Total synthesis of a monocyclofarnesane dinorsesquiterpenoid isolated from mushroom ingested by beetle: Selectivity in solid-state Baeyer–Villiger reaction

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Dinorsesquiterpenoid **1** is synthesised starting from (*S*)-(+)-Wieland–Miescher ketone analogue **5** *via* solid-state Baeyer–Villiger reaction as a key step.

Dinorsesquiterpenoid **1** was isolated by Hashimoto and Asakawa[1] along with norsesquiterpenoid **3** from the dry, powdery, inedible mushroom *Cryptoporus volvatus*, biotransformed by the beetle *Tibolium castaneum*, and might be one of the metabolites of cryptoporic acid **4** which has strong inhibitory activity against the release of superoxide anion radical from guinea pig peritoneal macrophages. The structure of compound **1** was determined as the methyl ester **2** because of the instability of **1** and the absolute stereostructure at C-2 was established to be *R* as depicted in Fig. 1 by applying Kusumi's PGME method (phenylglycine methyl ester).[2] Our continuing interest in total syntheses of monocyclofarnesane terpenoids delineates herein the first total synthesis of the dinorsesquiterpenoid **2** subsequent to our previous synthesis of **3**.[3]

Results and discussion

According to the plausible biogenetic pathway[1] of **3** *via* bio-Baeyer–Villiger reaction, synthesis has started from the known enone **6** derived from optically active (*S*)-(+)-Wieland–Miescher ketone analogue **5**[4] [>95% enantiomeric excess (ee)] targeting 1-decalones **14** or **16** as a key intermediate with all requisite stereocentres (Scheme 1). Reduction of α,β-unsaturated moiety of the enone **6** with lithium in liquid ammonia provided, in 84% yield, the ketone **7**, which was reduced with lithium aluminium hydride to give a mixture of two inseparable isomeric alcohols **8** and **9**. Deprotection of the ketal provided β-alcohol **10** and α-alcohol **11** in 83 and 12% yield, respectively in two steps. Coupling constants of the proton at C-5 of **10** (δ 2.64, ddq, J 14.0, 13.8 and 7.0 Hz) revealed the equatorial orientation of the methyl group at C-5 and the *trans* ring junction of the decalin framework. Protection of β-alcohol **10** with chlorotrimethylsilane (TMSCl) provided TMS ether **12** in 94% yield.

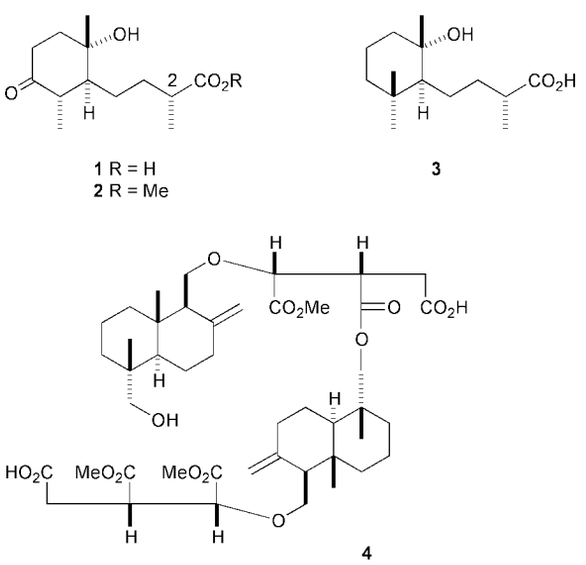

Fig. 1

Monomethylation at C-2 of **12** and its derivatives was not trivial, as anticipated from literature precedents.[3,5] Attempts to introduce a methoxycarbonyl or formyl group to activate C-2 have failed. Reaction with potassium hydride as a base gave an inseparable mixture of mono- and di-methylated products along with *O*-methylated product. Several initial attempts using lithium diisopropylamide (LDA) and iodomethane (MeI) led only to recovered ketone **12**. Addition of hexamethylphosphoric triamide (HMPA) increased the amount of dimethylated product. After several investigations, we finally found that treatment of the ketone **12** with LDA at −20 °C followed by addition of MeI provided an inseparable 1:1 diastereomeric mixture of monomethylated products **13** and **14** in 73% yield. When the hydroxy group at C-6 was protected as its *tert*-butyldimethylsilyl (TBDMS) ether, all similar attempts have failed.

