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Enantioselective synthesis of (+)-decipienin A

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Abstract—The enantioselective synthesis of (+)-decipienin A has been carried out. The oxidation of 7-*epi*-cyperone 2 with molecular oxygen in the presence of methanolic KOH provides de C-6-hydroxylated derivative in quantitative yield. The oxidation of glycols **5a** through a Swern oxidation and **14a** with TEMPO radical opens up a route to the synthesis of 11-hydroxy sesquiterpenolides. All attempts of oxidation of **5a** or **14a** with other different oxidation reagents led invariably to fragmentation products.

1. Introduction

Eudesmanolides belong to a class of substances widely spread in nature.[1] Antitumor, antiulcer, cardiotonic, and neurotoxic activities have been reported in some members of this diverse group.[2]

In the course of our programme, aimed at the synthesis and study of biological activities of sesquiterpene lactones, we have carried out the synthesis of decipienin A, **1**, an eudesmanolide isolated from *Melanoselinum decipiens* (Umbelliferae), a shrub endemic to the archipelago of Madeira (Portugal; Fig. 1).[3]

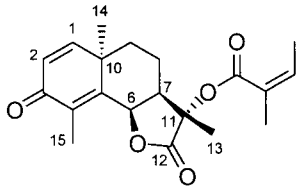
Although most eudesmanolides isolated to date from plants of Compositae family (their main source) display an α-methylene system conjugated to the carbonyl group of the lactone, this eudesmanolide bears an angeloyloxy function instead.[4]

Our group has already reported two syntheses of **1**, in its racemic[5] and enantiomerically pure forms.[6] In the latter synthesis, the oxidation of the glycol **A** formed at the isopropenyl group of the eudesmane skeleton was proposed as the simplest method to get the α-hydroxy-γ-lactone moiety **B**. However, this route had to be initially abandoned as an attempt of oxidation of the vicinal diol led to the methyl ketone **C** through an oxidative cleavage process (Fig. 2).

Providing a solution to this problem was considered interesting as not many efficient methods of oxidation of 1,2-diols, avoiding the cleavage of glycol, were available. Herein, we want to present how this problem was solved through oxidation with TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy radical) in the presence of a catalytic amount of NaClO and a stoichiometric amount of $NaClO_2$. We have successfully applied this methodology to the enantioselective synthesis of α-hydroxy acids starting from terminal olefins.[7]

2. Results and discussion

We envisioned an approach in which the skeleton of the



1, Decipienin A

Figure 1.

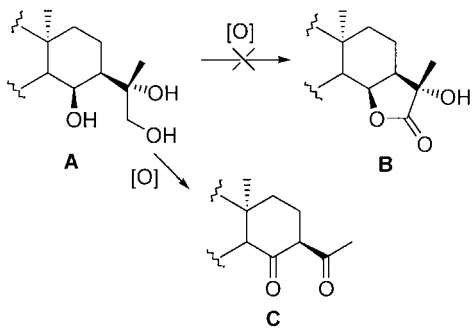


Figure 2.

Keywords: decipienin A; eudesmanolides; sesquiterpenolides; oxidation; Umbelliferae.

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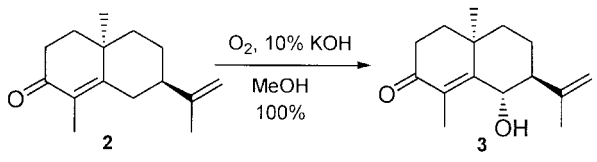


Scheme 1.

molecule is built starting from 7-*epi*-cyperone (**2**). Its transformation into decipienin A would mainly involve oxidative reactions in order to functionalise the appropriate centres.

The first reaction involved the basic treatment of 7-*epi*-cyperone **2**[8] with 10% methanolic KOH in the presence of molecular oxygen, affording the 6-hydroxylated derivative **3** in quantitative yield (Scheme 1). When the reaction was carried out under N_2 atmosphere, the reaction did not proceed at all. No differences were observed when O_2 was bubbled or introducing vigorous stirring open to air. Although oxidation of enolates with molecular oxygen is a well documented reaction,[9] the main advantages of this procedure are its technical simplicity and its high yield. Under the conditions of the reaction (see Section 3), we did not observe any self-condensation product. We examined several other substrates and confirmed its generality as long as the substrate presents certain key features, a methyl group located α to the carbonyl group seems to be needed to prevent decomposition of the molecule.[10]

2.1. First method of oxidation of the glycol: use of the Swern reaction

At this point, it was necessary to protect the hydroxyl group at C-6 in order to prevent secondary reactions in the subsequent oxidation steps (vide infra). Several protective groups were checked, acetate being the most effective one. Thus, we proceeded to acetylate **3** with Ac_2O/Py, yielding the acetate **4** quantitatively. Osmylation-mediated dihydroxylation of the exocyclic double bond was achieved employing AD-mix α, affording a 97:3 mixture of the desired/undesired products, **5a/5b**. No change was observed in the product ratio when AD-mix β was used. The stereochemistry of the resulting tertiary alcohol was confirmed in the subsequent steps.

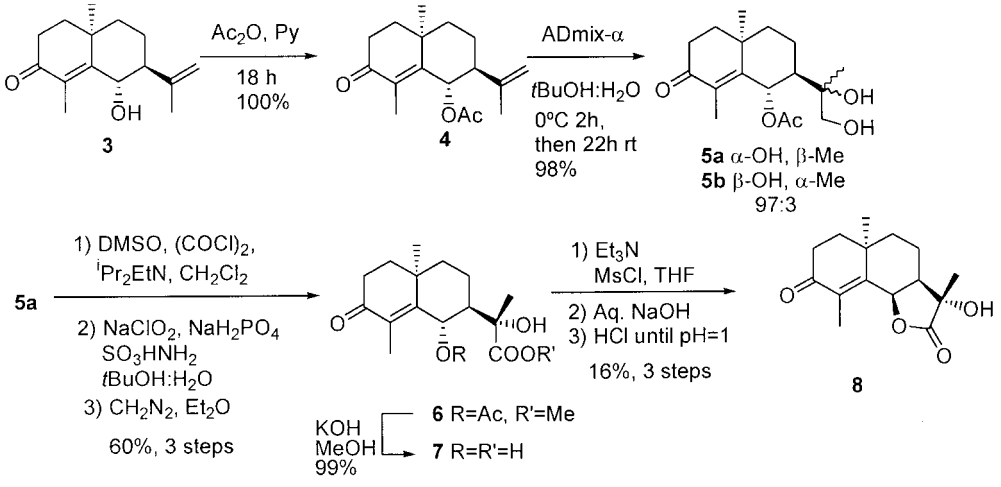
The next step was the oxidation of the primary alcohol to give the corresponding carboxylic acid. As previously pointed out, this reaction required extremely mild conditions since this glycol was easily cleaved to furnish a methyl ketone under most oxidation conditions. This oxidation was also impossible when the hydroxyl group at C-6 was unprotected. After trying several conditions, finally the Swern oxidation led to the desired aldehyde, as could be deduced from the spectrum of the crude mixture. However, this aldehyde resulted to be a very unstable compound,[11] and its isolation was impossible due to its rapid decomposition. The best results were obtained when the resulting mixture from the Swern oxidation was immediately submitted to treatment with $NaClO_2/NaH_2PO_4/SO_3HNH_2$.[12] Methylation with diazomethane then furnished **6** with an overall yield of 60% over three steps.

