±)-**10** with DIBAL and subsequent oxidation with PCC produced the corresponding aldehyde [i.e., (±)-**9**].[8] This aldehyde was treated with oxazolidin-2-one [(+)-**12**] and catalytic amounts of $MgCl_2$ and $NaSbF_6$[9] to give a 1:1 mixture of *anti* aldols (6′′*R*)-**13** and (6′′*S*)-**13** after methanolysis of the silyloxy derivatives (6′′*R*)-**14** and (6′′*S*)-**14** (Scheme 5). The mixture of (6′′*R*)-**13** and (6′′*S*)-**13** was subjected to oxidative hydrolysis[11] to give a 1:1 mixture of (2*R*,3*S*,4*E*,6*R*)- and (2*R*,3*S*,4*E*,6*S*)-3-hydroxy-2,4,6-trimethyloct-4-enoic acids, i.e., (6*R*)-**8** and (6*S*)-**8**.

The 1:1 mixture of (6*S*)-**8** and (6*R*)-**8** was subjected to a one-pot stereoselective epoxidation with *m*-CPBA, and subsequent lactonisation catalysed by $BF_3{\cdot}Et_2O$[12] to give a 1:1 mixture of compounds **1** and **4**, which were then separated by chromatographic methods. NOe's observed between the signals at δ_H = 3.01, 4.55, and 3.45 ppm (H-3, H-4, and H-1′, respectively) supported the assignment of the stereochemistry for compound **1** as 3*R*,4*S*,5*R*,1′*R*,2′*R*.

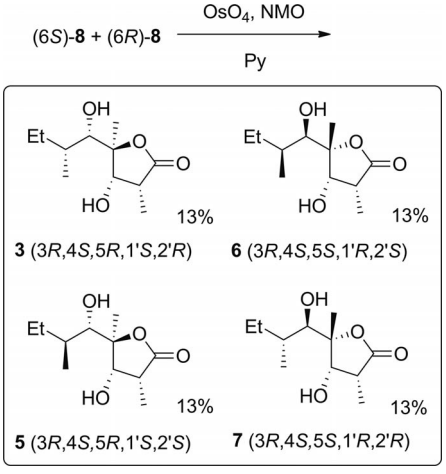
The ^{13}C NMR chemical shifts of lactone **1** were identical to those reported for xylariolide A (Table 1). However, there were slight differences in the signals corresponding to H-2′ and H-3′ in the ^1H NMR spectra (Table 2).

With the aim of ruling out the possibility that these differences were due to an alternative stereochemistry at C-1′, acids (6*S*)-**8** and (6*R*)-**8** were subjected to dihydroxylation



Scheme 5. Synthesis of lactones **1** and **4**.

catalysed by OsO_4[14] to give a 1:1:1:1 mixture of four triols resulting from *syn*-dihydroxylation on both faces of the olefin on each diastereomer, which, after in situ lactonisation, led to the corresponding lactones (i.e., **3** and **5**–**7**; Scheme 6). Lactone **3** showed nOe's consistent with those described for xylariolide A, but again its physical and spectroscopic data turned out to be different from those reported for the natural product (see Tables 1 and 2).



Scheme 6. Synthesis of lactones **3** and **5**–**7**.

All this data indicated that natural xylariolide A had a relative stereochemistry identical to that of compound **1**, and that the slight differences observed between their ^1H NMR spectra could be due to errors in the definition of the intervals in the original report.

Finally, the optical rotation of compound **1** [+5.3 (c = 0.66, $CHCl_3$)] was of the same sign and magnitude as the value originally described for xylariolide A ($[\alpha]_D^{20}$ = +7.55, c = 0.54, $CHCl_3$).[6]

Conclusions

We have synthesised four possible diastereoisomers of 4-hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one in which the configuration of the lactone ring was consistent with the stereochemical description made in the original report by Hu et al. for xylariolide A.[6] Only compound **1** showed spectroscopic and physical data consistent with those reported for the natural compound. The slight differences in the ^1H NMR data between the isolated and synthetic material could be due to errors in the definition of the intervals in the original report (see Tables 1 and 2). Compound **1** was synthesised stereoselectively from (*R*)-2-methylbutan-1-ol, whose preparation has been reported previously in the literature.[16]