The mixture of **13** and **14**, upon treatment with sodium methoxide, equilibrated in 98% yield with concomitant deprotection of the TMS group to afford thermodynamically stable α-isomer **15** in which orientation of the methyl group was apparent from coupling patterns of the proton at C-2 (δ 2.75, d × quint, J 12.8 and 6.4 Hz). All the requisite stereocentres of the target compound **1** were furnished at this stage.

Baeyer–Villiger reaction of **15** and its derivatives was not easy. Reaction of the ketone **15** in solvent with excess of trifluoroacetic acid (TFA), *m*-chloroperbenzoic acid (MCPBA) or monoperphthalic acid magnesium salt (MMPA) resulted in recovery of starting material **15** with partial decomposition. Solid-state reaction of **15** with MCPBA or MMPA gave a small amount of lactonic compounds. TMS ether **14** gave a similar result. Then, the hydroxy group of **15** was quantitatively protected as its acetate to provide **16**. Though conventional

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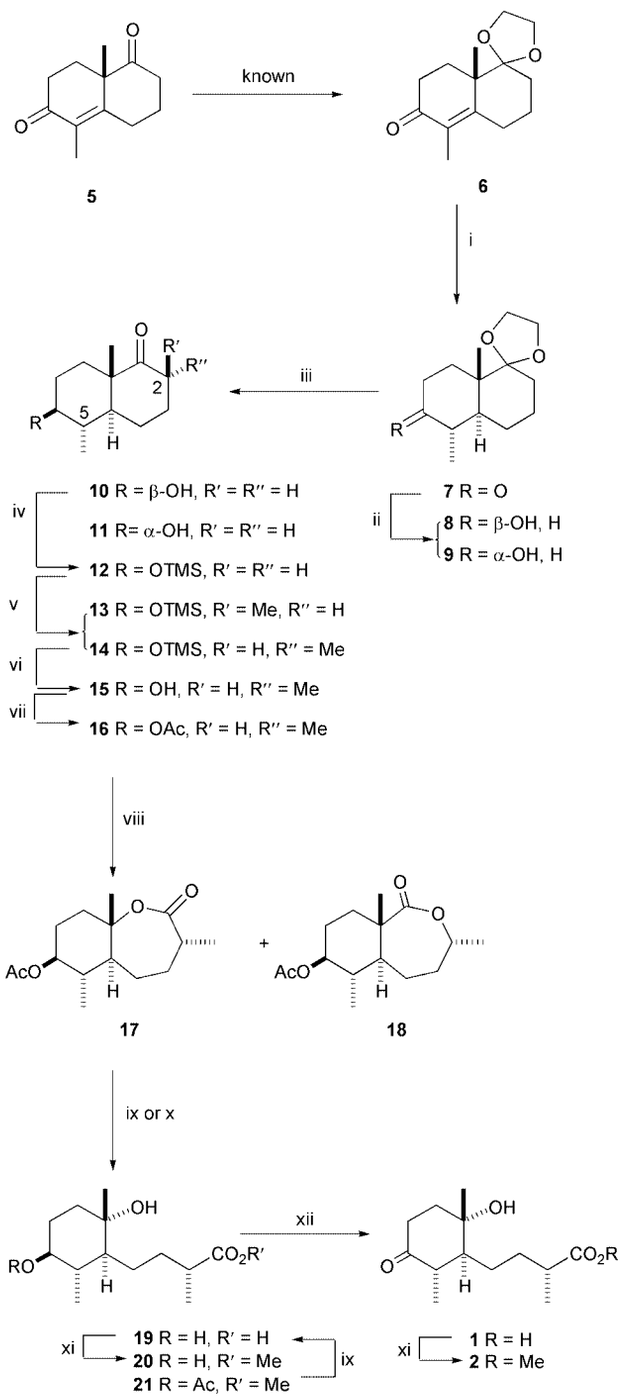

