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The first enantiospecific synthesis of (−)-heritol: absolute configuration determination

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Abstract—The first enantiospecific synthesis of (−)-heritol, from naturally occurring (*R*)-(+)-citronellal and confirmation of its absolute configuration, is described.

Miles et al.[1] isolated an active toxin, called heritol (**1**), a naturally occurring sesquiterpene, from the sap of the mangrove plant *Heritiera littoralis*, which was shown to possess ichthytoxicity in ppm quantities to *Tilapia nilotica* fingerlings. Further in 1989, the same authors reported the isolation of a new natural pesticide, called heritonin (**2**) (the methyl ether derivative of heritol) from the same mangrove plant *H. littoralis*, which also possesses similar toxicity.[2] Both these compounds have a novel structure of the cadinane sesquiterpene class containing an α,β-unsaturated γ-lactone moiety with an unusual oxygenation pattern. The relative stereochemistry in heritol was established by single crystal X-ray analysis, but its absolute stereochemistry was only tentatively proposed to be *R* at C10 by comparison with other cadinanes.

To our knowledge, there have been only three reports on the synthesis of *racemic* heritol (**1**). The first synthesis reported by Irie et al.[3] employed an intramolecular Wittig–Horner reaction as the key step for the construction of the butenolide moiety. Our group reported the second synthesis, where dihydroxylation of a β,γ-unsaturated ester and one-pot elimination–lactonisation under basic conditions were the key steps.[4] Apart from these two syntheses, three other methods have been developed by us[5] for butenolide synthesis, during which a synthesis of heritonin (**2**) was achieved. The third and latest formal synthesis of heritol (**1**) was reported by Silveira et al.[6] in 2004, where a Lewis acid catalysed reaction of aryl acetic acids with allylsilanes provided 4-alkyl-β-tetralones, which were further elaborated to heritonin (**2**) and its C8 epimer.

As, (i) it has been suggested that heritol is a potential biocompatible pesticide, coupled with difficulties associated in the introduction of chirality at the nonfunctionalised benzylic position and (ii) the absolute configuration of heritol was not unambiguously confirmed, our interest in employing renewable resources from Nature for the synthesis of natural products led us to undertake the synthesis of optically pure heritol. We identified (*R*)-(+)-citronellal as the key synthon which is abundantly available both from plants and synthetically. We earlier accomplished syntheses of laevigatin,[7] herbertenol[8] and parvifoline[9] using the same starting material.

This letter describes the first enantiospecific synthesis of (−)-heritol and thus the unambiguous assignment of the absolute configuration of naturally occurring (+)-heritol.

As outlined in the retrosynthetic analysis (Scheme 1), our main target was to construct the tetralone unit **3** enantiospecifically followed by butenolide ring construction using the strategy developed by us.[5]

Accordingly, (*R*)-(+)-citronellal was converted to enone **5** (1:1 diastereomeric mixture) as reported in the literature.[10] Enone **5** was then treated with LDA at −78 °C and quenched at the same temperature with chlorotrimethylsilane to provide the kinetically favoured silyl enol ether, which on oxidation using *m*CPBA[11] gave

