Total synthesis of a monocyclofarnesane norsesquiterpenoid isolated from mushroom ingested by beetle: utility of solid state Baeyer–Villiger oxidation

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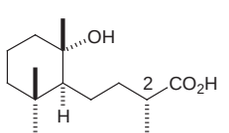
Norsesquiterpenoid **1** has been synthesised starting from (*S*)-(+)-Wieland–Miescher ketone analogue **3** *via* solid state Baeyer–Villiger oxidation as a key step.

Introduction

From the dry powders of the mushroom *Cryptoporus volvatus,* biotransformed by the beetle *Tibolium castaneum,* several novel metabolites have been isolated by Hashimoto and Asakawa,[1] whose relative stereostructures were determined by a combination of extensive 2D NMR studies. Among them, a norsesquiterpene hydroxy acid **1** which is thought to be one of the metabolites of cryptoporic acid **2** was isolated and its absolute stereostructure at C-2 was reported to be *R* as depicted in Fig. 1 by employing Kusumi's PGME (phenylglycine methyl ester) method.[2] We delineate herein the first total synthesis of **1**.

Results and discussion

One of the obvious synthetic routes to **1** is a Baeyer–Villiger oxidation of the decalone **11** (Scheme 1). Though optically active decalone **7** is known in the literature,[3] we took an alternative route from alcohol **4** derived from the optically active (*S*)-(+)-Wieland–Miescher ketone analogue **3**[4] (>95% ee). By employing Barton's radical protocol,[5] the hydroxy group at C-6 of alcohol **4** was removed to give ketal **6** in 92% yield followed by deprotection to give the decalone **7** {$[a]_D^{21}$ −42.2 (*c* 2.2, $CHCl_3$)}[3] in 95% yield. In order to ensure mono-methylation at C-2 of the decalone **7**, a methoxycarbonyl group was introduced to give **8**, which was followed by methylation to afford **9** and finally demethoxycarbonylation to give decalone **10**. However, overall yields of the reactions from decalones **7** to **10** were unsatisfactory. Fortunately, mono-methylation of **7** with an excess of LDA and methyl iodide furnished **10** as a 1:1 diastereomeric mixture in 97% yield. No dimethylation occurred



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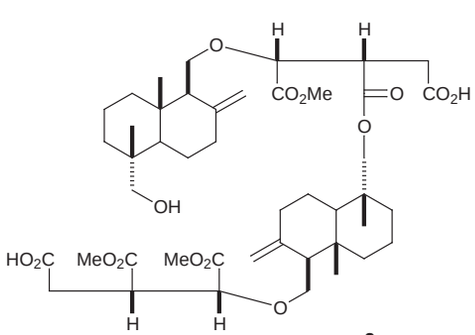

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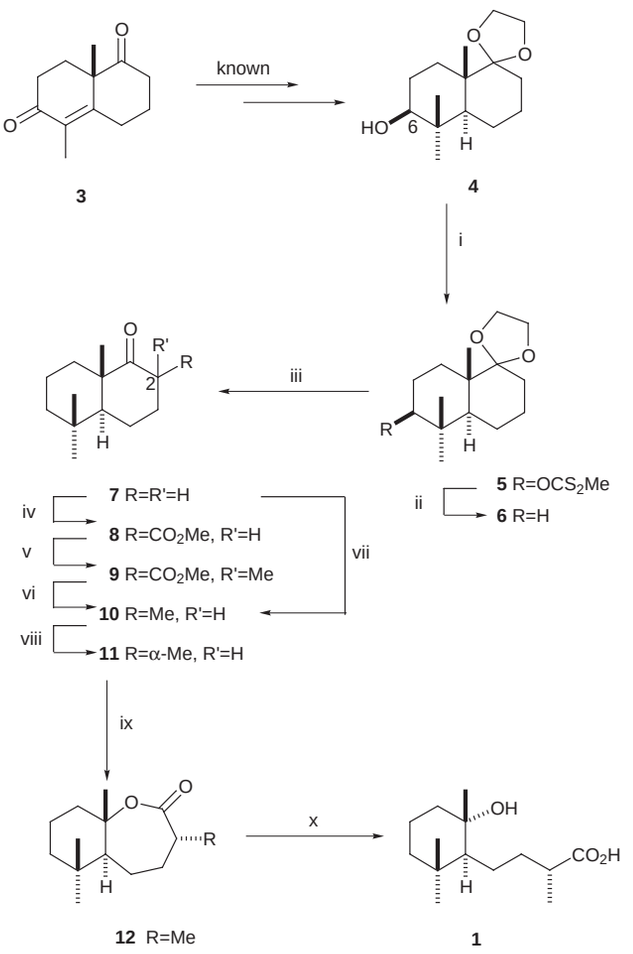
Fig. 1



