The First Total Synthesis of the Antimicrobial Sesquiterpenes (±)-Enokipodins A and B

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Abstract: Efficient first total synthesis of antimicrobial sesquiterpenes enokipodins A and B (**1** and **2**, respectively) and formal total synthesis of cuparene-1,4-diol (**5**) and cuparene-1,4-quinone (**7**) have been accomplished starting from 2,5-dimethoxy-4-methylacetophenone employing Claisen rearrangement and ring-closing metathesis reaction as key steps.

Key words: sesquiterpenes, enokipodins A and B, ring-closing metathesis, Claisen rearrangement

Flammulina velutipes (Curt.: Fr.) Sing. (Enokitake in Japanese) is a fresh edible mushroom frequently consumed in Japan. The natural compounds isolated (proteins, polysaccharides, glycolproteins, etc.) from the body of *F. velutipes* are known to have potent antitumor and immunomodulatory activities.[1] Recently, Takahashi and co-workers have reported[2] the bioassay guided isolation of four new sesquiterpenes enokipodins A–D (**1**–**4**) (Figure 1) from the mycelial culture medium of *F. velutipes*. Enokipodins A–D (**1**–**4**) exhibited significant antimicrobial activity against a fungus *Cladosporium herbarum*, and Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*. Structurally, enokipodins A–D (**1**–**4**) are related to the less oxidised sesquiterpenes cuparene-1,4-diol (**5**) isolated[3] from the Japanese liverwort *Lejeunea aquatica*, HM-1 **6** isolated[4] from phytopathogenic fungus *Helicobasidium mompa* and the cuparene-1,4-quinone **7** (Figure 1) isolated[5] from the liverwort *Radula javanica*, and more oxidised pigments lagopodins and helicobasidins.[6] The cuparenoid sesquiterpenes pose significant challenge because of the difficulty associated in the generation of two adjacent quaternary carbon atoms in a cyclopentane ring and the regiochemical incorporation of polysubstituted aromatic ring. Despite the reported significant microbial activity, there is no report on the synthesis of enokipodins **1**–**4**. Very recently, Mukherjee and co-workers reported the first total synthesis of HM-1 methyl ether, cuparene-1,4-diol (**5**) and cuparene-1,4-quinone (**7**).[7] The interesting biological properties associated with the enokipodins prompted us to develop a methodology for the synthesis of these sesquiterpenes. Herein, we report the first total synthesis of (±)-enokipodins A and B (**1** and **2**, respectively) along with a formal total synthesis of cuparene-1,4-diol (**5**) and cuparene-1,4-quinone (**7**).

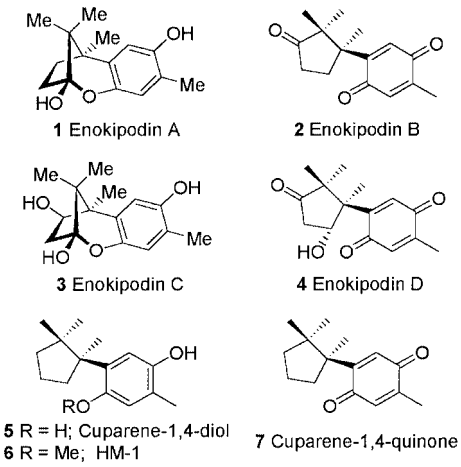
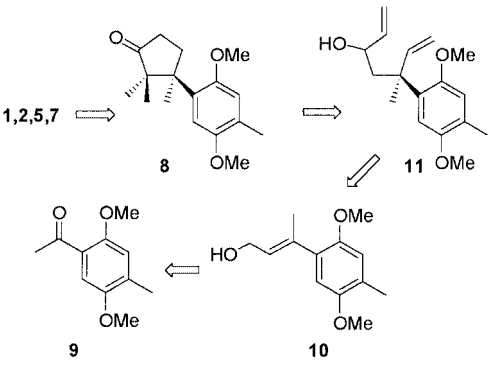


Figure 1



Scheme 1

As the enokipodin A (**1**) is a hemiketal, the cyclopentanone **8** was identified as an ideal precursor for the generation of the enokipodins A and B (**1** and **2**, respectively) as well cuparenediol **5** and quinone **7** (Scheme 1). A combination of Claisen rearrangement and ring closing metathesis (RCM)[8] reaction based strategy was envisaged for the synthesis of **8** starting from 2,5-dimethoxy-4-methylacetophenone (**9**) (readily available by Friedel–Crafts acylation of 2,5-dimethoxytoluene)[9] via the cinnamyl alcohol **10** and the dienol **11**. The synthetic sequence is depicted in Scheme 2. Thus, Horner–Wadsworth–Emmons reaction of the acetophenone **9** with triethyl phosphonoacetate and NaH generated the cinnamate **12**, which on regioselective reduction with $LiAlH_4$ in Et_2O at low temperature furnished the allyl alcohol **10**. A one-pot Claisen rearrangement[10] of the allyl alcohol **10** with ethyl vinyl

