Stereoselective Synthesis and Absolute Configuration Determination of Xylariolide A

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The asymmetric synthesis of the antibacterial and antitumor natural compound xylariolide A (1) and five stereoisomers has been achieved. The strategy is based on the one-pot epoxidation/lactonization or dihydroxylation/lactonization of the hypothetical biosynthetic intermediate xylarioic acid (8). The absolute configuration of xylariolide A was thus determined to be 3R,4S,5R,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.

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 3R,4S,5R,1’R,2’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 (3R,4S,5R,1’S,2’R)-3 (1’-epi-xylariolide A), (3R,4S,5R,1’R,2’S)-4 (2’-epi-xylariolide A), (3R,4S,5R,1’S,2’S)-5, (3R,4S,5S,1’R,2’S)-6, and (3R,4S,5S,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 3R,4S,5R,1’R,2’R.

Results and Discussion

The occurrence of xylarioic acid A (8) as a substructure of compound 2 suggests that 8 is a biosynthetic precursor of xylarioles 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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The synthetic 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 3R, 4S, 5R or 3S, 4R, 5S, 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.

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 (2S)-2-methylbutan-1-ol, the two epimers of (3R, 4S, 5R, 1’R)-xylariolide at C-2’ were obtained following the stereoselective synthetic route proposed in Scheme 2.

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

EnantiomERICALLY pure acid (6S)-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 per ruthenate (TPAP; 0.03 equiv.), in order to suppress the racemisation of the aldehyde intermediate, to produce (2E, 4S)-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 MgCl₂ and NaSbF₆[9] to give anti aldol product (6S)-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 (6S)-13, obtained by methanolysis of (6S)-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]


Scheme 2. Stereoselective synthesis of lactone 4 (TFA = trifluoroacetic acid; TMS = trimethylsilyl).
Acid [(6S)-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 (6S)-8 is the same as that of the side-chain of 1-(xylarenone A)xylariate A (2). The 1H NMR spectroscopic data of (6S)-8 were very similar to those described for the xylarioyl A moiety of compound 2,[6] although some variations were observed in their 13C NMR spectra, which could be due to stereochemical differences.

Acid (6S)-8 was subjected to a one-pot stereoselective epoxidation with m-CPBA (m-chloroperbenzoic acid), and a lactonisation catalysed by BF3·Et2O[12] to give γ-butyrolactone 4. A series of nOe effects between the signals at δH = 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 3R,4S,5R,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 (6S)-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 3R,4S,5R,1’R,2’S configuration.

Comparison of the spectroscopic data of compound 4 with those reported for xylariolide A showed significant differences in both the 1H and the 13C 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-