At this point, the stereochemistry of the acetate at C-6 had to be inverted. Acetate **6** was saponified with methanolic KOH, producing the dihydroxyacid **7** in quantitative yield. Several conditions of the Mitsunobu reaction on the free hydroxyl did not produce the desired β-hydroxyl group. Finally, treatment of **7** with $MsCl/Et_3N$ following the Landsbury procedure yielded the *cis*-lactone **8** in a 16% yield (Scheme 2).[13]

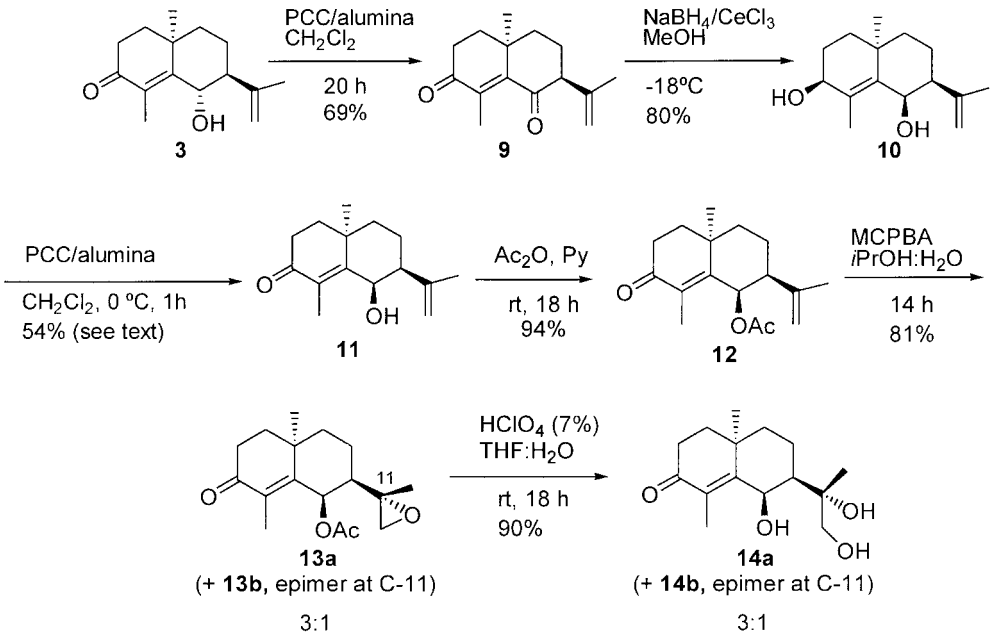
The low yields of the Landsbury inversion of the stereochemistry at C-6 prompted us to seek an alternative route to the target molecule.

2.2. Second method of oxidation of the glycol: use of TEMPO

Therefore we decided to use an oxidation–reduction sequence to invert the stereochemistry at C-6 in the early stages of the synthesis. Thus, oxidation of 6α-hydroxycyperone **3** with freshly prepared PCC on alumina afforded the enedione **9** in a 96% yield. Subsequent reduction of **9** with $NaBH_4$ under Luche conditions[14] led to **10** in a 80% yield. Careful oxidation of **10** with PCC on alumina



Scheme 2.



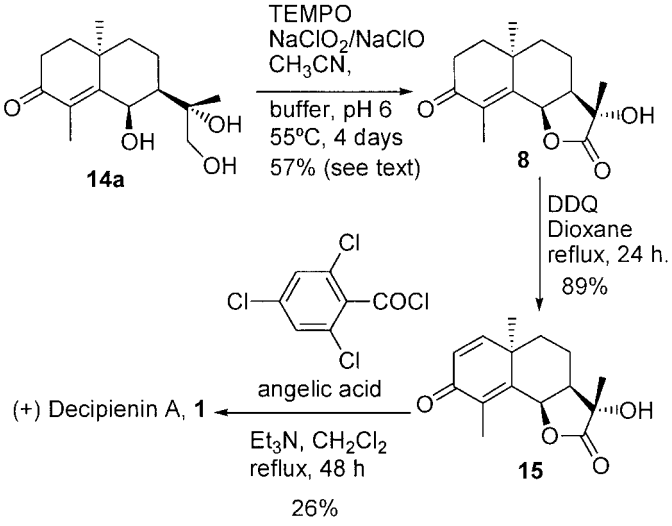
Scheme 3.

furnished **11**, which displayed the hydroxyl at C-6 with the desired stereochemistry. Although in this step, the yield was moderate (54%), the rest of the recovered material was starting material **10** (38%) and the overoxidation product **9** (8%), which could be recycled.

With the hydroxyenone **11** in hand, we proceeded to introduce an acetate group by treatment with Ac_2O in pyridine, affording **12** in 94% yield. Sharpless asymmetric dihydroxylation of **11** and **12** was attempted with negative results. Treatment of **11** with either AD-mix α or β led back to the enedione **9**. In the case of **12**, no reaction was observed. When MCPBA was employed, a 3:1 mixture of the epoxides **13a/13b** was produced, favouring the desired diastereomer. Opening of the epoxide ring was accomplished with a 7% $HClO_4$ solution in aqueous THF, affording triols **14a** and **14b**. This reaction was accompanied by removal of the acetate group (Scheme 3).

All our attempts to oxidize triol **14a** through a Swern reaction as in **5a** were unfruitful. At the same time that this research was taking place, we were studying the use of TEMPO in the preparation of optically active hydroxyacids. We discovered that TEMPO smoothly oxidized glycols to their corresponding hydroxyacids avoiding the cleavage of such a labile system.[7]

Triol **14a** was then oxidised with TEMPO in the presence of catalytic NaClO and stoichiometric $NaClO_2$, directly furnishing lactone **8** in a 57% yield (72% yield from recovered material). It is noteworthy that the allylic alcohol at C-6 in **14a** remains unaltered toward the oxidation under



Scheme 4.

these conditions.[15] Lactone **8** was dehydrogenated with DDQ in refluxing dioxane, affording **15** in a 89% yield (Scheme 4).