Experimental Section

General Methods: 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. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Purification by semi-preparative and analytical HPLC was performed with a 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 plates. Melting points were measured with a Reichert–Jung Kofler block. Optical rotations were determined with a digital polarimeter. Infrared spectra were recorded with a FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR measurements were recorded with Varian Unity 400 MHz, Agilent 500 MHz, and Varian Inova 600 MHz spectrometers with $SiMe_4$ as the internal reference. Chemical shifts 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 = quartet; quint = quintuplet; sext = sextuplet; m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded with a double-focussing magnetic sector mass spectrometer in positive ion mode, or with a QTOF mass spectrometer in positive ion APCI mode.

(2*E*,4*S*)-Ethyl 2,4-Dimethylhex-2-enoate [(*S*)-10]: A mixture of (*S*)-2-methylbutan-1-ol (600 mg, 6.82 mmol), 4-methylmorpholine *N*-oxide (NMO; 865 mg, 7.16 mmol) and molecular sieves (4 Å beads; 1.4 g) in dry CH_2Cl_2 (13.6 mL) was stirred for 15 min. TPAP (126 mg, 0.2 mmol) was added to the resulting mixture. After stirring for 6 h at room temperature, (ethoxycarbonylethylidene)triphenylphosphorane was added, and the solution was stirred for a further 12 h at 35 °C (3.9 g, 10.2 mmol). The mixture was then warmed to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/Et_2O, 97:3) to give ester (*S*)-**10** (776.6 mg, 67%). The spectroscopic data for compound (*S*)-**10** were identical to those described in the literature.[8]

(±)-(*E*)-Ethyl 2,4-Dimethylhex-2-enoate [(±)-10]: TEMPO (561 mg, 3.50 mmol) and [bis(acetoxyiodo)benzene] (BAIB; 12.4 g, 38.70 mmol) were added at 0 °C to a solution of (*S*)-2-methylbutan-1-ol (1550 mg, 17.60 mmol) in dry CH_2Cl_2 (38.7 mL), and the mixture was stirred for 6 h. Then, (ethoxycarbonylethylidene)triphenylphosphorane (16.3 g, 44.02 mmol) was added, and the solution was stirred for a further 12 h at 35 °C. The mixture was warmed to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/Et_2O, 97:3) to give ester (±)-**10** (1826.3 mg, 61%). The spectroscopic data for compound (±)-**10** were identical to those described in the literature.[18]

(2*E*,4*S*)-2,4-Dimethylhex-2-en-1-ol [(*S*)-11]: Diisobutylaluminum hydride (DIBAL; 1.0 M in CH_2Cl_2; 4.3 mL, 4.3 mmol) was slowly added to a solution of (2*E*,4*S*)-ethyl 2,4-dimethylhex-2-enoate [(*S*)-**10**] (726 mg, 4.27 mmol) in dry CH_2Cl_2 (13.4 mL), and the mixture was cooled to –78 °C. When TLC monitoring indicated that the reaction was complete, Rochelle's salt (saturated aq.; 25 mL) was added, and the mixture was warmed to room temperature while maintaining vigorous stirring. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were washed, dried with anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a crude residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 80:20) to give (2*E*,4*S*)-2,4-dimethylhex-2-en-1-ol [(*S*)-**11**] (400.2 mg, 73%), whose spectroscopic data were identical to those described in the literature.[18]

(±)-2,4-Dimethylhex-2-en-1-ol [(±)-11]: (±)-(*E*)-Ethyl 2,4-dimethylhex-2-enoate [(±)-**10**] (1400 mg, 8.24 mmol) was converted into (±)-2,4-dimethylhex-2-en-1-ol [(±)-**11**] (896.5 mg, 85%) following the method described above for the synthesis of (2*E*,4*S*)-2,4-dimethylhex-2-en-1-ol [(*S*)-**11**] from (*S*)-**10**.