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

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

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

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

<table>
<thead>
<tr>
<th>Proton</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Xylariolide A[6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3</td>
<td>3.01 (quint, 7.6)</td>
<td>3.11 (quint, 7.2)</td>
<td>3.07 (quint, 7.5)</td>
<td>3.08 (quint, 7.4)</td>
<td>3.03 (quint, 7.4)</td>
</tr>
<tr>
<td>C-3-Me</td>
<td>1.25 (d, 7.6)</td>
<td>1.24 (d, 7.2)</td>
<td>1.24 (d, 7.5)</td>
<td>1.25 (d, 7.4)</td>
<td>1.27 (d, 7.5)</td>
</tr>
<tr>
<td>H-4</td>
<td>4.55 (ddd, 5.0, 7.6)</td>
<td>4.45 (ddd, 4.2, 7.2)</td>
<td>4.58 (ddd, 4.8, 7.5)</td>
<td>4.41 (d, 7.4)</td>
<td>4.57 (d, 7.4)</td>
</tr>
<tr>
<td>C-5-Me</td>
<td>1.38 (s)</td>
<td>1.37 (s)</td>
<td>1.37 (s)</td>
<td>1.38 (s)</td>
<td>1.39 (s)</td>
</tr>
<tr>
<td>H-1’</td>
<td>3.45 (t, 5.6)</td>
<td>3.55 (d, 2.2, 7.0)</td>
<td>3.64 (ddd, 3.2, 5.6, 5.6)</td>
<td>3.45 (d, 3.6)</td>
<td>3.46 (d, 5.6)</td>
</tr>
<tr>
<td>H-2’</td>
<td>1.57–1.63 (m)</td>
<td>1.77 (d sext, 2.2, 7.2)</td>
<td>1.64–1.72 (m)</td>
<td>1.70–1.84 (m)</td>
<td>1.56–1.62 (m)</td>
</tr>
<tr>
<td>C-2’-Me</td>
<td>1.00 (d, 6.8)</td>
<td>0.95 (d, 7.2)</td>
<td>0.96 (d, 6.8)</td>
<td>1.01 (d, 7.2)</td>
<td>1.02 (d, 6.8)</td>
</tr>
<tr>
<td>H-3’a</td>
<td>1.19–1.28 (m)</td>
<td>1.29–1.36 (m)</td>
<td>1.28–1.37 (m)</td>
<td>1.05–1.16 (m)</td>
<td>1.19–1.21 (m)</td>
</tr>
<tr>
<td>H-3’b</td>
<td>1.64–1.71 (m)</td>
<td>1.38–1.44 (m)</td>
<td>1.40–1.49 (m)</td>
<td>1.70–1.84 (m)</td>
<td>1.56–1.62 (m)</td>
</tr>
<tr>
<td>H-4’</td>
<td>0.92 (t, 7.6)</td>
<td>0.92 (t, 7.2)</td>
<td>0.91 (t, 7.2)</td>
<td>0.91 (t, 7.2)</td>
<td>0.94 (t, 7.4)</td>
</tr>
<tr>
<td>C-4-OH</td>
<td>1.79 (d, 5.0)</td>
<td>1.71 (d, 4.2)</td>
<td>1.72 (d, 4.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C-1’-OH</td>
<td>1.86 (d, 5.6)</td>
<td>1.64 (d, 7.0)</td>
<td>1.84 (d, 5.6)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] Chemical shift values, δ, are in ppm, and coupling constants, J, are in Hz (in parentheses).
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-enooate ([±]-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 MgCl₂ and NaSbF₆[9] to give a 1:1 mixture of anti-aldols (6(RS)-13 and (6(RS)-13 after methanolysis of the silyloxy derivatives (6(RS)-14 and (6(SR)-14 (Scheme 5). The mixture of (6(RS)-13 and (6(SR)-13 was subjected to oxidative hydrolysis[13] to give a 1:1 mixture of (2R,3S,4E,6R)– and (2R,3S,4E,6S)-3-hydroxy-2,4,6-trimethyloct-4-enoic acids, i.e., (6(RS)-8 and (6(SR)-8).

The 1:1 mixture of (6(SR)-8 and (6(RS)-8 was subjected to a one-pot stereoselective epoxidation with m-CPBA, and subsequent lactonisation catalysed by BF₃·Et₂O[12] to give a 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).

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 [\(+5.3\) (\(c = 0.66, \text{CHCl}_3\))] was of the same sign and magnitude as the value originally described for xylariolide A (\([\alpha]_D^{20} = +7.55, c = 0.54, \text{CHCl}_3\)).\(^{[6]}\)

**Conclusions**

We have synthesised four possible diastereoisomers of 4-hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3H)-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 \(^1\)H 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 of the products was achieved by flash chromatography (petroleum ether/EtO\(_2\)O) and the residue was purified by silica gel column chromatography (petroleum ether/EtO\(_2\)O; 97:3) to give ester (\(\pm\)-10) (1826.3 mg, 61%). The spectroscopic data for compound (\(\pm\)-10) were identical to those described in the literature.\(^{[8]}\)

**Conclusions**

We have synthesised four possible diastereoisomers of 4-hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3H)-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 \(^1\)H 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.\(^{[16]}\)
the residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 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; τ<sub>9</sub> = 14 min for minor isomer and τ<sub>R</sub> = 21 min for (6′-S)-14]. Data for (6′-S)-14: [α]<sub>D</sub> = +35.9 (c = 2.1, CHCl<sub>3</sub>). IR (film): ν = 2960, 2874, 1783, 1700, 1455, 1387, 1250, 1055, 882, 841 cm<sup>−1</sup>. 1H NMR (400 MHz, CDCl<sub>3</sub>): 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 (d, 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, 0.83 H), 0.73 (t, J = 7.6 Hz, 3 H), 0.04 (s, 9 H) ppm. 13C NMR (100 MHz, CDCl<sub>3</sub>): δ = 176.6, 153.2, 136.4, 135.6, 133.4, 129.9, 127.2, 82.5, 65.5, 56.1, 41.4, 38.1, 34.0, 30.2, 20.2, 14.4, 12.1, 10.5, 0.2 ppm. HRMS (APCI<sup>+</sup>): calcld. for C<sub>21</sub>H<sub>28</sub>NO<sub>3</sub> [M+H–(CH<sub>3</sub>)<sub>3</sub>SiOH]<sup>+</sup> 342.2069; found 342.2087.