Finally, the angeloylation was achieved following the Yamaguchi procedure with angelic acid and 2,4,6-trichlorobenzoyl chloride in the presence of Et_3N.[5,6,16]

Summing up, we have synthesized enantiomerically pure (+)-decipienin A. The control of the involved oxidative processes is of primary importance. The oxidation of the 7-*epi*-cyperone **2** with oxygen in the presence of methanolic KOH provides the C6-hydroxylated derivative in quantitative yield. The oxidation of the glycols **5a** through a Swern reaction and **14a** with the TEMPO radical opens up a route to the synthesis of 11-hydroxy sesquiterpenolides. Other attempts of oxidation of **5a** or **14a** with different oxidation reagents led almost invariably to fragmentation products.

3. Experimental

3.1. General

All non-aqueous reactions were carried out under nitrogen atmosphere unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Reactions were monitored through TLC on commercial silica gel plates. Visualization of the developed plate was performed by fluorescence quenching and/or aqueous ceric ammonium molybdate/anisaldehyde stains. HPLC purification was carried out in a Merck-Hitachi L6270 equipped with a silica gel column (LiChrosorb Si 60, 7 μm particle size, 1×25 cm). THF, dioxane, diethyl ether, and toluene were distilled from sodium metal. Dichloromethane and triethylamine were distilled from calcium hydride prior to use. Melting points are uncorrected and were measured in a Reichert–Jung apparatus. NMR spectra were recorded on a Varian Gemini 200 or on a Varian Unity 400. Spectra were referenced internally to residual solvent signals. Data for ^1H are reported as follows: chemical shift (δ, ppm), integration, multiplicity and coupling constant (J, Hz). Data for ^{13}C are reported in terms of chemical shift (δ, ppm). IR spectra were recorded in a Mattson Genesis Series FTIR, using NaCl plates, data are reported in cm^{-1}. Mass spectra were obtained using a Voyager GCMS or a VG Autospec-Q. TEMPO and AD-mixes α and β were purchased from Aldrich and used without further purification.

3.1.1. 6α-Hydroxy-7-*epi*-α-cyperone (3). 7-*epi*-Cyperone (**2**) (4.54 g, 0.021 mmol) was dissolved in a 10% methanolic solution of KOH (70 mL) and vigorously stirred open to the air at room temperature for 48 h. Then it was neutralised with 1N HCl. MeOH was removed under reduced pressure. Saturated aqueous NH_4Cl (200 mL) was added to the remaining aqueous layer which was subsequently extracted with EtOAc (3×100 mL). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed (SiO_2, EtOAc/hexanes, 1:4) to yield **3** (5.02 g, 0.021 mol, 100%).

3. Yellow oil. $[\alpha]_D^{20}$=44 (c 0.1, $CHCl_3$). IR (thin film) ν 3454, 2923, 2862, 1662, 1464, 1343, 1199, 1021, 991, 895, 748 cm^{-1}. MS, *m/z* (relative intensity) 234 $[M]^+$ (63.8), 219 $[M-CH_3]^+$ (20.2), 205 $[M-CO]^+$ (42.9), 191 $[M-CO-CH_3]^+$ (35.0), 135 $[C_8H_7O_2]^+$ (78.5), 123 $[C_7H_7O_2]^+$ (92.4), 107 $[C_7H_7O]^+$ (76.5), 91 (82.9), 55 (100.0). HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1610. ^1H NMR δ (400 MHz, $CDCl_3$): 4.90 (1H, d, J=1.3 Hz, H-6), 4.82 (1H, d, J=1.7 Hz, H-12), 4.37 (1H, d, J=1.7 Hz, H-12′), 2.60 (1H, ddd, J=17.9, 14.8, 5.4 Hz, H-2α), 2.54 (1H, bs, H-7), 2.40 (1H, ddd, J=17.9, 5.1, 2.2 Hz, H-2β), 2.21 (1H, dddd, J=13.6, 13.6, 5.3, 2.9 Hz, H-8α), 1.88 (3H, s, 3H-15), 1.83 (1H, ddd, J=14.8, 13.4, 5.1 Hz, H-1β), 1.74 (3H, s, 3H-13), 1.65 (1H, ddd, J=13.4, 5.4, 2.2 Hz, H-1α), 1.38 (3H, s, 3H-14), 1.52–1.36 (3H, m, H-8β, H-9α, H9β). ^{13}C NMR δ (100 MHz, $CDCl_3$): 200.5 (C-3), 160.6 (C-5), 145.8 (C-11), 132.5 (C-4), 111.9 (C-12), 70.0 (C-6), 48.2 (C-7), 39.3 (C-1), 35.6 (C-9), 35.6 (C-10), 34.6 (C-2), 26.2 (C-14), 23.5 (C-13), 19.1 (C-8), 10.9 (C-15).

3.1.2. Acetylation of 3. Acetic anhydride (2 mL) was added to a solution of **3** (76 mg, 0.324 mmol) in pyridine (1 mL). The reaction was stirred at room temperature for 18 h. Then it was poured onto water (10 mL) and the mixture was vigorously stirred for 15 min and then extracted with Et_2O (3×25 mL). The combined organic layers were washed with 1N HCl (2×20 mL), saturated aqueous $NaHCO_3$ (2×20 mL), brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield **4** (89 mg, 100%).

4. Yellow oil. $[\alpha]_D^{20}$=126.4 (c 0.1, $CHCl_3$). IR (thin film) ν 2938, 2867, 1738, 1681, 1451, 1388, 1227, 1023, 964, 890 cm^{-1}. MS, *m/z* (relative intensity) 276 $[M]^+$ (3.1), 234 $[M-CH_3CO]^+$ (18.6), 216 $[M-CH_3CO-H_2O]^+$ (100.0), 105 (35.7), 91 (66.5), 77 (54.5). HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1709. ^1H NMR δ (400 MHz, $CDCl_3$): 5.97 (1H, bs, H-6), 4.77 (1H, bs, H-12), 4.41 (1H, bs, H-12′), 2.55 (1H, ddd, J=17.7, 14.7, 5.3 Hz, H-2α), 2.41 (1H, bs, H-7), 2.34 (1H, ddd, J=17.7, 4.9, 2.2 Hz, H-2β), 2.01 (1H, dddd, J=13.8, 13.6, 5.0, 3.7 Hz, H-8α), 1.97 (3H, bs, –OAc), 1.80 (1H, ddd, J=14.7, 13.0, 4.9 Hz, H-1β), 1.79 (3H, s, 3H-15), 1.65 (3H, bs, 3H-13), 1.57 (1H, ddd, J=13.0, 5.3, 2.2 Hz, H-1α), 1.50 (1H, ddd, J=13.8, 13.6, 4.0 Hz, H-8β), 1.42 (1H, m, H-9β), 1.33 (1H, ddd, J=13.7, 4.0, 3.7 Hz, H-9α), 1.26 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 199.2 (C-3), 169.1 (–*O*C*O*–CH_3), 155.0 (C-5), 133.7 (C-4), 143.9 (C-11), 111.7 (C-12), 71.1 (C-6), 45.6 (C-7), 38.5 (C-1), 35.0 (C-10), 34.8 (C-9), 33.8 (C-2), 24.3 (C-14), 22.6 (C-13), 21.0 (–OCO–*C*H_3), 19.0 (C-8), 10.8 (C-15).