(2*E*,4*S*)-2,4-Dimethylhex-2-enal [(*S*)-9]: (2*E*,4*S*)-2,4-Dimethylhex-2-en-1-ol [(*S*)-**11**] (400.2 mg, 3.13 mmol) was dissolved in CH_2Cl_2 (5 mL), and the solution was added dropwise to a suspension of PCC (1.031 g, 4.71 mmol) and powdered molecular sieves (4 Å, 2.062 g) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 2 h, then diethyl ether (50 mL) was added, and the mixture was stirred for an additional 1 h. The suspension was filtered through a silica gel pad (pentane/Et_2O, 80:20, 300 mL). The solvent was concentrated under reduced pressure at 0 °C to give aldehyde (*S*)-**9** (364.0 mg, 92%), which was used immediately in the next step. The spectroscopic data for compound (*S*)-**9** were identical to those described in the literature.[8]

(±)-2,4-Dimethylhex-2-enal [(±)-9]: (±)-2,4-Dimethylhex-2-en-1-ol [(±)-**11**] (400.5 mg, 3.12 mmol) was converted into (±)-2,4-dimethylhex-2-enal [(±)-**9**] (354.4 mg, 90%) following the method described above for the synthesis of (*S*)-**9** from (2*E*,4*S*)-2,4-dimethylhex-2-en-1-ol [(*S*)-**11**].

(4*S*,2′′*R*,3′′*S*,4′′*E*,6′′*S*)-4-Benzyl-3-[2,4,6-trimethyl-3-(trimethylsilyloxy)oct-4-enoyl]-oxazolidin-2-one [(6′′*S*)-14]: (+)-(4*S*)-4-Benzyl-3-propionyloxazolidin-2-one [(+)-(*S*)-**12**] (509 mg, 2.18 mmol) was treated with $MgCl_2$ (20.8 mg, 0.22 mmol), $NaSbF_6$ (169.2 mg, 0.65 mmol), triethylamine (0.52 mL, 4.4 mL), aldehyde (*S*)-**9** (330.0 mg, 2.62 mmol), and chlorotrimethylsilane (0.37 mL, 3.3 mmol) in ethyl acetate (5.4 mL) at 25 °C for 48 h. The resulting orange slurry was passed through a pad of silica, eluting with Et_2O (200 mL). The solvent was removed under reduced pressure, and

the residue was purified by silica gel column chromatography (petroleum ether/Et_2O, 94:6) to give (6′′*S*)-**14** (357.7 mg, 38%) with 88% *dr* as a colourless oil. The mixture was separated by analytical HPLC [hexane/ethyl acetate (92:8), flow: 0.8 mL/min; t_R = 14 min for minor isomer and t_R = 21 min for (6′′*S*)-**14**]. Data for (6′′*S*)-**14**: $[\alpha]_D^{20}$ = +35.9 (*c* = 2.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2960, 2874, 1783, 1700, 1455, 1387, 1250, 1055, 882, 841 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 2 H), 7.28–7.24 (m, 3 H), 5.16 (d, *J* = 9.2 Hz, 1 H), 4.71 (m, 1 H), 4.29 (d, *J* = 10.0 Hz, 1 H), 4.18–4.08 (m, 3 H), 3.33 (dd, *J* = 13.2, 3.2 Hz, 1 H), 2.70 (dd, *J* = 13.2, 9.6 Hz, 1 H), 2.31 (m, 1 H), 1.62 (d, *J* = 0.8 Hz, 3 H), 1.40–1.31 (m, 1 H), 1.27–1.15 (m, 1 H), 0.97–0.94 (m, 6 H), 0.83 (t, *J* = 7.6 Hz, 3 H), 0.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 153.2, 136.4, 135.6, 133.4, 129.5, 129.0, 127.2, 82.5, 65.6, 55.1, 41.4, 38.1, 34.0, 30.2, 20.2, 14.4, 12.1, 10.5, 0.2 ppm. HRMS (APCI$^+$): calcd. for $C_{21}H_{28}NO_3$ [M + H – $(CH_3)_3SiOH]^+$ 342.2069; found 342.2087. Data for the minor isomer: Colourless oil. $[\alpha]_D^{20}$ = +11.2 (*c* = 0.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2960, 2837, 1783, 1705, 1445, 1250, 1055, 887 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 2 H), 7.28–7.20 (m, 3 H), 5.14 (d, *J* = 9.8 Hz, 1 H), 4.66 (m, 1 H), 4.34 (d, *J* = 9.6 Hz, 1 H), 4.16–4.08 (m, 3 H), 3.26 (dd, *J* = 13.2, 3.3 Hz, 1 H), 2.80 (dd, *J* = 13.2, 9.6 Hz, 1 H), 2.29 (m, 1 H), 1.58 (s, 3 H), 1.40–1.22 (m, 2 H), 0.97 (d, *J* = 6.0 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.86 (t, *J* = 7.4 Hz, 3 H), 0.01 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5, 153.4, 136.3, 135.5, 133.3, 129.5, 128.9, 127.2, 82.8, 65.8, 55.5, 41.0, 38.2, 33.9, 30.0, 20.6, 13.9, 12.1, 10.4, 0.0 ppm. HRMS (APCI$^+$): calcd. for $C_{21}H_{28}NO_3$ [M + H – $(CH_3)_3SiOH]^+$ 342.2069; found 342.2070.