Scheme 1 *Reagents, conditions and yields*: i, Li/liq. NH_3, THF, H_2O, 84%; ii, LAH, Et_2O; iii, PTSA, aq. acetone, 95% from **7**; iv, TMSCl, Et_3N, CH_2Cl_2, 94%; v, LDA, THF, MeI, 73%; vi, NaOMe, HOMe, 98%; vii, Ac_2O, DMAP, pyridine, quant.; viii, MCPBA, solid state, 85%; ix, aq. NaOH, quant. (**17** ⟶ **19**, **21** ⟶ **19**); x, K_2CO_3, aq. MeOH, 82% (**20**:**21** = 62:38); xi, CH_2N_2, Et_2O, quant.; xii, Jones reagent, 79% (**20** ⟶ **2**) (**17** ⟶ **19** ⟶ **1** ⟶ **2** 52% overall in 3 steps).

Baeyer–Villiger oxidation of **16** in a solvent with MCPBA or trifluoroperacetic acid[6] with or without $Yb(OTf)_3$[7] was very sluggish and resulted again in recovery of **16**, solid-state reaction[8] of the acetate **16** with MCPBA furnished desired lactonic compound **17** and its regioisomer **18** in 58 and 27% yield, respectively.

Hydrolysis of the lactone **17** with aq. sodium hydroxide followed by Jones oxidation provided very unstable acid **1**, which was soon esterified with diazomethane to give methyl ester **2** in 52% overall yield in three steps. Alternatively, an attempt of selective hydrolysis of the keto ester **17** provided a mixture of hydroxy ester **20** and acetoxy ester **21** in 82% combined yield (62:38 ratio). Jones oxidation of the hydroxy ester afforded the ester **2** in 79% yield. Spectral data of synthetic **2** were completely identical with the data of natural **2** including optical rotation $[\alpha]_D^{23}$ −13.1 (*c* 0.26, $CHCl_3$) {lit.,[1] $[\alpha]_D^{23}$ −14.3 (*c* 0.28, $CHCl_3$)}.†

Table 1 Solid-state Baeyer–Villiger oxidation of the decalones **14**–**16**, **22** and **24**

Entry	Decalone	Reagent	Reaction conditions	Product Yield (%)
1	**14**	MCPBA	rt, 144 h	**26** 0 (73)[a]
2	**15**	MMPA[b]	50 °C, 7 h	**26** 22 (54)[a]
3	**15**	MCPBA	rt, 112 h	**26** 15 (52)[a]
4	**16**	MCPBA	rt, 72 h	**17** 58 **18** 27
5	**22**	MCPBA	rt, 16 h	**23** 90
6	**24**	MCPBA	rt, 16 h	**25** 84[c]

[a] The decalone **15** was recovered. [b] Monoperoxyphthalic acid magnesium salt. [c] See ref. 3.