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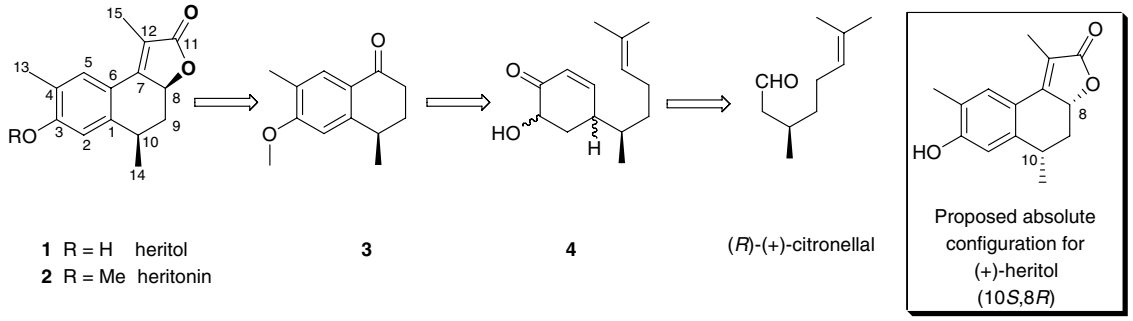
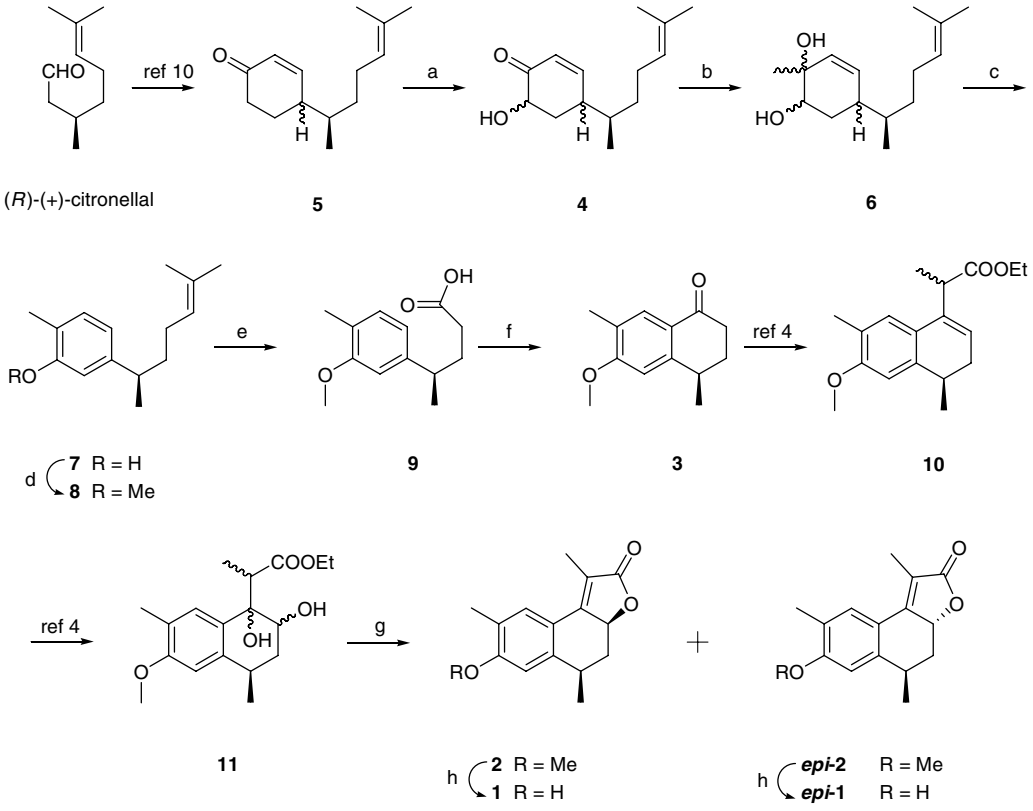


Scheme 1. Retrosynthetic analysis.

the corresponding trimethylsilyl ether of α-hydroxyenone **4**, which was then hydrolysed with dilute HCl to give α-hydroxyenone **4** in 70% overall yield. α-Hydroxy enone **4** was then subjected to 1,2-addition using MeMgI to give the corresponding diol **6** as a mixture of diastereomers in 95% yield. Both **4** and **6** were mixtures of diastereomers and as the newly generated chiral centres were to be destroyed in the next step, no attempt was made to isolate and/or determine the isomer ratios. The secondary hydroxyl group of diol **6** was oxidised under Swern conditions[12] followed by mesylation using methanesulfonyl chloride and triethylamine at reflux in CH_2Cl_2. Under these conditions, the tertiary hydroxyl group underwent elimination resulting in aromatisation of the cyclohexene unit to provide a mixture of the required phenol derivative **7** and the corresponding mesyl ester which was hydrolysed using KOH in methanol under reflux to give phenol intermediate **7** in 47% overall yield (Scheme 2).

Phenol **7** was then protected as the methyl ether using dimethyl sulfate and potassium carbonate under reflux to give **8** in 90% yield. The double bond in **8** was then removed using Weinreb's method[13] to provide acid **9** in 82% isolated yield. Acid **9** underwent smooth cyclisation on treatment with trifluoroacetic anhydride to furnish the key tetralone intermediate **3** in 80% isolated yield. Tetralone **3** was then converted to diol **11** (mixture