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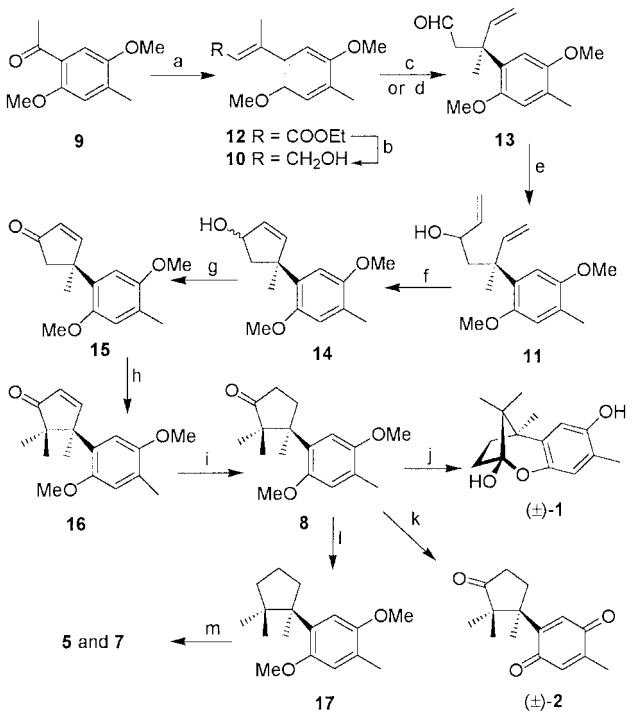
ether in the presence of mercuric acetate in a sealed tube at 175 °C furnished γ,δ-unsaturated aldehyde **13**. Alternatively, the aldehyde **13** was also prepared via the Johnson's orthoester variant of Claisen rearrangement of the cinnamyl alcohol **10** employing triethyl orthoacetate and propionic acid in a sealed tube at 180 °C followed by conversion of the resultant ester into the aldehyde **13** by $LiAlH_4$ reduction and PCC oxidation strategy. Grignard reaction of the aldehyde **13** with vinylmagnesium bromide furnished a 1:1 diastereomeric mixture of the key intermediate dienol **11**. RCM reaction of the diastereomeric mixture of the dienol **11** with 5 mol% of Grubbs' first generation catalyst furnished a 1:1 diastereomeric mixture of the cyclopentenol **14** in near quantitative yield, which on oxidation with pyridinium chlorochromate (PCC) and NaOAc generated the cyclopentenone **15**. One-step dialkylation of the enone **15** with NaH and MeI created the second quaternary carbon and generated the enone **16**, which on hydrogenation with 5% palladium over carbon as the catalyst at one atmosphere pressure of hydrogen (balloon) furnished the cyclopentanone **8**. Finally, demethylation of **8** with BBr_3 furnished directly the enokipodin A **1** (mp 135–136 °C; lit.[2] 138.5–138.9 °C). On the other hand, direct oxidation of the dimethyl ether **8** with ceric ammonium nitrate (CAN) in aqueous MeCN furnished enokipodin B **2** in a near quantitative yield. Huang–Minlon modified Wolff–Kishner reduction of the cyclopentanone **8** with hydrazine hydrate KOH in digol furnished the HM-1 methyl ether **17**, whose conversion to cuparene-1,4-diol (**5**) and cuparene-1,4-quinone (**7**) has already been reported.[7] The synthetic enokipodins A and B have exhibited spectral data (IR, ^1H and ^{13}C NMR and mass) identical to those of natural products.[2]

In conclusion, we have developed the first total synthesis of (±)-enokipodins A and B employing a combination of Claisen rearrangement and RCM reactions as key steps. Starting from the readily available acetophenone **9**, enokipodin A and enokipodin B were obtained in 9 steps in 20.0% and 24.4% overall yields, respectively. In addition, a formal total synthesis of cuparene-1,4-diol (**5**) and cuparene-1,4-quinone (**7**) has also been accomplished. Currently, we are investigating the synthesis of optically active enokipodins and their higher oxidised analogues logopodins and helicobasidins for evaluating their biological potential.