(4*S*,2′′*R*,3′′*S*,4′′*E*,6′′*S*)-4-Benzyl-3-[3-hydroxy-2,4,6-trimethyloct-4-enoyl]oxazolidin-2-one [(6′′*S*)-13]: Trifluoroacetic acid (0.15 mL, 1.78 mmol) was added to a stirred solution of (6′′*S*)-**14** (357.7 mg, 0.83 mmol) in dry methanol (30 mL) at 0 °C, and the mixture was stirred for 15 min. Evaporation of the solvent gave a crude residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 90:10) to give (6′′*S*)-**13** (282.7 mg, 95%) as a colourless oil. $[\alpha]_D^{20}$ = +61.8 (*c* = 1.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3504, 2960, 2874, 1781, 1691, 1458, 1389, 1210, 1016, 968, 707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (tt, *J* = 7.2, 1.6 Hz, 2 H), 7.27.7.22 (m, 3 H), 5.22 (dd, *J* = 9.6, 1.0 Hz, 1 H), 4.69 (m, 1 H), 4.20–4.06 (m, 4 H), 3.31 (dd, *J* = 13.6, 3.2 Hz, 1 H), 2.78 (dd, *J* = 13.6, 9.6 Hz, 1 H), 2.30 (m, 1 H), 1.67 (d, *J* = 1.0 Hz, 3 H), 1.35 (m, 1 H), 1.22 (m, 1 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 153.9, 136.6, 135.3, 132.9, 129.5, 128.9, 127.3, 81.8, 66.0, 55.7, 40.6, 37.8, 33.9, 30.2, 20.5, 14.8, 12.0, 10.8 ppm. HRMS (CI$^+$): calcd. for $C_{21}H_{29}NO_4$ [M]$^+$ 359.2097; found 359.2086.

(4*S*,2′′*R*,3′′*S*,4′′*E*,6′′*R*)-4-Benzyl-3-[3-hydroxy-2,4,6-trimethyloct-4-enoyl]oxazolidin-2-one [(6′′*R*)-14]: (±)-2,4-Dimethylhex-2-enal [(±)-**9**] (550 mg, 4.36 mmol) was converted into an inseparable 1:1 mixture of (4*S*,2′′*R*,3′′*S*,4′′*E*,6′′*R*)-4-benzyl-3-[3-hydroxy-2,4,6-trimethyloct-4-enoyl]oxazolidin-2-one [(6′′*R*)-**13**] and (4*S*,2′′*R*,3′′*S*,4′′*E*,6′′*S*)-4-benzyl-3-[3-hydroxy-2,4,6-trimethyloct-4-enoyl]oxazolidin-2-one [(6′′*S*)-**13**] (547.8 mg, 35%; 88% *dr*) following the method described above for the synthesis of (6′′*S*)-**13** from (*S*)-**9**.