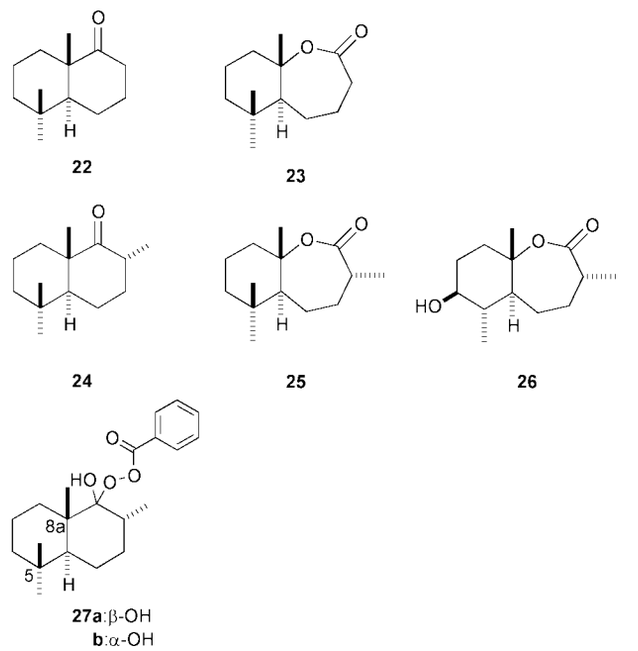

Fig. 2

Some of our results in the solid-state Baeyer–Villiger reactions are compiled in Table 1. Smooth reactions and complete regioselectivities with the decalones **22** and **24** in entries 5 and 6 rather than with the decalone **16** in entry 4 might be the result of 1,3-steric repulsion between two axial methyl groups at C-5 and C-8a in **22** and **24** (Fig. 2). The rate-determining step of Baeyer–Villiger reaction is migration from Crieege's intermediate *via* an early transition state.[9,10] To this end, semiempirical molecular orbital calculations, PM3,[11] on Crieege's intermediates **27a** and **27b** derived from the decalone **24** were performed by using Gaussian 98, Revision A.6,[12] with Silicon Graphics Onyxs. Though the difference in heat of formation between intermediates **27a** and **27b** was little (0.07 kcal‡), the C-1–C-8a bond in the more stable intermediate **27a** was longer (1.61 Å)[13] than the C-1–C-2 bond (1.56 Å) and was antiperiplanar (dihedral angle 173°) to the O–O bond. These results explain the regioselectivity of the present Baeyer–Villiger reactions. Substrates **14**–**16**, **22** and **24** in Table 1 were all unreactive in Baeyer–Villiger reactions in a solvent. However, an exact explanation of solid-state Baeyer–Villiger reactions is yet to be published.

† $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.
‡ 1 cal = 4.184 J.

In conclusion, we have completed the total synthesis of dinorsesquiterpenoid **1**, demonstrating the utility of solid-state Baeyer–Villiger oxidation in natural-product synthesis.

Experimental

Mps were determined with a Yanaco MP hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer for solutions in tetrachloromethane. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. *J*-Values are in Hz. The ^{13}C NMR spectrum for ester **2** was run on a Varian unity 500plus (125 MHz) instrument with chloroform as internal standard. Mass spectral data were obtained with a JEOL GC-Mate spectrometer. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for solutions in chloroform. Medium-pressure liquid chromatography (MPLC) was carried out on a JASCO PRC-50 instrument with a silica gel-packed column. Microanalyses were carried out in the Instrumental Analysis Center for Chemistry, Tohoku University.

(4a*S*,5*S*,8a*S*)-(−)-3,4,4a,5,8,8a-Hexahydro-5,8a-dimethylnaphthalene-1(2*H*),6(7*H*)-dione 1-ethylene ketal 7

To a solution of lithium (445 mg, 64 mml) in distilled liquid ammonia (100 cm^3) was added a solution of the enone **6** (3.03 g, 12.8 mmol) in THF (50 cm^3) at −78 °C under nitrogen atmosphere. After being refluxed for 30 min, water (0.23 cm^3, 12.8 mmol) was added at −78 °C. After being refluxed for 40 min, the reaction was quenched by cautious addition of water (0.495 cm^3, 24 mmol) and ammonium chloride (3 g). After evaporation of liquid ammonia, the organic layer was extracted with ethyl acetate (×2) and the combined extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by column chromatography of the residue on silica gel (ethyl acetate–*n*-hexane 1 : 5) gave **7** (2.58 g, 84%) as a colourless oil, $[a]_D^{23}$ −8.7 (*c* 1.22, $CHCl_3$); ν_{max}/cm^{-1} 2955, 1713, 1186, 1088 and 1042; δ_H(200 MHz) 0.99 (3H, d, *J* 6.6), 1.24 (3H, s), 1.32–2.04 (9H, m), 2.15–2.53 (3H, m) and 3.82–4.05 (4H, m) (Found: C, 70.29; H, 9.48. Calc. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.3%).