Scheme 2 *Reagents, conditions and yields*: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, reflux, 5 h, 88%; (b) $LiAlH_4$, Et_2O, –70 °C to r.t., 2 h, 91%; (c) CH_2=CHOEt, $Hg(OAc)_2$, sealed tube, 100 °C, 10 h; 175 °C, 48 h, 63%; (d) i. $CH_3C(OEt)_3$, EtCOOH, sealed tube, 180 °C, 48 h, 70%; ii. LAH, Et_2O, –40 °C to r.t., 2 h, 92%; iii. PCC-silica gel, CH_2Cl_2, r.t., 1 h, 87%; (e) CH_2=CHMgBr, THF, r.t., 1 h, 88%; (f) 5 mol% $PhCH{=}Ru(Cl)_2(PCy_3)_2$, CH_2Cl_2, r.t., 4 h, 95%; (g) PCC, NaOAc, CH_2Cl_2, r.t., 1 h, 86%; (h) NaH, THF–DMF, MeI, r.t., 12 h, 77%; (i) H_2, 5% Pd/C, EtOH, 1 h, 92%; (j) BBr_3, CH_2Cl_2, 0 °C to r.t., 4 h, 78%; (k) CAN, CH_3CN–H_2O, r.t., 1 h, 95%; (l) $NH_2NH_2.H_2O$, digol, 120 °C, 3 h; KOH, digol, 190 °C, 12 h, 75%; (m) ref:[7]

Yields refer to isolated and chromatographically pure compounds. All compounds exhibited spectral data (IR, ^1H and ^{13}C NMR and Mass) consistent with the structures. Selected spectral data for the enone **15**: IR (neat): 1714 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4): δ = 7.70 (d, *J* = 6.9 Hz, 1 H, H-3), 6.63 (s, 1 H, Ar-H), 6.56 (s, 1 H, Ar-H), 6.09 (d, *J* = 6.9 Hz, 1 H, H-2), 3.75 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 2.70, 2.50 (AB q, *J* = 18.6 Hz, 2 H, CH_2CO), 2.15 (s, 3 H, Ar-CH_3), 1.54 (s, 3 H, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4): δ = 208.7 (C, C=O), 169.8 (CH, C-3), 151.3 (C), 151.1 (C), 131.3 (CH, C-2), 131.0 (C), 125.8 (C), 114.8 (CH, C-6′), 109.6 (CH, C-3′), 55.9 (CH_3, OCH_3), 55.5 (CH_3, OCH_3), 50.3 (CH_2, C-5), 47.1 (C, C-4), 27.6 (CH_3, *tert*-CH_3), 16.1 (CH_3, Ar-CH_3). MS: *m*/*z* (%) = 246 (96) [M^+], 231 (100), 216 (16), 203 (15), 188 (14), 173 (15), 128 (12), 115 (19), 91 (18). HRMS: *m*/*z* [M + 1] calcd for $C_{15}H_{19}O_3$: 247.1334; found: 247.1337. For the enone **16**: IR (neat): 1707, 1600, 1505, 1393, 1375, 1213, 1044, 861, 834, 789 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4): δ = 7.84 (d, *J* = 6.0 Hz, 1 H, H-3), 6.66 (s, 1 H, Ar-H), 6.45 (s, 1 H, Ar-H), 6.10 (d, *J* = 6.0 Hz, 1 H, H-2), 3.78 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.19 (s, 3 H, Ar-CH_3), 1.48 (s, 3 H, *tert*-CH_3), 1.24 (s, 3 H, *tert*-CH_3), 0.65 (s, 3 H, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4): δ = 214.2 (C, C=O), 170.2 (CH, C-3), 151.6 (C), 151.5 (C), 129.8 (C), 127.0 (CH, C-2), 125.8 (C), 114.6 (CH, C-6′), 111.2 (CH, C-3′), 56.0 (CH_3, OCH_3), 55.4 (CH_3, OCH_3), 54.8 (C, C-5), 50.9 (C, C-4), 25.8 (CH_3), 20.1 (CH_3), 16.2 (2 C, CH_3). MS: *m*/*z* (%) = 274 (42) [M^+], 260 (17), 259 (100), 244 (13), 229 (12), 216 (10). HRMS: *m*/*z* [M + Na] calcd for $C_{17}H_{22}O_3Na$: 297.1467; found: 297.1466. For the cyclopentanone **8**: IR (neat): 1735, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4): δ = 6.78 (s, 1 H, Ar-H), 6.62 (s, 1 H, Ar-H), 3.78 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 2.65–2.30 (m, 3 H), 2.18 (s, 3 H, Ar-CH_3), 2.15–1.90 (m, 1 H), 1.37 (s, 3 H, *tert*-CH_3), 1.20 (s, 3 H, *tert*-CH_3), 0.67 (s, 3 H, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4): δ = 221.4 (C, C=O), 151.9 (C), 151.4 (C), 132.5 (C), 125.2 (C), 114.4 (CH, C-6′), 111.2 (CH, C-3′), 56.0 (CH_3, OCH_3), 54.8 (CH_3, OCH_3), 52.7 (C), 48.9 (C), 34.3 (CH_2), 32.7 (CH_2), 23.7 (CH_3), 21.9 (CH_3), 21.7 (CH_3), 16.0 (CH_3). MS: *m*/*z* (%) = 276 (92) [M^+], 261 (28), 227 (16), 205 (100), 192 (27), 177 (32), 175 (24), 174 (22), 149 (24), 105 (15), 91 (28). HRMS: *m*/*z* [M + 1] calcd for $C_{17}H_{25}O_3$: 277.1803; found: 277.1803. For enokipodin A (±)-**1**: IR (neat): 3390, 1288, 1194, 1146, 1036, 992, 943, 905 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–