Scheme 1 *Reagents and conditions*: i, *n*-BuLi, CS_2, MeI, 96%; ii, AIBN, *n*-Bu_3SnH, 92%; iii, PTSA, 95%; iv, NaH, $(MeO)_2CO$, HMPA, 43%; v, NaH, MeI, 50%; vi, NaCl, H_2O, HMPA, 46%; vii, LDA–THF, MeI, 97%; viii, NaOMe–HOMe, 95%; ix, MCPBA, solid state, 72%; x, aq. NaOH, 79%.

Table 1 Baeyer–Villiger oxidation of the decalone **11**

Entry	Reagent	Solvent	Reaction conditions	Yield (%)
1	MCPBA	CH_2Cl_2	Reflux, 26 h	17
2	MCPBA–BF_3·OEt_2	CH_2Cl_2	Reflux, 4.3 h	(18)[a]
3	MCPBA–Yb(OTf)$_3$	CH_2Cl_2	Reflux, 3.3 h	(12)[a]
4	CF_3CO_3H	CH_2Cl_2	−20 °C ~ rt, 3 days	(80)[a]
5	MCPBA	—	rt, 6 h then 60 °C, 12 h	72

[a] The decalone **11** was recovered.

under the reaction conditions employed. The methyl group at C-2 of the decalone **10** was isomerised in 95% yield by treatment with base into the thermodynamically more stable α-isomer **11** in which the orientation of the methyl group was apparent from the coupling patterns of the proton at C-2 (δ 2.68, ddq, J = 12.8, 6.4, 6.4 Hz). Under normal circumstances, sterically congested and less strained carbonyl groups are resistant to Baeyer–Villiger oxidation. In fact, Baeyer–Villiger oxidation of the decalone **11** by a conventional procedure afforded lactone **12** in low yield (Table 1, entry 1). In the presence of Lewis acid,[6] a small amount of lactone **12** was obtained (entry 2). Changing the Lewis acid to Yb(OTf)$_3$ resulted in the recovery of a small amount of the decalone **11** (entry 3). The method of Demnitz and Raphael[7] employing trifluoroperacetic acid, was not successful when applied to ketone **11** (entry 4). Hence, we then turned our attention to solid state Baeyer–Villiger oxidation[8] whose advantages have been underestimated in natural product synthesis. Solid state reaction of the decalone **7** provided lactone **13** in 90% yield at room temperature overnight. Encouraged by this success, the solid state Baeyer–Villiger oxidation of **11** was then investigated. While monitoring the progress of the solid state reaction by TLC, we observed the formation of a new reaction product which was supposed to be an adduct of decalone **11** with MCPBA, since it disappeared gradually with an increasing amount of the lactone **12**. In order to enhance rearrangement, the reaction mixture was heated to 60 °C to give lactone **12** in 72% yield (entry 5). Finally, alkaline hydrolysis of the lactone **12** furnished hydroxy acid **1** in 79% yield as a crystalline compound (mp 102–104 °C, natural product 103–104 °C). The spectral data were in complete agreement with those of the natural product **1** which indicates no epimerisation at C-2 during alkaline hydrolysis of the lactone **12**. On the basis of the sign and the value of the optical rotation reported for the natural product {$[a]_D^{21}$ −6.8 (c 0.6, $CHCl_3$)} and the one obtained for the synthetic compound {$[a]_D^{21}$ −7.9 (c 0.5, $CHCl_3$)}, the synthetic compound of absolute configuration 1′*S*, 2′*S*, 2*R* is identical to the natural product.

In summary, we have shown that this total synthesis unambiguously established the absolute stereostructure of the norsesquiterpenoid as depicted in formula **1**, thereby demonstrating the utility of the solid state Baeyer–Villiger oxidation in natural product synthesis.

Experimental

IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. ^{1}H-NMR spectra were obtained for solutions in deuteriochloroform with a Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. Mass spectral data were run on a JEOL SX-102A spectrometer. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for solutions in chloroform and are given in 10^{-1} deg cm^2 g^{-1}. 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 microanalytical laboratory of the Institute for Chemical Reaction Science, and the Instrumental Analysis Center for Chemistry, Tohoku University.