(2*R*,3*S*,4*E*,6*S*)-3-Hydroxy-2,4,6-trimethyloct-4-enoic Acid [(6*S*)-8]: H_2O_2 (30%; 0.12 mL, 1.12 mmol) and $LiOH·H_2O$ (26.0 mg, 0.56 mmol) were added to a stirred solution of (6′′*S*)-**13** (100 mg, 0.28 mmol) in THF/H_2O (4:1; 1.8 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. Sodium sulfite (1 M aq.; 1.12 mL, 1.12 mmol) was then added, and the mixture was stirred for an additional 20 min. The organic solvent was removed under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (3× 4 mL). The aqueous phase was acidified with HCl (1 M) to pH = 2 and then extracted with ethyl acetate (3× 15 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure to give acid (6*S*)-**8** (52.4 mg, 94%) as a colourless oil, which was used in the next step without further purification. $[\alpha]_D^{20}$ = +37.3 (*c* = 0.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3418, 2961, 2874, 1715, 1456, 1379, 1200, 1004, 876 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 9.2 Hz, 1 H), 4.09 (d, *J* = 8.8 Hz, 1 H), 2.64 (dq, *J* = 8.8, 6.8 Hz, 1 H), 2.28 (m, 1 H), 1.59 (s, 3 H), 1.37–1.29 (m, 1 H), 1.25–1.16 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.81 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 137.1, 132.2, 80.4, 43.1, 33.9, 30.1, 20.5, 14.2, 12.0, 10.5 ppm. HRMS (CI$^+$): calcd. for $C_{11}H_{20}O_3$ [M]$^+$ 200.1412; found 200.1410.

(2*R*,3*S*,4*E*,6*R*)-3-Hydroxy-2,4,6-trimethyloct-4-enoic Acid [(6*R*)-8]: A 1:1 mixture of (6′′*R*)-**13** and (6′′*S*)-**13** (102 mg, 0.28 mmol) was converted into an inseparable 1:1 mixture of epimeric acids (6*R*)-**8** and (6*S*)-**8** (52.6 mg, 94%) following the method described above for the synthesis of (6*S*)-**8** from (6′′*S*)-**13**.

(3*R*,4*S*,5*R*,1′*R*,2′*S*)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (4): *m*-Chloroperbenzoic acid (36.7 mg, 0.17 mmol) was added to a stirred solution of acid (6*S*)-**8** (29.8 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL). After stirring for 2 h, the mixture was cooled to 0 °C, and $BF_3·Et_2O$ (0.2 M in CH_2Cl_2; 0.15 mL, 0.03 mmol) was added. The mixture was then warmed to room temperature and stirred for a further 1 h. The solvent was removed under reduced pressure, and ethyl acetate (5 mL) was added. The organic phase was washed with sodium hydrogen carbonate (saturated aq.; 3× 3 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column (petroleum ether/EtOAc, 80:20) to give lactone **4** (17.0 mg, 53%) as a white solid, m.p. 109–111 °C. $[\alpha]_D^{20}$ = +2.4 (*c* = 0.7, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3416, 2968, 2882, 1751, 1452, 1381, 1233, 1168, 1053, 990 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.58 (dd, *J* = 7.5, 4.8 Hz, 1 H), 3.64 (dd, *J* = 5.6, 3.2 Hz, 1 H), 3.07 (quint, *J* = 7.5 Hz, 1 H), 1.84 (d, *J* = 5.6 Hz, C-1′-O*H*), 1.72 (d, *J* = 4.8 Hz, C-4-O*H*), 1.72–1.64 (m, 1 H), 1.49–1.40 (m, 1 H), 1.37 (s, 3 H), 1.37–1.28 (m, 1 H), 1.24 (d, *J* = 7.5 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.7, 91.3, 78.0, 71.5, 40.8, 35.9, 28.1, 17.5, 13.5, 11.6, 9.2 ppm. HRMS (CI): calcd. for $C_{11}H_{21}O_4$ [M + H]$^+$ 217.1440; found 217.1432.