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CCl_4): δ = 6.54 (s, 1 H, Ar-H), 6.50 (s, 1 H, Ar-H), 4.34 (s, 1 H, OH), 2.77 (s, 1 H, OH), 2.17 (s, 3 H, Ar-CH_3), 2.25–2.00 (m, 2 H), 1.87 (ddd, *J* = 12.3, 11.1, 6.9 Hz, 1 H), 1.76 (ddd, *J* = 12.3, 9.6, 3.3 Hz, 1 H), 1.23 (s, 3 H, *tert*-CH_3), 1.09 (s, 3 H, *tert*-CH_3), 0.80 (s, 3 H, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4): δ = 147.5 (C), 146.1 (C), 131.1 (C), 122.4 (C), 116.9 (CH, C-5), 111.0 (CH, C-2), 109.6 (C, HO-C-O), 47.3 (C), 43.3 (C), 38.2 (CH_2), 34.8 (CH_2), 18.5 (CH_3), 16.0 (CH_3), 15.5 (2 × C, CH_3). MS: *m*/*z* (%) = 248 (37) [M^+], 178 (9), 177 (100), 162 (32), 149 (67). HRMS: *m*/*z* calcd [M + Na] for $C_{15}H_{20}O_3Na$: 271.1310; found: 271.1307. For enokipodin B (±)-**2**: IR (neat): 1732, 1650, 1346, 1251, 1066, 998, 932, 842 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CCl_4): δ = 6.66 (s, 1 H, H-5), 6.55 (q, *J* = 1.5 Hz, 1 H, H-2), 2.55–2.20 (m, 3 H), 2.04 (d, *J* = 1.5 Hz, 3 H, *olefinic*-CH_3), 1.87 (ddd, *J* = 12.7, 8.0, 3.0 Hz, 1 H), 1.32 (s, 3 H, *tert*-CH_3), 1.22 (s, 3 H, *tert*-CH_3), 0.75 (s, 3 H, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4): δ = 219.9 (C, C=O), 187.8 (C, C=O), 187.5 (C, C=O), 153.5 (C), 144.4 (C), 135.3 (CH), 134.1 (CH), 52.3 (C), 49.0 (C), 33.7 (CH_2), 31.2 (CH_2), 23.2 (CH_3), 22.3 (CH_3), 20.6 (CH_3), 15.0 (CH_3). MS: *m*/*z* (%) = 246 (3) [M^+], 218 (20), 203 (12), 190 (47), 175 (100), 161 (21), 147 (16). HRMS: *m*/*z* [M + Na] calcd for $C_{15}H_{18}O_3Na$: 269.1154; found: 269.1166. For HM-1 methyl ether **17**: IR (neat): 1504, 1389, 1372, 1260, 1212, 1181, 1048, 861, 808, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CCl_4): δ = 6.77 (s, 1 H, Ar-H), 6.60 (s, 1 H, Ar-H), 3.77 (s, 3 H, Ar-OCH_3), 3.73 (s, 3 H, Ar-OCH_3), 2.55–2.40 (m, 1 H), 2.17 (s, 3 H, Ar-CH_3), 1.85–1.50 (m, 5 H), 1.34 (s, 3 H, *tert*-CH_3), 1.14 (s, 3 H, *tert*-CH_3), 0.70 (s, 3 H, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4): δ = 152.6 (C), 151.1 (C), 133.9 (C), 124.4 (C), 115.0 (CH, C-6′), 112.1 (CH, C-3′), 56.0 (CH_3, OCH_3), 55.5 (CH_3, OCH_3), 51.4 (C), 44.6 (C), 41.9 (CH_2), 40.0 (CH_2), 27.6 (CH_3), 26.0 (CH_3), 23.4 (CH_3), 20.8 (CH_2), 16.0 (CH_3, Ar-CH_3). MS: *m*/*z* = 262 (91) [M^+], 248 (15), 205 (21), 192 (45), 191 (23), 179 (100), 177 (30), 165 (33), 152 (32), 149 (26).

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