An inseparable 1:1 mixture of (6′-S)−13 and (6′-R)−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)−13 from (6′-S)-13.

(2R,3S,4E,6R)-3-Hydroxy-2,4,6-trimethyleto-4-enoxyloxazolidin-2-one ([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)-13 from (6′-S)-13.

(3R,4S,5R,1′R,2′R)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyleto-4-chloroperbenzoic acid ([6′-R]-9): A 1:1 mixture of epimeric acids (S)-9 and (R)-9 (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)-9.

(3R,4S,5R,1′R,2′R)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyleto-4-chloroperbenzoic acid ([6′-R]-9): A 1:1 mixture of epimeric acids (S)-9 and (R)-9 (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)-9.

(3R,4S,5R,1′R,2′R)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyleto-4-chloroperbenzoic acid ([6′-R]-9): A 1:1 mixture of epimeric acids (S)-9 and (R)-9 (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)-9. 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; τ<sub>9</sub> = 25 min for lactone 1 and τ<sub>R</sub> = 20 min for lactone 4]. Data for 1: Colourless oil. [α]<sub>D</sub> = +5.3 (c = 0.66, CHCl<sub>3</sub>). IR (film): ν = 2433, 2926, 1751, 1458, 1380, 1224, 1168, 1036, 992 cm<sup>−1</sup>. 1H NMR (600 MHz, CDCl<sub>3</sub>): 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), 1.96 (d, J = 5.6 Hz, C-1′-OH), 1.79 (d, J = 5.0 Hz, C-4-OH), 1.71–1.64 (m, 1 H), 1.63–1.57 (m, 1 H), 1.35 (s, 3 H), 1.28–1.19 (m, 1 H), 1.25 (d, J = 7.6 Hz, 3 H), 1.19 (s, 3 H), 0.83 (t, J = 7.2 Hz, 3 H) ppm. 13C NMR (150 MHz, CDCl<sub>3</sub>): δ = 178.7, 191.3, 78.0, 71.5, 40.8, 35.9, 28.1, 17.5, 13.5, 11.6, 9.2 ppm. HRMS (Cl<sup>+</sup>): calcld. for C<sub>11</sub>H<sub>20</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 217.1440; found 217.1432.
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 rBuOH (0.2 mL), and the mixture was stirred at 25 °C. OsO₄ (2.5% w/w solution in rBuOH; 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 rBuOH 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 12 (2.5 mg, 69%).

(3R,4S,5R,1’S,2’S)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3’H)-one (5): Colourless oil; trf = 43 min. [α]D²⁰ = −2.4 (c = 0.1, CHCl₃). IR (film): ν = 3430, 2964, 2878, 2783, 1759, 1748, 1645, 1468, 1415, 1268, 1170, 1064, 991 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.4 (3 H), 7.0 (1 H), 1.75 (dsext, J = 6.0 Hz, 3 H), 0.96 (d, J = 7.0 Hz, C-1), 1.24 (J, J = 7.2 Hz, 3 H) ppm. 13C NMR (125 MHz, CDCl₃): δ = 178.7, 178.5, 87.0, 78.5, 75.0, 39.7, 35.6, 28.3, 17.0, 13.0, 11.9, 9.3 ppm. HRMS (CI⁺): calcd. for C₁₁H₂₁O₄ [M+H⁺]⁺ 217.1440; found 217.1440.

(3R,4S,5R,1’S,2’S)-4-Hydroxy-5-(1-hydroxy-2-methylbutyl)-3,5-dimethyl-4,5-dihydrofuran-2(3’H)-one (6): Colourless oil; trf = 18 min. [α]D²⁰ = +10.6 (c = 0.16, CHCl₃). IR (film): ν = 3434, 2964, 2878, 1760, 1456, 1380, 1222, 1064, 991 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 3.45 (dd, J = 7.2, 1.7 Hz, 1 H), 3.25 (qint, J = 7.2, 1.7 Hz, 1 H), 1.74 (dsext, J = 6.0 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H) ppm. 13C NMR (100 MHz, CDCl₃): δ = 187.5, 87.0, 78.5, 75.0, 39.7, 35.6, 27.5, 21.2, 12.8, 10.5, 3.8 ppm. HRMS (CI⁺): calcd. for C₁₁H₂₁O₄ [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, 0.10 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.

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[15] (R)-2-Methylbutan-1-ol is not a commercially available reagent, but it can be prepared as described in ref.[16]


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