(3*R*,4*S*,5*R*,1′*R*,2′*R*)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (1): An inseparable 1:1 mixture of epimeric acids (*S*)-**8** and (*R*)-**8** (35.2 mg, 0.18 mmol) was converted into a mixture of lactones **1** and **4** (20.2 mg, 52%) following the method described above for the synthesis of lactone **4** from acid (*S*)-**8**. The reaction mixture was purified by silica gel column chromatography (petroleum ether/EtOAc, 80:20) to give a mixture of lactones **1** and **4**, which was further purified by semi-preparative HPLC [Hexane/ethyl acetate (63:37), flow: 3.0 mL/min; t_R = 25 min for lactone **1** and t_R = 20 min for lactone **4**]. Data for **1**: Colourless oil. $[\alpha]_D^{20}$ = +5.3 (*c* = 0.66, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3433, 2926, 1751, 1458, 1380, 1224, 1168, 1036, 992 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.55 (dd, *J* = 5.0, 7.6 Hz, 1 H), 3.45 (t, *J* = 5.6 Hz, 1 H), 3.01 (quint, *J* = 7.6 Hz, 1 H), 1.86 (d, *J* = 5.6 Hz, C-1′-O*H*), 1.79 (d, *J* = 5.0 Hz, C-4-O*H*), 1.71–1.64 (m, 1 H), 1.63–1.57 (m, 1 H), 1.38 (s, 3 H), 1.28–1.19 (m, 1 H), 1.25 (d, *J* = 7.6 Hz, 3 H),

1.00 (d, J = 6.8 Hz, 3 H), 0.92 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.4, 90.4, 79.7, 72.4, 40.2, 36.5, 24.1, 16.9, 16.6, 11.2, 9.3 ppm. HRMS (CI^+): calcd. for $C_{11}H_{21}O_4$ [M + H]$^+$ 217.1440; found 217.1436.

Dihydroxylation/Lactonisation of Acid (*S*)-8: Trimethylamine *N*-oxide (13.4 mg, 0.10 mmol), pyridine (25 μL, 0.17 mmol), and water (0.2 mL) were added to a 1:1 solution of acids (*S*)-**8** and (*R*)-**8** (16.8 mg, 0.08 mmol) in *t*BuOH (0.2 mL), and the mixture was stirred at 25 °C. OsO_4 (2.5% w/w solution in *t*BuOH; 63 μL, 0.025 mmol) was added dropwise, and the reaction mixture was stirred for 18 h at room temperature. Sodium bisulfite (20% aq. w/v; 2 mL) was then added, and the mixture was stirred for a further 1 h. Most of the *t*BuOH was removed under reduced pressure, and the residue was then extracted into EtOAc (3× 5 mL). The combined organic extracts were washed with brine (10 mL), dried with anhydrous sodium sulfate, and filtered, and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography (petroleum ether/EtOAc, 60:40) and analytical HPLC [hexane/ethyl acetate (65:35); flow: 0.8 mL/min] gave a 1:1 mixture of epimeric acids **5** and **6** (12.5 mg, 69%).

(3*R*,4*S*,5*R*,1′*S*,2′*S*)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (5): Colourless oil; t_R = 43 min. $[\alpha]_D^{20}$ = –2.4 (c = 0.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3430, 2964, 2939, 1748, 1461, 1380, 1232, 1170, 1064, 991 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (d, J = 7.4 Hz, 1 H), 3.45 (d, J = 3.6 Hz, 1 H), 3.08 (quint, J = 7.4 Hz, 1 H), 1.84–1.70 (m, 2 H), 1.38 (s, 3 H), 1.25 (d, J = 7.4 Hz, 3 H), 1.16–1.05 (m, 1 H), 1.01 (d, J = 7.2 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 90.7, 79.4, 73.7, 40.1, 36.2, 22.8, 17.5, 16.6, 11.7, 9.2 ppm. HRMS (CI^+): calcd. for $C_{11}H_{21}O_4$ [M + H]$^+$ 217.1440; found 217.1433.