(4a*S*,5*S*,6*S*,8a*S*)-(−)-3,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-5,8a-dimethylnaphthalen-1(2*H*)-one 10 and (4a*S*,5*S*,6*R*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-hydroxy-5,8a-dimethylnaphthalen-1(2*H*)-one 11

To a stirred solution of the ketone **7** (1.06 g, 4.44 mmol) in anhydrous diethyl ether (13 cm^3) was added lithium aluminium hydride (82 mg, 2.28 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 1 h, the reaction mixture was quenched by cautious addition of aq. ammonium chloride. Filtration through anhydrous Na_2SO_4 followed by evaporation of diethyl ether provided an inseparable mixture of *(4aS,5S,6S,8aS)- and (4aS,5S,6R,8aS)-3,4,4a,5,6,7,8,8a-octahydro-6-hydroxy-5,8a-dimethylnaphthalen-1(2H)-one ethylene ketal* **8** and **9** (1.00 g).

A stirred solution of mixture of **8** and **9** (1.00 g) and toluene-*p*-sulfonic acid (PTSA) monohydrate (173 mg, 0.91 mmol) in acetone (20 cm^3) and water (4 cm^3) was refluxed for 16 h. After addition of aq. sodium hydrogen carbonate, product was extracted with ethyl acetate (×2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Column chromatography (ethyl acetate–*n*-hexane 1 : 2) gave **10** (727 mg, 83% in two steps) and its isomer **11** (106 mg, 12% in two steps) as crystals.

Compound **10** had $[a]_D^{23}$ −54.3 (*c* 0.388, $CHCl_3$); mp 79 °C; ν_{max}/cm^{-1} 3630, 2938, 1709, 1454, 1103, 1044 and 1022; δ_H(200 MHz) 1.03 (3H, d, *J* 6.4), 1.14 (3H, s), 1.19–2.30 (12H, m), 2.64 (1H, ddq, *J* 14.0, 13.8, 7.0) and 3.10 (1H, m) (Found: C, 73.05; H, 10.0. Calc. for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3%).

Compound **11** had mp 72–73 °C; ν_{max}/cm^{-1} 3634, 3514, 2868, 1709, 1448, 1373, 1311, 1263, 1165, 1101, 1038 and 964; δ_H(200 MHz) 0.99 (3H, d, *J* 6.3), 1.12 (3H, s), 1.19–2.30 (12H, m), 2.64 (1H, ddd, *J* 14.0, 13.8 and 6.8) and 3.86 (1H, m).

(4a*S*,5*S*,6*S*,8a*S*)-(−)-3,4,4a,5,6,7,8,8a-Octahydro-5,8a-dimethyl-6-(trimethylsiloxy)naphthalen-1(2*H*)-one 12

A solution of the alcohol **10** (1.38 g, 7.04 mmol), chlorotrimethylsilane (1.10 cm^3, 8.69 mmol) and triethylamine (2.0 cm^3, 14.3 mmol) in dichloromethane (20 cm^3) was stirred at room temperature for 20 min under nitrogen atmosphere. The reaction was quenched by addition of aq. sodium hydrogen carbonate and extracted with ethyl acetate (×2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Column chromatography (ethyl acetate–*n*-hexane 1 : 5) gave **12** (1.78 g, 94%) as a colourless oil; $[a]_D^{20}$ −26.1 (*c* 0.56, $CHCl_3$); ν_{max}/cm^{-1} 2955, 1709, 1449, 1371, 1252, 1103, 1096 and 1028; δ_H(200 MHz) 0.12 (9H, s), 0.95 (3H, d, *J* 6.3), 1.14 (3H, s), 1.15–1.90 (9H, m), 2.01–2.26 (2H, m), 2.63 (1H, ddd, *J* 13.8, 13.6 and 7.0) and 3.05 (1H, ddd, *J* 10.8, 9.8 and 5.1) (Found: C, 67.1; H, 10.3. Calc. for $C_{15}H_{28}O_2Si$: C, 67.1; H, 10.5%).