Scheme 2. Reagents and conditions: (a) (i) LDA, THF, −78 °C, 2 h, then TMSCl, −78 °C to rt, 5 h; (ii) *m*CPBA, CH_2Cl_2, 0 °C–rt, 5 h; (iii) HCl, CH_2Cl_2, overnight, 70% overall; (b) Mg, MeI, THF, 0 °C, then **4**, 0 °C–rt, overnight, 95%; (c) (i) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, then **6**, 30 min, Et_3N, −78 °C to rt, 5 h; (ii) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C–rt, 3 h, reflux, 4 h; (iii) KOH, methanol, reflux, 7 h, 47% overall; (d) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 90%; (e) OsO_4 (cat), Jones' reagent, acetone, rt, 7 h, 82%; (f) trifluoroacetic anhydride, trifluoroacetic acid, 0 °C, 3 h, 80%; (g) *p*TSA, benzene, reflux, 1 h, 90% overall and (h) $AlCl_3$, EtSH, CH_2Cl_2, rt, 12 h, 80%.

of diastereomers) via β,γ-unsaturated ester **10** using previously reported conditions in good yields.[4] Since, the stereochemistry at the newly incorporated chiral centres in **10** and **11** was to be destroyed in the next step during formation of the butenolide moiety, no attempt was made to identify the diastereomers. Butenolide ring construction was achieved using the protocol developed in our group,[5] according to which diol **11** was treated with *p*-toluenesulfonic acid in refluxing benzene to give a 3:2 diastereomeric mixture of heritonin (**2**) and its C8 epimer (***epi*-2**) in 90% overall yield. Both diastereomers were separated by repeated crystallisation.[4]

Accordingly, on crystallisation from petroleum ether, heritonin (**2**)[14] was first to crystallise as white needles (mp 115–116 °C), and from the remaining solution, *epi*-heritonin (***epi*-2**)[14] was purified by crystallisation using petroleum ether: ethyl acetate (9:1), as a white solid (mp 172–173 °C). Demethylation of (**2**) using ethanethiol–aluminium chloride gave pure heritol (**1**)[14] without any epimerisation at C8 in 80% yield. Epi-heritol (***epi*-1**)[14] was also synthesised similarly in 80% yield. The synthetic heritol (**1**) showed a specific rotation $[\alpha]_D^{25}$ −240.5 (*c* 0.18, $CHCl_3$), which was opposite in sign to that of naturally isolated **1** {$[\alpha]_D^{25}$ +261, no solvent or concentration were reported}.[1] Assuming that the solvent was $CHCl_3$, naturally isolated (+)-heritol should have (*S*,*R*) configuration at C10 and C8, respectively.

Thus, (−)-heritol (**1**) has been synthesised enantiospecifically for the first time from naturally occurring (*R*)-(+)-citronellal and the absolute configuration of natural heritol proposed to be (*S*,*R*) at C10, C8 by comparison of the specific rotation with that of synthetic **1**.