(3*R*,4*S*,5*S*,1′*R*,2′*S*)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (6): Colourless oil; t_R = 18 min. $[\alpha]_D^{20}$ = +10.6 (c = 0.16, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3434, 2964, 2878, 1760, 1456, 1222, 1062, 940 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (d, J = 6.0 Hz, C-4-O*H*), 4.15 (t, J = 6.0 Hz, 1 H), 4.03 (d, J = 7.2 Hz, 1 H), 2.85 (dq, J = 7.0, 6.0 Hz, 1 H), 2.26 (d, J = 9.6 Hz, C-1′-OH), 1.75 (dsext, J = 7.2, 2.2 Hz, 1 H), 1.54–1.44 (m, 1 H), 1.43–1.33 (m, 1 H), 1.31 (s, 3 H), 1.26 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.95 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5, 87.0, 78.5, 75.0, 39.7, 35.6, 27.5, 21.3, 12.8, 12.0, 8.3 ppm. HRMS (CI^+): calcd. for $C_{11}H_{21}O_4$ [M + H]$^+$ 217.1440; found 217.1443.

Dihydroxylation/Lactonisation of Acids (*S*)-8 and (*R*)-8: A 1:1 mixture of (*S*)-**8** and (*R*)-**8** (20 mg, 0.1 mmol) was converted into lactones **3** (2.9 mg, 13%), **5** (2.9 mg, 13%), **6** (2.9 mg, 13%), and **7** (2.9 mg, 13%), following the method described above for the dihydroxylation/lactonisation of (*S*)-**6**. Purification by silica gel column chromatography (petroleum ether/EtOAc, 60:40) and analytical HPLC [Hexane/ethyl acetate (65:35); flow: 0.8 mL/min] gave a 1:1:1:1 mixture of epimeric acids **3**, **5**, **6**, and **7**.

(3*R*,4*S*,5*R*,1′*S*,2′*R*)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (3): Colourless oil; t_R = 40 min. $[\alpha]_D^{20}$ = +8.0 (c = 0.11, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3434, 2964, 2878, 1747, 1460, 1380, 1238, 1177, 1062, 991 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45 (dd, J = 7.2, 4.2 Hz, 1 H), 3.55 (dd, J = 7.0, 2.2 Hz, 1 H), 3.11 (quint, J = 7.2 Hz, 1 H), 1.77 (dsext, J = 7.2, 2.2 Hz, 1 H), 1.71 (d, J = 4.2 Hz, C-4-O*H*), 1.64 (d, J = 7.0 Hz, C-1′-O*H*), 1.44–1.38 (m, 1 H), 1.37 (s, 3 H), 1.36–1.29 (m, 1 H), 1.24 (d, J = 7.2 Hz, 3 H), 0.95 (d, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.7, 90.6, 77.4, 73.8, 40.2, 35.7, 28.3, 17.0, 13.0, 11.9, 9.3 ppm. HRMS (CI^+): calcd. for $C_{11}H_{21}O_4$ [M + H]$^+$ 217.1440; found 217.1442.

(3*R*,4*S*,5*S*,1′*R*,2′*R*)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one (7): Colourless oil; t_R = 16 min. $[\alpha]_D^{20}$ = +1.9 (c = 0.10, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3434, 2964, 2878, 1759, 1456, 1226, 1062, 940 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (d, J = 6.8 Hz, 1 H), 3.93 (d, J = 3.6 Hz, 1 H), 2.87 (quint, J = 6.8 Hz, 1 H), 1.82–1.72 (m, 2 H), 1.43–1.33 (m, 1 H), 1.32 (s, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 87.3, 78.2, 77.2, 39.9, 35.9, 22.2, 20.8, 16.6, 11.8, 8.3 ppm. HRMS (CI^+): calcd. for $C_{11}H_{21}O_4$ [M + H]$^+$ 217.1440; found 217.1438.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all key intermediates and final products, and nOe spectra of **1** and **3**–**7**.

Acknowledgments

This research was supported by grants from Ministerio de Ciencia e Innovación (MICINN) (AGL-2009-13359-C02-01) and from the Junta de Andalucía (P07-FQM-02689). Jose Manuel Botubol is grateful to the Junta de Andalucía for his research fellowship. The use of the NMR facilities at the Servicio Centralizado de Ciencia y Tecnología (SCCYT) of the University of Cádiz is acknowledged.

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Received: November 14, 2012
Published Online: March 5, 2013