3.1.3. Dihydroxylation of 4. A solution of **4** (601 mg, 2.18 mmol) in *t*BuOH/H_2O (10 mL, 1:1) was added over an AD-mix α (3.25 g) solution in the same solvent mixture (10 mL) at 0°C. The mixture was stirred at 0°C for 2 h and at room temperature for 22 h. The reaction was quenched with Na_2SO_3 (3.45 g) and the suspension was stirred for 1 additional hour. Then it was poured onto water (20 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The mixture was cromatographed (SiO_2, EtOAc/hexanes 1:1) yielding

632 mg of a mixture of **5a/5b** (92%, 97:3). Analytical samples were obtained by HPLC (EtOAc/hexanes 1:2).

5a. Colourless crystals. Mp (EtOAc/hexanes) 104–106°C. $[\alpha]_D^{20}$=30.5 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3455, 2934, 2866, 1752, 1661, 1456, 1394, 1238, 1183, 1061, 1017, 940, 754 cm^{-1}. MS, *m/z* (relative intensity) 310 $[M]^+$ (<1.0), 250 $[M-CH_3CO-H_2O]^+$ (3.0), 232 $[M-CH_3CO-2H_2O]^+$ (9.9), 217 $[M-CH_3CO-2H_2O-CH_3]^+$ (6.0), 177 $[C_{12}H_{17}O]^+$ (100.0), 161 (14.2), 91 (11.6), 75 (16.9). HMRS calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1763. ^1H NMR δ (400 MHz, $CDCl_3$): 6.08 (1H, s, H-6), 3.45 (1H, d, *J*=11.3 Hz, H-12), 3.40 (1H, d, *J*=11.3 Hz, H-12′), 2.67 (1H, ddd, *J*=18.7, 14.2, 5.8 Hz, H-2α), 2.46 (1H, ddd, *J*=18.7, 5.6, 1.6 Hz, H-2β), 2.23 (1H, dd, *J*=10.9, 6.7 Hz, H-7), 2.15 (1H, m, H-1β), 2.07 (3H, s, OCO–*Me*), 1.89 (3H, s, 3H-15), 1.80–1.52 (4H, m, H-8α, H-8β, H-9β, H-9α), 1.32 (3H, s, 3H-13), 0.95 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 199.6 (C-3), 171.1 (O*C*O–Me), 156.7 (C-5), 133.7 (C-4), 74.3 (C-11), 72.2 (C-6), 68.6 (C-12), 48.9 (C-7), 36.1 (C-1), 35.8 (C-9), 35.2 (C-10), 34.0 (C-2), 27.3 (C-13), 21.5 (OCO–*C*H_3), 20.2 (C-14), 20.0 (C-8), 11.7 (C-15).

5b. Yellow oil. $[\alpha]_D^{20}$=23.9 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3447, 2933, 2869, 1739, 1662, 1649,1472, 1374, 1173, 1045, 1020, 756 cm^{-1}. MS, *m/z* (relative intensity) 310 $[M]^+$ (< 1.0), 250 $[M-CH_3CO-H_2O]^+$ (3.0), 177 $[C_{12}H_{17}O]^+$ (100.0), 161 (17.4), 91 (14.8), 75 (27.4). HMRS calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1747. ^1H NMR δ (400 MHz, $CDCl_3$): 5.99 (1H, s, H-6), 3.55 (1H, d, *J*=11.2 Hz, H-12), 3.36 (1H, d, *J*=11.2 Hz, H-12′), 3.14 (1H, OH), 2.89 (1H, OH), 2.60 (1H, ddd, *J*=18.5, 14.3, 5.6 Hz, H-2α), 2.40 (1H, ddd, *J*=18.5, 4.0, 1.7 Hz, H-2β), 2.12–1.93 (3H, m, H-1β, H-7α, H-8α), 2.02 (3H, s, OCO–*Me*), 1.84 (3H, s, 3H-15), 1.57–1.49 (3H, m, H-1α, H-8β, H-9β), 1.26 (3H, s, 3H-13), 1.09 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 199.8 (C-3), 170.3 (O*C*O–Me), 156.7 (C-5), 133.6 (C-4), 73.9 (C-11), 71.5 (C-6), 67.7 (C-12), 49.1 (C-7), 36.3 (C-1), 36.2 (C-9), 35.1 (C-10), 33.9 (C-2), 26.9 (C-13), 22.1 (C-14), 21.3 (OCO–*Me*), 18.7 (C-8), 11.4 (C-15).

3.1.4. Swern oxidation of 5a. DMSO (1.56 g, 1.42 mL, 20 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added drowpwise to a solution of oxalyl chloride (0.9 mL, 10 mmol) in dry CH_2Cl_2 (5 mL) under N_2 atmosphere at 60°C. The mixture was stirred for 5 min and then a solution of **5a** (1.536 g, 4.95 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. After 15 min DIPEA (5.5 mL) was added dropwise and then it was allowed to reach room temperature. After 30 min, the reaction was poured onto water (50 mL) and stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layers were washed with 1N HCl (100 mL), H_2O (100 mL), aqueous 2% Na_2CO_3 (100 mL) and brine (100 mL), and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure.

The crude material was dissolved in *t*BuOH (5 mL). Sulfamic acid (SO_3HNH_2) (780 mg, 8 mmol) and NaH_2PO_4 (500 mg) dissolved in H_2O (10 mL) was added. Then, a $NaClO_2$ solution (2.5 mL, 25% w/w, 8.5 mmol) was added dropwise. After 30 min, the reaction was quenched with Na_2SO_3 (800 mg) and extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure affording 1.12 g of crude material which was treated with ethereal diazomethane. The solvent was removed under vacuum and the residue was chromatographed (SiO_2, EtOAc/hexanes 1:4) to yield **6** (1.00 g, 2.97 mmol, 60%).