O-[(4a*S*,8a*S*)-5,5-Ethylenedioxydecahydro-1,1,4a-trimethylnaphthalen-2-yl] *S*-methyl dithiocarbonate 5

To a stirred solution of alcohol **4** (259 mg, 1.0 mmol) in THF (10 cm^3) was added an *n*-hexane solution of *n*-BuLi (1.3 cm^3, 2.0 mmol, 1.6 M) at 0 °C. After 5 min, carbon disulfide (0.306 cm^3, 5.1 mmol) was added. The solution was stirred for 1 h and then methyl iodide (0.317 cm^3, 5.1 mmol) was added. After being stirred for 1 h, the reaction was quenched by addition of sat. NH_4Cl. The organic layer was extracted with EtOAc (×2), washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (EtOAc–*n*-hexane = 1 : 20) of the residue provided **5** (335.4 mg, 96%) as orange crystals from *n*-hexane–EtOAc (mp 138–140 °C) (Found: C, 59.1; H, 7.9. $C_{17}H_{28}O_3S_2$ requires C, 59.3; H, 8.2%); $[a]_D^{23}$ +27.7 (c 0.32); ν_{max}/cm^{-1} 2953, 1227, 1065 and 1047; δ_H (200 MHz) 0.92 (s, 3H), 0.98 (s, 3H), 1.10 (s, 3H), 1.30–1.80 (m, 10H), 1.87–2.02 (m, 1H), 2.54 (s, 3H), 3.78–4.00 (m, 4H) and 5.36 (dd, 1H, J 11.4, 4.5 Hz).

(4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalen-1(2*H*)-one ethylene acetal 6

A solution of xanthate **5** (335.4 mg, 0.97 mmol), *n*-Bu_3SnH (0.525 cm^3, 1.95 mmol) and AIBN (16 mg, 0.097 mmol) in xylene (10 cm^3) was heated at 150 °C for 30 min. After cooling to room temperature, the solution was diluted with *n*-hexane and passed through a silica gel column to remove xylene. Evaporation of solvents followed by column chromatography (EtOAc–*n*-hexane = 1 : 20) of the residue provided ketal **6** (225.3 mg, 92%) as a colorless oil (Found: C, 75.3; H, 11.3. $C_{15}H_{26}O_2$ requires C, 75.6; H, 11%); ν_{max}/cm^{-1} 2951, 1132, 1117 and 1101; δ_H (200 MHz) 0.83 (s, 3H), 0.87 (s, 3H), 1.06 (s, 3H), 1.10–1.75 (m, 13H) and 3.80–3.98 (m, 4H); m/z 239 (M^+ + 1, 2.8%), 238 (17), 113 (7), 100 (10), 99 (100), 86 (14), 55 (6) and 41 (7).

(−)-(4a*S*,8a*S*)-5,5,8a-Trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one 7

A stirred solution of the ketal **6** (1.65 g, 6.9 mmol) and PTSA monohydrate (133 mg, 0.69 mmol) in acetone (70 cm^3) and water (14 cm^3) was refluxed for 1 h. The reaction was quenched by addition of sat. $NaHCO_3$ and extracted with EtOAc (×2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Column chromatography (EtOAc–*n*-hexane = 1 : 10) gave **7** (1.28 g, 95%) as a colorless oil (Found: C, 80.0; H, 11.3. $C_{13}H_{22}O$ requires C, 80.4; H, 11.4%); $[a]_D^{24}$ −42.2 (c 2.17);[3] ν_{max}/cm^{-1} 2936, 1709 and 1462; δ_H (200 MHz) 0.90 (s, 3H), 0.93 (s, 3H), 1.15 (s, 3H), 1.10–1.20 (m, 1H), 1.34–1.81 (m, 9H), 1.98–2.12 (m, 1H), 2.19 (ddd, 1H, J 13.8, 4.0, 2.0 Hz) and 2.59 (ddd, 1H, J 13.8, 13.7, 7.0 Hz); m/z (EI) 194 (M^+, 100%), 179 (72), 161 (51), 123 (78), 111 (50), 95 (65), 81 (51), 69 (52), 55 (56) and 41 (67).