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14. Spectral data: Compound (**7**): Specific rotation: $[\alpha]_D^{25}$ −37.91 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3411, 1621, 1589. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.19 (d, $J = 7.0$ Hz, 3H); 1.52–1.66 (m, 2H); 1.52 (s, 3H); 1.66 (s, 3H); 1.80–1.91 (m, 2H); 2.20 (s, 3H); 2.50–2.67 (m, 1H); 5.05 (m, 1H); 6.56–6.65 (m, 2H); 6.98 (d, $J = 7.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.5 (CH_3); 17.8 (CH_3); 22.5 (CH_3); 25.8 (CH_3); 26.2 (CH_2); 38.5 (CH_2); 39.1 (CH); 113.6 (CH); 119.4 (CH); 120.9 (C); 124.8 (CH); 130.8 (CH); 131.2 (C); 147.0 (C); 153.7 (C). MS-ESI *m*/*z*: 218 $(M)^+$. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.29; H, 10.35. Compound (**9**): Specific rotation: $[\alpha]_D^{25}$ −26.11 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2961 (br), 1708, 1612. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.27 (d, $J = 7.0$ Hz, 3H); 1.82–1.96 (m, 2H); 2.17 (s, 3H); 2.17–2.27 (m, 2H); 2.60–2.78 (m, 1H); 3.82 (s, 3H); 6.62–6.69 (m, 2H); 7.03 (d, $J = 7.5$ Hz, 1H); 8.9 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.9 (CH_3); 22.4 (CH_3); 32.3 (CH_2); 33.0 (CH_2); 39.4 (CH); 55.2 (CH_3); 108.8 (CH); 118.6 (CH); 124.4 (C); 130.6 (CH); 144.9 (C); 157.8 (C); 179.9 (C). MS-ESI *m*/*z*: 221 $(M-1)^+$. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.44; H, 8.33. Compound (**3**): mp 110 °C. Specific rotation: $[\alpha]_D^{25}$ +26.87 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 1670, 1607, 1570. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.38 (d, $J = 7.0$ Hz, 3H); 1.79–1.95 (m, 1H); 2.18 (s, 3H); 2.21–2.30 (m, 1H); 2.43–2.79 (m, 2H); 2.94–3.07 (m, 1H); 3.88 (s, 3H); 6.63 (s, 1H); 7.79 (d, $J = 0.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.8 (CH_3); 20.8 (CH_3); 30.8 (CH_2); 33.1 (CH); 35.8 (CH_2); 55.3 (CH_3); 107.4 (CH); 124.9 (C); 125.4 (C); 129.7 (CH); 149.2 (C); 162.1 (C); 196.8 (C). MS-ESI *m*/*z*: 205 $(M+1)^+$. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.11; H, 8.18. Compound (**2**): mp 115–116 °C. Specific rotation: $[\alpha]_D^{25}$ −312.97 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3019, 1738, 1654, 1613. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.43 (d, $J = 6.7$ Hz, 3H); 1.36–1.64 (m, 1H); 2.11 (d, $J = 1.6$ Hz, 3H); 2.23 (s, 3H); 2.56–2.67 (m, 1H); 3.02–3.21 (m, 1H); 3.87 (s, 3H); 4.90 (ddq, $J = 12.9$, 4.8, 1.6 Hz, 1H); 6.84 (s, 1H); 7.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 9.8 (CH_3); 15.9 (CH_3); 21.7 (CH_3); 31.9 (CH); 38.6 (CH_2); 55.3 (CH_3); 78.1 (CH); 108.3 (CH); 115.8 (C); 120.6 (C); 125.6 (C); 129.5 (CH); 142.2 (C); 156.7 (C); 159.5 (C); 175.5 (C). Compound (***epi*-2**): mp 172–173 °C. Specific rotation: $[\alpha]_D^{25}$ +397.03 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 2962, 1744, 1651, 1612. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.41 (d, $J = 7.5$ Hz, 3H); 1.79–1.95 (m, 1H); 2.10 (d, $J = 1.6$ Hz, 3H); 2.22 (s, 3H); 2.38 (ddd, $J = 12.0$, 4.8, 1.5 Hz, 1H); 3.21–3.35 (m, 1H); 3.86 (s, 3H); 5.07 (ddq, $J = 13.1$, 4.6, 1.6 Hz, 1H); 6.64 (s, 1H); 7.37 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 10.0 (CH_3); 16.1 (CH_3); 24.0 (CH_3); 33.3 (CH); 36.5 (CH_2); 55.3 (CH_3); 75.4 (CH); 110.1 (CH); 116.7 (C); 120.2 (C);

125.8 (C); 129.7 (CH); 142.7 (C); 156.1 (C); 159.5 (C); 175.2 (C). Compound (**1**): mp 270 °C. Specific rotation: $[\alpha]_D^{25}$ −240.5 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3259, 3020, 2926, 2401, 1713, 1646, 1611, 1581. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (d, $J = 6.8$ Hz, 3H); 1.43–1.46 (m, 1H); 2.12 (d, $J = 1.5$ Hz, 3H); 2.28 (s, 3H); 2.57–2.63 (m, 1H); 3.01–3.13 (m, 1H); 4.88 (ddq, $J = 12.8$, 4.8, 1.8 Hz, 1H); 5.20 (s, 1H); 6.82 (s, 1H); 7.40 (s, 1H). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.51; H, 6.38. Compound (***epi*-1**): mp 275 °C. Specific rotation: $[\alpha]_D^{25}$ +321.8 (*c* 0.17 Hz, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3257, 3020, 1704, 1643, 1611, 1582. ^1H NMR($CDCl_3$, 400 MHz): δ 1.39 (d, $J = 7.3$ Hz, 3H); 1.83–1.90 (m, 1H); 2.11 (d, $J = 1.5$ Hz, 3H); 2.27 (s, 3H); 2.35–2.40 (m, 1H); 3.20–3.27 (m, 1H); 5.00 (ddq, $J = 13.1$, 4.5, 1.5 Hz, 1H); 5.33 (s, 1H); 6.66 (s, 1H); 7.38 (s, 1H). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.59; H, 6.48.