6. Yellow oil. $[\alpha]_D^{20}$=34.8 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3494, 2935, 2869, 1738, 1667, 1471, 1374, 1234, 1186, 1019, 963 cm^{-1}. MS, *m/z* (relative intensity) 339 $[M+1]^+$ (7.1), 278 $[M-COOCH_3]^+$ (3.3), 235 $[M+1-COOCH_3-COCH_3]^+$ (45.2), 219 $[M+1-COOCH_3-COCH_3-CH_3]^+$ (10.3), 193 $[C_{13}H_{21}O]^+$ (100.0), 177 $[C_{12}H_{17}O]^+$ (53.9), 91 (29.1). HMRS calcd for $C_{18}H_{27}O_6$ 339.1808, found 339.1781. ^1H NMR δ (400 MHz, $CDCl_3$): 6.02 (1H, bs, H-6), 3.59 (3H, s, COO–*Me*), 2.46 (1H, ddd, *J*=18.5, 14.6, 5.4 Hz, H-2α), 2.25 (1H, dd, *J*=18.5, 4.4 Hz, H-2β), 2.08 (1H, dd, *J*=10.1, 6.5 Hz, H-7), 1.89 (3H, s, OCO–*Me*), 1.74 (3H, s, 3H-15), 1.42–1.32 (2H, m, H-1α, H-9β), 1.35 (3H, s, 3H-13), 1.16 (2H, m, H-9α, H-8β), 1.12 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 199.5 (C-3), 183.3 (C-12), 169.1 (O*C*O–Me), 155.9 (C-5), 133.4 (C-4), 76.2 (C-11), 75.6 (C-6), 52.4 (COO–*Me*), 49.4 (C-7), 35.9 (C-1), 35.7 (C-9), 34.7 (C-10), 33.6 (C-2), 26.4 (C-14), 24.3 (C-13), 20.8 (OCO-*Me*), 19.2 (C-8), 10.5 (C-15).

3.1.5. Saponification of 6. Compound **6** (675 mg, 2 mmol) was treated with 10% methanolic KOH (50 mL) at room temperature for 24 h. An aqueous saturated solution of NH_4Cl (25 mL) was then added and the reaction was extracted with EtOAc (3×25 mL), washed with saturated aqueous NH_4Cl (3×25 mL) and brine (3×25 mL), and dried over anhydrous Na_2SO_4, furnishing **7** (560 mg, 1.98 mmol, 99%).

7. Colourless crystals. Mp (EtOAc/hexanes) 162–164°C. $[\alpha]_D^{20}$=28 (*c* 0.1, MeOH). IR (thin film) ν 3415, 2932, 2866, 1643, 1413, 1009, 711 cm^{-1}. MS, *m/z* (relative intensity) 282 $[M]^+$ (4.0), 250 $[M-H_2O-CH_3]^+$ (8.5), 236 $[M-CO_2H_2]^+$ (12.5), 220 $[M-CO_2H_2-CH_3]^+$ (17.3), 193 $[C_{13}H_{21}O]^+$ (100.0), 177 $[C_{12}H_{17}O_2]^+$ (49.5), 133 (35.7), 105 (36.6), 91 (41.3). HMRS calcd for $C_{15}H_{22}O_5$ 282.1467, found 282.1473. ^1H NMR δ (400 MHz, $CDCl_3$): 4.84 (1H, d, *J*=1.7 Hz, H-6), 2.45 (1H, ddd, *J*=18.5, 13.8, 5.6 Hz, H-2α), 2.19 (1H, ddd, *J*=18.5, 5.2, 1.7 Hz, H-2β), 1.95 (1H, ddd, *J*=10.2, 5.6, 1.7 Hz, H-7), 1.84 (1H, ddd, *J*=13.8, 13.3, 5.2 Hz, H-1β), 1.64 (3H, s, 3H-15), 1.56 (1H, ddd, *J*=12.8, 12.2, 2.5 Hz, H-8α), 1.47–1.28 (3H, m, H-1α, H-8β, H-9α), 1.30 (3H, s, 3H-13), 1.17 (3H, s, 3H-14), 1.11 (1H, ddd, *J*=12.2, 10.8, 10.8 Hz, H-9β). ^{13}C NMR δ (100 MHz, $CDCl_3$): 201.5 (C-3), 177.9 (C-12), 162.9 (C-5), 131.4 (C-4), 75.5 (C-11), 67.4 (C-6), 51.3 (C-7), 36.3 (C-9), 36.3 (C-1), 34.8 (C-10), 33.7 (C-2), 27.0 (C-14), 23.9 (C-13), 19.5 (C-8), 9.9 (C-15).

3.1.6. Preparation of lactone 8. Et_3N (1.7 mL, 12 mmol) was added to a solution of **7** (166 mg, 0.59 mmol) in dry THF (10 mL) under N_2 atmosphere at 0°C. Then, MsCl (0.78 mL, 10 mmol) was added dropwise. After 1.5 h, a 1N solution of NaOH (15 mL) was added. The mixture was refluxed for 40 min, allowed to reach room temperature

and then poured onto 1N HCl (50 mL), being stirred for 30 min at room temperature. The mixture was extracted with EtOAc (2×100 mL) and the combined organic layers were washed with 1N HCl (100 mL), water (100 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude was chromatographed (SiO_2, EtOAc/hexanes 3:7) to yield **8** (24 mg, 16%).

8. Yellow crystals. Mp (EtOAc/hexanes) 134–136°C. $[\alpha]_D^{20}$=60.8 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3421, 2930, 2868, 1784, 1669, 1521, 1198, 1097, 1043, 1018, 942, 770 cm^{-1}. MS, *m/z* (relative intensity) 264 $[M]^+$ (12.2), 236 $[M-CO]^+$ (10.4), 220 $[M-CO_2]^+$ (100.0), 205 $[M-CO_2-CH_3]^+$ (47.2), 177 $[C_{12}H_{17}O_2]^+$ (85.4), 161 (27.7), 137 (43.9), 124 (64.4), 91 (55.9). HMRS calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1330. ^{1}H NMR δ (400 MHz, $CDCl_3$): 5.51 (1H, dq, *J*=6.7, 1.2 Hz, H-6), 2.73 (1H, ddd, *J*=9.1, 8.3, 6.7 Hz, H-7), 2.62 (1H, ddd, *J*=17.9, 13.6, 5.4 Hz, H-2α), 2.47 (1H, ddd, *J*=17.9, 5.3, 2.8 Hz, H-2β), 1.96 (1H, ddd, *J*=13.6, 13.3, 5.3 Hz, H-1β), 1.87 (3H, d, *J*=1.2 Hz, 3H-15), 1.71 (1H, ddd, *J*=13.3, 5.4, 2.8 Hz, H-1α), 1.64–1.52 (2H, m, H-9α, H-9β), 1.40 (3H, s, 3H-13), 1.21 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 198.8 (C-3), 177.9 (C-12), 154.2 (C-5), 134.7 (C-4), 76.7 (C-6), 75.6 (C-11), 44.9 (C-7), 36.7 (C-1), 35.4 (C-9), 35.0 (C-10), 33.8 (C-2), 25.4 (C-14), 20.2 (C-13), 17.7 (C-8), 11.6 (C-15).