(2*S*,4a*S*,5*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,8a-trimethyl-6-(trimethylsiloxy)naphthalen-1(2*H*)-one 13 and (2*R*,4a*S*,5*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-2,5,8a-trimethyl-6-(trimethylsiloxy)naphthalen-1(2*H*)-one 14

To a stirred solution of diisopropylamine (0.76 cm^3, 5.8 mmol) in THF (15 cm^3) was added an *n*-hexane solution (1.57 M) of *n*-butyllithium (3.7 cm^3, 5.8 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 20 min the mixture was treated with a solution of decalone **12** (750 mg, 2.91 mmol) in THF (15 cm^3) at −78 °C and the solution was stirred at −20 °C for 20 min. MeI (0.50 cm^3, 8.03 mmol) was added at −78 °C and the reaction temperature was raised gradually from −78 to 0 °C over a period of 5 h. The reaction was quenched by addition of aq. ammonium chloride and extracted with ethyl acetate (×2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. MPLC purification (ethyl acetate–*n*-hexane 1 : 5) gave a diastereomeric mixture of decalones **13** and **14** (595 mg, 73%, ratio 1 : 1) as an oil along with recovered starting decalone **12** (53 mg, 7% recovery).

Compound **13** had ν_{max}/cm^{-1} 2965, 1709, 1454, 1261, 1217, 1126, 1076 and 1036; δ_H(200 MHz) 0.12 (9H, s), 0.92 (3H, d, *J* 6.4), 0.98 (3H, d, *J* 6.4), 1.14 (3H, s), 1.16–1.96 (9H, m), 2.09 (1H, m), 2.74 (1H, dqd, *J* 12.8, 6.4 and 6.4) and 3.05 (1H, m).

Compound **14** had ν_{max}/cm^{-1} 2973, 1702, 1455, 1378, 1035 and 993; δ_H(200 MHz) 0.12 (9H, s), 0.94 (3H, d, *J* 5.9), 1.04 (3H, d, *J* 6.6), 1.05 (3H, s), 1.10–2.10 (10H, m), 2.49 (1H, d × quint, *J* 12.6 and 6.4) and 3.06 (1H, m).

(2*R*,4a*S*,5*S*,6*S*,8a*S*)-(−)-3,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-2,5,8a-trimethylnaphthalen-1(2*H*)-one 15

To sodium hydride washed with *n*-hexane (60% in mineral oil; 251 mg, 6.29 mmol) was added anhydrous methanol (10 cm^3) at 0 °C under nitrogen atmosphere. A solution of decalones **13** and **14** (592 mg, 2.09 mmol) in methanol (10 cm^3) was added at 0 °C and the resulting solution was stirred at room temperature for 15.5 h. Reaction was quenched by addition of aq. ammonium chloride. After extraction with ethyl acetate (×2), the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent followed by column chromatography on silica gel (ethyl acetate–*n*-hexane 1 : 1) provided decalone **15** (434 mg, 98%) as crystals; $[a]_D^{20}$ −37.6 (*c* 0.94, $CHCl_3$); mp 75 °C; ν_{max}/cm^{-1} 3654, 2932, 1707, 1543, 1377 and 976; δ_H(200 MHz) 0.98 (3H, d, *J* 6.4), 1.01 (3H, d, *J* 6.4), 1.14 (3H, s), 0.80–1.95 (10H, m), 2.10 (1H, m), 2.75

(1H, d × quint, *J* 12.8 and 6.4) and 3.00–3.15 (1H, m) (Found: C, 73.8; H, 10.4. Calc. for $C_{13}H_{22}O_2$: C, 73.8; H, 10.5%).

(2*R*,4a*S*,5*S*,6*S*,8a*S*)-(−)-6-Acetoxy-3,4,4a,5,6,7,8,8a-octahydro-2,5,8a-trimethylnaphthalen-1(2*H*)-one 16