Methyl (2ξ,4a*S*,8a*S*)-Decahydro-5,5,8a-trimethyl-1-oxonaphthalene-2-carboxylate 8

NaH (80 mg, 60%, 2.0 mmol) was washed with *n*-hexane three times. To a stirred slurry of NaH in THF (3 cm^3) was added the decalone **7** (97.2 mg, 0.5 mmol) in THF (2 cm^3), dimethyl carbonate (0.084 cm^3, 1.0 mmol) and HMPA (1.7 cm^3, 10 mmol) successively. After refluxing for 6 h, the reaction was quenched by addition of sat. NH_4Cl. The organic layer was extracted with EtOAc (×2), washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (EtOAc–*n*-hexane = 1 : 20) of the residue afforded ester **8** (53.6 mg, 43%) as a pale yellow oil (Found: C, 71.35; H, 9.5. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%); δ_H (200 MHz) 0.91 (s, 3H), 0.93 (s, 3H), 1.20 (s, 3H), 1.24 (dd, 1H, J 12.5, 3.0 Hz),

1.35–2.07 (m, 9H), 2.13–2.28 (m, 1H), 3.70 (dd, 1H, *J* 13.0, 6.5 Hz) and 3.74 (s, 3H).

Methyl (2ξ,4a*S*,8a*S*)-Decahydro-2,5,5,8a-tetramethyl-1-oxo-naphthalene-2-carboxylate 9

To a stirred slurry of NaH (57.3 mg, 60%, 1.4 mmol, washed with *n*-hexane) in THF (3 cm^3) was added the ester **8** (90.3 mg, 0.36 mmol) in THF (1 cm^3) at room temperature. Methyl iodide (0.111 cm^3, 1.8 mmol) was added and stirring was continued for 45 min. After addition of sat. NH_4Cl, the organic layer was extracted with EtOAc (×2), washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (EtOAc–*n*-hexane = 1 : 20) of the residue gave **9** (47.3 mg, 50%) as a colorless oil; ν_{max}/cm^{-1} 2951, 1740, 1715 and 1458; δ_H (200 MHz) 0.89 (s, 3H), 0.91 (s, 3H), 1.12 (s, 3H), 1.32 (s, 3H), 1.22–1.73 (m, 8H), 1.84–2.02 (m, 2H), 2.38 (dd, 1H, *J* 8.7, 8.7 Hz) and 3.70 (s, 3H); *m*/*z* (EI) 266 (M^+, 33%), 238 (14), 223 (16), 138 (31), 123 (100), 101 (54), 95 (27), 82 (33), 69 (24) and 41 (29).

(2ξ,4a*S*,8a*S*)-2,5,5,6a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1(2*H*)-one 10

Procedure 1. A solution of ester **9** (47.3 mg, 0.18 mmol) and sodium chloride (51.9 mg, 0.89 mmol) in HMPA (1 cm^3) and H_2O (0.016 cm^3, 0.89 mmol) was heated at 120 °C for 10 h. After addition of sat. NH_4Cl, the organic layer was extracted with EtOAc (×2), washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC purification (EtOAc–*n*-hexane = 1 : 40 to 1 : 20) of the residue afforded decalone **10** (17.0 mg, 46%) along with recovered starting ester **9** (11.3 mg, 24%).

Procedure 2. To a stirred solution of diisopropylamine (0.405 cm^3, 3.1 mmol) in THF (10 cm^3) was added an *n*-hexane solution (1.6 M) of *n*-BuLi (1.95 cm^3, 3.1 mmol) at 0 °C. After stirring for 45 min, a solution of decalone **7** (295.9 mg, 1.52 mmol) in THF (15 cm^3) at −78 °C was added and the solution was stirred for 35 min. Methyl iodide (0.5 cm^3, 8.03 mmol) was added and stirring was continued from −78 to 0 °C over 5 h. The reaction was quenched by addition of sat. NH_4Cl and extracted with EtOAc (×2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. MPLC purification (EtOAc–*n*-hexane = 1 : 10) gave a diastereomeric mixture of decalone **10** (306.8 mg, 97%) as a colorless oil; δ_H (200 MHz) 0.89 (s, 3H), 0.93 (s, 3H), 0.98 (d, 1.5H, *J* 6.5 Hz), 1.06 (d, 1.5H, *J* 6.8 Hz), 1.09 (s, 1.5H), 1.14 (s, 1.5H), 1.34–1.96 (m, 10.5H), 2.10 (dddd, 0.5H, *J* 13.0, 6.5, 3.2, 3.2 Hz), 2.46–2.59 (m, 0.5H) and 2.69 (qdd, 0.5H, *J* 13.0, 6.5, 6.5 Hz).