3.1.7. Oxidation of 3 with PCC on neutral alumina. A solution of **3** (2.36 g, 10 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of PCC on neutral alumina (13.97 g, 11.25 mmol, 1 mmol/806 mg) in CH_2Cl_2 (30 mL) and was stirred at room temperature for 20 h. Then, Et_2O (100 mL) was added and the mixture was filtered through a plug of celite. The solvent was removed under vacuum to yield **9** (2.23 g, 96%).

9. Yellow oil. $[\alpha]_D^{20}$=333.8 (*c* 0.1, $CHCl_3$). IR (thin film) ν 2734, 2877, 1684, 1471, 1378, 1260, 1211, 1034, 939, 894 cm^{-1}. MS, *m/z* (relative intensity) 232 $[M]^+$ (100.0), 217 $[M-CH_3]^+$ (52.8), 204 $[M-CO]^+$ (34.0), 189 $[M-CO-CH_3]^+$ (96.3), 161 $[M-2CO-CH_3]^+$ (61.1), 147 (47.0), 81 (97.6). HMRS calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1453. ^{1}H NMR δ (400 MHz, $CDCl_3$): 4.81 (1H, bs, H-12), 4.59 (1H, bs, H-12′), 2.97 (1H, dd, *J*=5.0, 5.0 Hz, H-7), 2.47 (1H, dddd, *J*=17.4, 14.5, 4.8, 0.6 Hz, H-2α), 2.31 (1H, ddd, *J*=17.4, 3.1, 3.1 Hz, H-2β), 1.93 (3H, m, H-1α, H-8α, H-8β), 1.78 (1H, ddd, *J*=13.8, 11.1, 3.8 Hz, H-9β), 1.71 (1H, dddd, *J*=13.3, 4.8, 3.1, 0.7 Hz, H-1β), 1.63 (3H, s, 3H-13), 1.62 (3H, s, 3H-15), 1.41 (1H, ddd, *J*=13.8, 4.4, 3.6 Hz, H-9α), 1.07 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 206.1 (C-6), 199.0 (C-3), 155.9 (C-5), 141.3 (C-11), 132.6 (C-4), 112.9 (C-12), 57.4 (C-7), 38.5 (C-10), 36.6 (C-1), 35.9 (C-9), 33.5 (C-2), 23.7 (C-8), 23.3 (C-14), 22.2 (C-13), 12.2 (C-15).

3.1.8. Reduction of 9 with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$. To a solution of **9** (163 mg, 0.70 mmol) in MeOH (15 mL) was added $CeCl_3{\cdot}7H_2O$ (312.5 mg, 0.84 mmol). The mixture was cooled to −18°C and $NaBH_4$ was added until no more starting material was observed (TLC). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. It was extracted with EtOAc (2×50 mL), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The residue was chromatographed (SiO_2, EtOAc/hexanes, 2:8) to yield diol **10** (133 mg, 80%).

10. Colourless crystals. Mp (EtOAc/hexanes) 108–110°C. $[\alpha]_D^{20}$=69.2 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3418, 2934, 2869, 1661, 1451, 1386, 1260, 1212, 1114, 1017, 932, 887, 819, 754 cm^{-1}. MS, *m/z* (relative intensity) 236 $[M]^+$ (5.1), 218 $[M-H_2O]^+$ (41.7), 203 $[M-H_2O-CH_3]^+$ (36.4), 177 $[C_{12}H_{17}O_2]^+$ (20.6), 154 (49.8), 123 (60.3), 109 (100.0), 93 (74.6). HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1755. ^{1}H NMR δ (400 MHz, $CDCl_3$): 4.96 (1H, s, H-12), 4.94 (1H, s, H-12′), 4.54 (1H, d, *J*=1.7 Hz, H-6), 4.07 (1H, dd, *J*=8.4, 8.2 Hz, H-3), 2.51 (1H, dd, *J*=9.3, 9.3 Hz, H-7), 2.04 (2H, m, H-2α, H-2β), 1.83 (3H, s, 3H-15), 1.81 (3H, s, 3H-13), 1.15 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 146.2 (C-11), 140.7 (C-5), 133.7 (C-4), 111.6 (C-12), 71.4 (C-3), 66.5 (C-6), 41.9 (C-7), 39.3 (C-1), 34.1 (C-9), 33.1 (C-10), 29.0 (C-2), 26.3 (C-14), 23.2 (C-13), 18.9 (C-8), 14.5 (C-15).

3.1.9. Oxidation of 10 with PCC on neutral alumina. A solution of **10** (200 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of PCC on neutral alumina (1.05 g, 0.85 mmol, 1mmol/806 mg) in CH_2Cl_2 (20 mL) at 0°C. The mixture was stirred until the formation of overoxidation products began (followed by TLC). Then, Et_2O (40 mL) was added and the mixture was filtered through a plug of celite. The solvent was removed under vacuum and the residue was chromatographed (SiO_2, EtOAc/hexanes, 3:17) to yield **11** (107 mg, 54%), **10** (76 mg, 38%) and **9** (15.7 mg, 8%).