A solution of the alcohol **15** (255 mg, 1.21 mmol), 4-(dimethylamino)pyridine (DMAP) (18 mg, 0.147 mmol) and acetic anhydride (0.36 cm³, 3.82 mmol) in pyridine (5 cm³) was stirred at room temperature for 3.5 h. Water was added and stirring was continued for 2 h. After extraction with ethyl acetate (×2), the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography (ethyl acetate–*n*-hexane 1:2) provided acetate **16** (306 mg, 100%) as a colourless oil; $[\alpha]_D^{20}$ −5.43 (*c* 1.14, $CHCl_3$); mp 71–72 °C; ν_{max}/cm^{-1} 2974, 1936, 1711, 1552, 1454, 1242, 1110, 1028 and 990; δ_H(200 MHz) 0.87 (3H, d, *J* 6.4), 0.99 (3H, d, *J* 6.4), 1.16 (3H, s), 1.28–2.28 (10H, m), 2.06 (3H, s), 2.74 (1H, d × quint, *J* 12.8 and 6.4) and 4.35 (1H, m) (Found: C, 71.1; H, 9.65. Calc. for $C_{15}H_{24}O_3$: C, 71.4; H, 9.6%).

(1*S*,4*R*,7*S*,8*S*,9*S*)-(+)-9-Acetoxy-1,4,8-trimethyl-2-oxabicyclo[5.4.0]undecan-3-one 17 and (1*S*,4*R*,7*S*,8*S*,9*S*)-(+)-9-acetoxy-1,4,8-trimethyl-3-oxabicyclo[5.4.0]undecan-2-one 18

A mixture of the decalone **16** (64 mg, 0.25 mmol) and MCPBA (80%; 131 mg, 0.76 mmol) was stored at room temperature for 25 h under nitrogen atmosphere. The resulting mixture was dissolved in ethyl acetate and the organic layer was washed successively with aq. sodium hydrogen carbonate (×2), water and brine. After being dried over anhydrous Na_2SO_4, the organic layer was evaporated to dryness and MPLC purification of the residue (ethyl acetate–*n*-hexane 1:2) gave lactones **17** (39 mg, 58%) and **18** (19 mg, 27%) as crystals.

Compound **17** had $[\alpha]_D^{20}$ +3.92 (*c* 0.63, $CHCl_3$), mp 139 °C; ν_{max}/cm^{-1} 2936, 1732, 1385, 1359, 1240, 1201, 1115 and 1022; δ_H(200 MHz) 0.93 (3H, d, *J* 5.9), 1.20 (3H, d, *J* 6.7), 1.52 (3H, s), 1.30–2.20 (10H, m), 2.06 (3H, s), 2.58 (1H, m) and 4.46 (1H, m) (Found: C, 67.0; H, 9.1. Calc. for $C_{15}H_{24}O_4$: C, 67.1; H, 9.0%).

Compound **18** had $[\alpha]_D^{20}$ +4.03 (*c* 0.83, $CHCl_3$), mp 104–105 °C; ν_{max}/cm^{-1} 2936, 1738, 1451, 1380, 1238, 1107, 1022 and 974; δ_H(200 MHz) 0.93 (3H, d, *J* 5.9), 1.32 (3H, s), 1.33 (3H, d, *J* 6.2), 1.20–2.18 (10H, m), 2.06 (3H, s), 4.47 (1H, m) and 4.70 (1H, m).

Methyl (1′*S*,2*R*,2′*S*,6′*S*)-4-(2′-hydroxy-2′,6′-dimethyl-5′-oxocyclohexyl)-2-methylbutanoate 2

A solution of the lactone **17** (26 mg, 0.096 mmol) in THF (0.5 cm³) and 10% aq. sodium hydroxide (0.5 cm³) was stirred at room temperature for 12 h. The reaction was quenched by addition of dil. aq. hydrochloric acid. After extraction with ethyl acetate (×4), the combined organic layer was washed with brine (×2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided crude (1′*S*,2*R*,2′*S*,5′*S*,6′*S*)-4-(2′,5′-dihydroxy-2′,6′-dimethylcyclohexyl)-2-methylbutanoic acid **19** (27 mg).