(−)-(2*R*,4a*S*,8a*S*)-2,5,5,6a-Tetramethyl-3,4,4a,5,6,7,8,8a-octa-hydronaphthalen-1(2*H*)-one 11

To sodium hydride washed with *n*-hexane (106.5 mg, 55%, 4.5 mmol) was added anhydrous MeOH (5 cm^3) at 0 °C under nitrogen atmosphere. A solution of decalone **10** (306.8 mg, 1.5 mmol) in MeOH (15 cm^3) was added and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched by addition of sat. NH_4Cl. 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 MPLC purification (EtOAc–*n*-hexane = 1 : 10) provided decalone **11** (293.3 mg, 95%) as a colorless oil (Found: C, 80.5; H, 11.7. $C_{14}H_{24}O$ requires C, 80.7; H, 11.6%); $[\alpha]_D^{24}$ −32.2 (*c* 0.774); ν_{max}/cm^{-1} 2939, 1709 and 1462; δ_H (200 MHz) 0.88 (s, 3H), 0.93 (s, 3H), 0.97 (d, 3H, *J* 6.4 Hz), 1.14 (s, 3H), 1.07–1.78 (m, 10H), 2.10 (dddd, 1H, *J* 13.0, 6.4, 3.2, 3.2 Hz) and 2.68 (ddq, 1H, *J* 12.8, 6.4, 6.4 Hz); *m*/*z* (EI) 208 (M^+, 100%), 193 (52), 150 (59), 123 (80), 109 (39), 95 (59), 81 (43), 69 (47) and 41 (50).

(−)-(1*S*,4*R*,7*S*)-1,4,8,8-Tetramethyl-2-oxabicyclo[5.4.0]-undecan-3-one 12

A mixture of the decalone **11** (40.8 mg, 196 μmol) and MCPBA (127 mg, 80%, 589 μmol) was left to stand at room temp. for 8 h and at 60 °C for 12 h. The resulting mixture was diluted with EtOAc and the organic layer was washed with sat. $NaHCO_3$ (×2), water and brine. Evaporation of the solvent followed by MPLC purification of the residue (EtOAc–*n*-hexane = 1 : 10) gave lactone **12** (31.5 mg, 72%) as a colorless oil (Found: C, 74.5; H, 10.6. $C_{14}H_{24}O_2$ requires C, 74.9; H, 10.8%); $[\alpha]_D^{21}$ −16.4 (*c* 0.425); $\nu_{max}(CHCl_3)/cm^{-1}$ 2944, 2872, 1703, 1462, 1383, 1219 and 1090; δ_H (200 MHz) 0.80 (s, 3H), 0.98 (s, 3H), 1.18 (d, 3H, *J* 6.7 Hz), 1.51 (s, 3H), 1.23–1.85 (m, 9H), 1.90–2.06 (m, 2H) and 2.61 (qdd, 1H, *J* 6.7, 2.1, 1.9 Hz); *m*/*z* (EI) 224 (M^+, 48%), 209 (75), 142 (100), 135 (42), 124 (37), 123 (48), 63 (41), 55 (42), 42 (37) and 41 (55).

(−)-(1′*S*,2′*S*,2*R*)-4-(2′-Hydroxy-2′,6′,6′-trimethylcyclohexyl)-2-methylbutanoic acid 1

A solution of the lactone **12** (18 mg, 80 μmol) in EtOH (2 cm^3) and 2 M aq. NaOH (0.4 cm^3) was stirred at room temperature for 7 h. The reaction was quenched by addition of 1 M aq. HCl. After extraction with EtOAc (×4), the combined organic layer was washed with sat. NaCl (×2) and dried over anhydrous Na_2SO_4. MPLC purification (EtOAc–*n*-hexane = 2 : 1 as an eluent) gave hydroxy acid **1** (15.4 mg, 79%) as crystals (from *n*-hexane); mp 102–104 °C (natural product, 103–104 °C); $[\alpha]_D^{21}$ −7.9 (*c* 0.5, $CHCl_3$) {natural product, $[\alpha]_D^{21}$ −6.8 (*c* 0.6, $CHCl_3$)}; ν_{max}/cm^{-1} 3407, 2936, 2762, 1707, 1462, 1236, 1167, 1103 and 912; δ_H (200 MHz) 0.80 (s, 3H), 0.93 (s, 3H), 1.17 (s, 3H), 1.21 (d, 3H, *J* 7.0 Hz), 1.10–2.05 (m, 12H), 2.47 (qt, 1H, *J* 7.0, 6.6 Hz) and 3.3–4.6 (m, 2H).

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