11. Colourless crystals. Mp (EtOAc/hexanes) 81–83°C. $[\alpha]_D^{20}$=136.7 (*c* 1.0, $CHCl_3$). IR (thin film) ν 3458, 2930, 2878, 1661, 1456, 1117, 1020, 888 cm^{-1}. MS, *m/z* (relative intensity) 234 $[M]^+$ (11.1), 219 $[M-CH_3]^+$ (7.1), 205 $[M-2CH_3]^+$ (21.3), 191 $[C_{13}H_{19}O]^+$ (17.5), 177 $[C_{12}H_{17}O]^+$ (13.9), 118 (100.0), 107 (79.0), 95 (69.9). HMRS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1600. ^{1}H NMR δ (400 MHz, $CDCl_3$): 5.06 (1H, bs, H-12), 4.99 (1H, bs, H-12′), 4.65 (1H, bs, H-6), 2.66 (1H, ddd, *J*=18.7, 14.5, 5.7 Hz, H-2α), 2.54 (1H, dd, *J*=8.9, 7.7 Hz, H-7), 2.44 (1H, ddd, *J*=18.7, 5.3, 1.7 Hz, H-2β), 1.88–1.79 (4H, m, H-1β, H-8α, H-8β, H-9α), 1.87 (3H, bs, 3H-15), 1.85 (3H, bs, 3H-13), 1.68 (1H, ddd, *J*=12.9, 5.7, 1.7 Hz, H-1α), 1.54 (1H, ddd, *J*=11.1, 7.7, 3.7 Hz, H-9β), 1.25 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 200.0 (C-3), 160.6 (C-5), 145.4 (C-11), 132.4 (C-4), 112.3 (C-12), 67.2 (C-6), 41.6 (C-7), 38.8 (C-1), 34.2 (C-10), 33.9 (C-2), 33.4 (C-9), 24.3 (C-14), 23.2 (C-13), 18.9 (C-8), 10.8 (C-15).

3.1.10. Acetylation of 11. Ac_2O (2 mL) was added to a solution of **11** (76 mg, 0.32 mmol) in pyridine (1 mL). The reaction was stirred for 18 h after which time was poured onto water and vigorously stirred for 15 additional min. Then, it was extracted with Et_2O (3×25 mL). The combined organic layers were washed with 1N HCl (2 × 20 mL), aqueous saturated $NaHCO_3$ (2 × 20 mL), brine, and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield **12** (84 mg, 94%).

12. Yellow oil. $[\alpha]_D^{20}$=40.5 (*c* 0.1, $CHCl_3$). IR (thin film) ν 2934, 2870, 1739, 1669, 1463, 1373, 1226, 1018 cm^{-1}. MS, *m/z* (relative intensity) 276 $[M]^+$ (2.3), 234 $[M-COCH_3]^+$ (12.0), 216 $[M-COCH_3-H_2O]^+$ (46.4), 105 (59.8), 91 (100.0), 77 (79.5). HMRS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1660. ^1H NMR δ (400 MHz, $CDCl_3$): 6.00 (1H, d, *J*=2.9 Hz, H-6), 4.88 (1H, bs, H-12), 4.81 (1H, bs, H-12′), 2.64 (1H, ddd, *J*=18.5, 14.2, 5.7 Hz, H-2α), 2.53 (1H, ddd, *J*=9.3, 9.3, 2.9 Hz, H-7), 2.42 (1H, ddd, *J*=18.5, 5.4, 1.9 Hz, H-2β), 1.95 (3H, s, OCO–*Me*), 1.87–1.63 (5H, m, H-1α, H-1β, H-8α, H-8β, H-9α), 1.79 (3H, bs, 3H-15), 1.76 (3H, bs, 3H-13), 1.56 (1H, m, H-9β), 1.25 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 199.6 (C-3), 169.5 (O*C*O–Me), 157.8 (C-5), 144.2 (C-11), 132.9 (C-4), 112.0 (C-12), 69.4 (C-6), 41.5 (C-7), 38.3 (C-1), 34.7 (C-10), 33.8 (C-2), 33.7 (C-9), 24.6 (C-14), 23.1 (C-13), 20.9 (OCO–*Me*), 19.5 (C-8), 11.2 (C-15).

3.1.11. Epoxidation of 12. MCPBA (92 mg, 0.30 mmol) was added to a solution of **12** (56 mg, 0.20 mmol) in *i*PrOH/H_2O (15 mL, 4:1). After stirring for 14 h, *i*PrOH was removed under reduced pressure and the remaining aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ (2×50 mL), NaOH (1N, 2×50 mL), brine, and dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:4) to provide a 3:1 mixture of the epoxides **13a/13b** (47 mg, 81%). We were unable to obtain analytical samples of epoxides **13a** and **13b** due to their rapid decomposition on different chromatographic systems.

3.1.12. Triols 14a and 14b. A 7% solution of $HClO_4$ in H_2O (10 mL) was added to a 3:1 mixture of epoxides **13a/13b** (169 mg, 0.72 mmol) in THF/H_2O (60 mL, 4:1). The reaction was stirred for 18 h, after which time, was carefully neutralised with 1N NaOH and THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc (2×50 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to provide a mixture of triols **14a** and **14b**. The mixture was chromatographed (SiO_2, MeOH/$CHCl_3$ 2:98) affording **14a** (131 mg, 0.48 mmol, 90% from **13a**) and **14b** (43 mg, 0.17 mmol, 90% from **13b**).

14a. Colourless crystals. Mp (EtOAc/hexanes) 167–169°C. $[\alpha]_D^{20}$=58.7 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3373, 2929, 1651, 1463, 1260, 1045, 1025, 799 cm^{-1}. MS, *m/z* (relative intensity) 268 $[M]^+$ (7.2), 250 $[M-H_2O]^+$ (8.0), 177 $[C_{12}H_{17}O]^+$ (100.0), 164 (22.1), 123 (27.3). HMRS calcd for $C_{15}H_{24}O_4$ 268.1675 found 268.1671. ^1H NMR δ (400 MHz, $CDCl_3$): 5.09 (1H, s, H-6), 3.73 (1H, d, *J*=11.2 Hz, H-12), 3.34 (1H, d, *J*=11.2 Hz, H-12′), 2.69 (1H, ddd, *J*=18.6, 5.3, 1.7 Hz, H-2α), 2.46 (1H, ddd, *J*=18.6, 14.1, 5.7 Hz, H-2β), 1.88 (3H, s, 3H-15), 1.80–1.70 (5H, m, H-1β, H-7, H-8α, H-8β, H-9α), 1.71 (1H, ddd, *J*=12.9, 5.7, 1.7 Hz, H-1α), 1.55 (1H, m, H-9β), 1.34 (3H, s, 3H-13), 1.21 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 200.9 (C-3), 161.5 (C-5), 131.4 (C-4), 74.8 (C-11), 66.2 (C-12), 66.2 (C-6), 40.4 (C-7), 38.5 (C-1), 34.0 (C-10), 33.9 (C-2), 32.6 (C-9), 24.4 (C-13), 23.9 (C-14), 16.3 (C-8), 10.5 (C-15).