To a stirred solution of the dihydroxy acid **19** (27 mg) in acetone (1 cm³) was added Jones reagent dropwise at 0 °C until the orange colour persisted. The reaction was quenched by addition of propan-2-ol. After extraction with ethyl acetate (×4), combined organic layer was washed with brine (×2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded unstable (1′*S*,2*R*,2′*S*,6′*S*)-4-(2′-hydroxy-2′,6′-dimethyl-5′-oxocyclohexyl)-2-methylbutanoic acid **1** (20 mg), δ_H(200 MHz) 0.8–1.95 (10H, m), 1.07 (3H, d, *J* 6.1), 1.15 (3H, s), 1.2 (3H, d, *J* 7), 1.97–2.9 (4H, m) and 3.19 (1H, ddd, *J* 10.4, 9.5 and 4.9).

A solution of the acid **1** (20 mg) in ethyl acetate was treated with an ethereal solution of diazomethane at 0 °C until the yellow colour persisted. Evaporation of diethyl ether followed by MPLC purification of the residue (ethyl acetate–*n*-hexane 10:1) provided ester **2** (13 mg, 52% from **17**) as a colourless oil, $[\alpha]_D^{23}$ −13.1 (*c* 0.26, $CHCl_3$) {natural product, $[\alpha]_D^{23}$ −14.3 (*c* 0.28, $CHCl_3$)}; ν_{max}/cm^{-1} 3491, 2937, 1728, 1712, 1462, 1331, 1169, 1138 and 1092; δ_H(500 MHz) 1.13 (3H, d, *J* 7), 1.17 (3H, d, *J* 7), 1.24 (1H, m), 1.36 (3H, s), 1.44 (1H, ddd, *J* 10.5, 6.5 and 3.5), 1.58 (1H, m), 1.65 (1H, m), 1.74 (1H, br s), 1.76 (1H, m), 1.82 (1H, ddd, *J* 13, 11.5 and 6.0), 2.0 (1H, ddd, *J* 13.0, 6.5 and 4.5), 2.16 (1H, dq, *J* 10.5 and 7.5), 2.36 (1H, ddd, *J* 15.0, 11.5 and 6.5), 2.45 (1H, qdd, *J* 7.0, 3.5 and 3.5), 2.47 (1H, ddd, *J* 15.0, 6.0 and 4.5) and 3.68 (3H, s); δ_C(125 MHz) 13.9 (q), 17 (q), 22.4 (q), 27.9 (t), 33.7 (t), 37.7 (t), 39.6 (t), 39.8 (d), 47.4 (d), 52.6 (q), 53.9 (d), 72.5 (s), 177.2 (s) and 212 (s).

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References

1 T. Hashimoto and Y. Asakawa, *Heterocycles*, 1998, **47**, 1067.
2 Y. Nagai and T. Kusumi, *Tetrahedron Lett.*, 1995, **36**, 1853.
3 H. Hagiwara, H. Nagatomo, S. Kazayama, H. Sakai, T. Hoshi, T. Suzuki and M. Ando, *J. Chem. Soc., Perkin Trans. 1*, 1999, 457.
4 H. Hagiwara and H. Uda, *J. Org. Chem.*, 1988, **53**, 2308.
5 W. S. Cheung and H. N. C. Wong, *Tetrahedron*, 1999, **55**, 11001.
6 F. W. J. Demnitz and R. A. Raphael, *Synthesis*, 1996, 1305.
7 H. Kotsuki, T. Araki and K. Arimura, Abstract of 74th annual meeting of Chemical Society of Japan, Kyoto (The Chemical Society of Japan, Tokyo), 1998, p. 746, 3C1 36.
8 F. Toda, M. Yagi and K. Kiyoshige, *J. Chem. Soc., Chem. Commun.*, 1988, 958.
9 V. A. Stout, M. A. Winnik and I. G. Csizmadia, *J. Am. Chem. Soc.*, 1974, **96**, 6388.
10 R. M. Goodman and Y. Kishi, *J. Am. Chem. Soc.*, 1998, **120**, 9392.
11 J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209.
12 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian 98, Revision A.6, Gaussian Inc., Pittsburgh, PA, USA, 1998.
13 M.-C. Pierre, A. Tenaglia and M. Santelli, *Tetrahedron*, 1998, **54**, 14803.