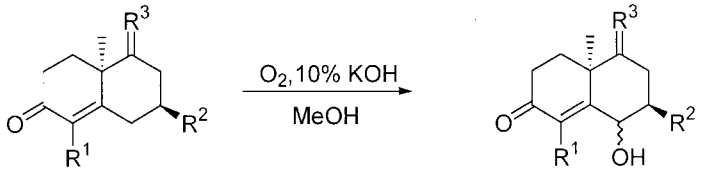
14b. Colourless crystals. Mp (EtOAc/hexanes) 265–267°C. $[\alpha]_D^{20}$=40.0 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3378, 2927, 1652, 1436, 1379, 1353, 1260, 1116, 799 cm^{-1}. MS, *m/z* (relative intensity) 268 $[M]^+$ (7.1), 250 $[M-H_2O]^+$ (8.0), 177 $[C_{12}H_{17}O]^+$ (100.0), 164 (20.9), 123 (26.5). HMRS calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1668. ^1H NMR δ (400 MHz, $CDCl_3$): 5.10 (1H, s, H-6), 3.78 (1H, d, *J*=11.9 Hz, H-12), 3.62 (1H, d, *J*=11.9 Hz, H-12′), 3.14 (1H, bs, OH), 2.68 (1H, ddd, *J*=18.7, 5.0, 1.7 Hz, H-2α), 2.45 (1H, ddd, *J*=18.7, 14.1, 5.7 Hz, H-2β), 2.07 (2H, m, H-7, H-8β), 1.87–1.78 (3H, m, H-1β, H-8α, H-9β), 1.85 (3H, s, 3H-15), 1.71 (1H, m, H-1α), 1.57 (1H, m, H-9α), 1.23 (3H, s, 3H-13), 1.19 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 200.5 (C-3), 160.9 (C-5), 131.6 (C-4), 75.7 (C-11), 69.2 (C-12), 67.5 (C-6), 38.6 (C-1), 38.0 (C-7), 34.0 (C-2), 34.0 (C-10), 33.1 (C-9), 23.5 (C-14), 22.8 (C-13), 15.8 (C-8), 10.7 (C-15).

3.1.13. Lactonization of 14a. The triol **14a** (148 mg, 0.55 mmol) was dissolved in CH_3CN (6 mL) and sodium phosphate buffer (4,5 mL, pH 6.5). Then, TEMPO (22 mg, 0.25 mmol), $NaClO_2$ solution (0.329 mL, 25% w/w, 2 mmol) and diluted bleach (37 μL, 0.02 mmol, 4% active chlorine) was added and the mixture was heated to 55°C. After four days, the reaction was allowed to cool to room temperature and 1N NaOH was added until pH 8. Then, a saturated solution of Na_2SO_3 (5 mL) was added and the pH was set to 2 by adding 1N HCl. The mixture was extracted with EtOAc (2×50 mL) and the combined organic layers was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (SiO_2, EtOAc/hexanes 3:7) to provide lactone **8** (84 mg, 57%) and **14a** (22 mg, 15%).

3.1.14. Dehydrogenation of 8. DDQ (30 mg, 0.128 mmol) dissolved in dry dioxane (5 mL) was added to a solution of lactone **8** (17 mg, 0.064 mmol) in dry dioxane (5 mL) under N_2 atmosphere. The reaction was refluxed for 24 h, after which time, a saturated solution of $Na_2S_2O_3$ (5 mL) was added. The mixture was then extracted with EtOAc (3×25 mL) and the combined organic layers were washed with 1N HCl (25 mL), saturated solution of $NaHCO_3$ (25 mL), brine, and dried over Na_2SO_4. The crude mixture was chromatographed (SiO_2, EtOAc/hexanes 1:3) to yield lactone **15** (15 mg, 89%).

15. Colourless crystals. Mp (EtOAc/hexanes) 155–157°C. $[\alpha]_D^{20}$=20.4 (*c* 0.1, $CHCl_3$). IR (thin film) ν 3445, 2963, 2954, 2935, 2863, 1773, 1655, 1542, 1473, 1419, 1313, 1208, 1042, 986 cm^{-1}. MS, *m/z* (relative intensity) 262 $[M]^+$ (6.6), 244 $[M-H_2O]^+$ (3.2), 218 $[M-CO_2]^+$ (7.4), 203 $[M-CO_2-CH_3]^+$ (14.6), 175 $[M-C_3H_3O_3]^+$ (47.7), 135 (100.0), 91 $[C_7H_7]^+$ (32.0), 77 $[C_6H_5]^+$ (19.6). HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1188. ^1H NMR δ (400 MHz, $CDCl_3$): 6.75 (1H, d, *J*=10.0 Hz, H-1), 6.23 (1H, d, *J*=10.0 Hz, H-2), 5.62 (1H, dq, *J*=7.2 1.6 Hz, H-6), 2.93 (1H, ddd, *J*=7.2, 7.2, 7.2 H-7), 2.41 (1H, s, OH), 2.09 (3H, d, *J*=1.6 Hz, 3H-15), 1.98 (1H, m, H-8α), 1.79 (1H, td, *J*=13.8, 6.9, H-9β), 1.75 (1H, m, H-9α), 1.62 (1H, dddd, *J*=13.7, 7.2, 6.9, 6.9, H-8β), 1.34 (3H, s, 3H-13), 1.31 (3H, s, 3H-14). ^{13}C NMR δ (100 MHz, $CDCl_3$): 185.9 (C-3), 177.3 (C-12), 155.6 (C-1), 151.0 (C-5), 134.8 (C-4), 125.4 (C-2), 76.5 (C-6), 74.8 (C-11), 45.3 (C-7),

Table 1.



R^1=Me, R^2= isopropenyl, R^3=H,H	100%, only α-OH
R^1=Me, R^2=H, R^3=H,H	35%
R^1=Me, R^2=H, R^3=O	25%
R^1=Me, R^2=H, R^3=O-$(CH_2)_2$-O	56%
R^1=H, R^2=isopropenyl, R^3=H,H	complex mixture
R^1= R^2=H, R^3=H,H	complex mixture
R^1= R^2=H, R^3=O	complex mixture
R^1= R^2=H, R^3=O-$(CH_2)_2$-O	complex mixture

39.5 (C-10), 32.8 (C-9), 26.9 (C-14), 20.7 (C-8), 18.3 (C-13), 12.5 (C-15).

3.1.15. Esterification of 15. 2,4,6-Trichlorobenzoyl chloride (17 μL, 0.11 mmol) and Et_3N (15 μL, 0.11 mmol) was added to a solution of angelic acid (11 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 2 h at room temperature. After that time, a solution of lactone **15** (13 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was refluxed for 48 h, then diluted with Et_2O (15 mL) and filtered. Solvent was removed under reduced pressure and the crude was chromatographed (SiO_2, EtOAc/hexanes 3:7) to provide (+)-decipienin A **1**[5,6] (4.7 mg, 0.013 mmol, 26%). Spectroscopic data and optical activity were in agreement with those of the natural compound.

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