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The first total synthesis of (±)-lagopodin A

A. Srikrishna,* B. Vasantha Lakshmi and P. C. Ravikumar

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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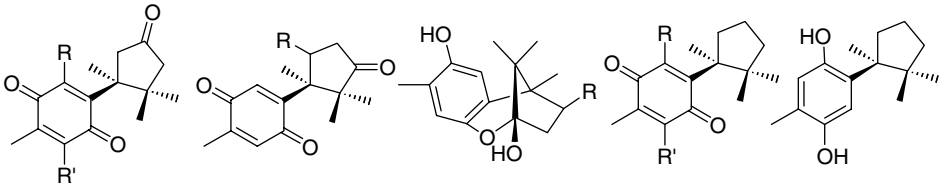
Abstract—The first total synthesis of (±)-lagopodin A and a formal total synthesis of enokipodins A and B is described. The requisite precursors containing two vicinal quaternary carbon atoms were assembled employing Claisen rearrangement and an RCM reaction as key steps starting from 2,5-dimethoxy-4-methylacetophenone.

Fungal sesquiterpenes, lagopodins **1a**–**c** were isolated from the cultures of the basidomycete *Coprinus macrorhizus* var. *microsporus* and *C. lagopus*.[1] Recently, Takahashi and co-workers reported[2] bioassay guided isolation of four new sesquiterpenes, enokipodins A and C **2a**,**b** and B and D **3a**,**b** from the mycelial culture of *Flammulina velutipes*. Structurally, lagopodins and enokipodins A–D are related to cuparene-1,4-quinone



4a, isolated[3] from the liverwort *Radula javanica*, cuparene-1,4-diol **5**, isolated[4] from the Japanese liverwort *Lejeunea aquatica*, and the more oxidized pigments helicobasidins **4b**,**c**, isolated from *Helicobasidium mompa*.[5] Enokipodins A–D exhibited significant antimicrobial activity against the fungus *Cladosporium herbarum* and the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*. Lagopodins and enokipodins are interesting synthetic targets because of the presence of a sterically congested 1-aryl-1,2,2-trimethylcyclopentane moiety, in addition to their potential biological properties. However, there is no report on the synthesis of lagopodins[6] **1** and only two approaches[7] have appeared in the literature on the synthesis of enokipodins **2** and **3**. Herein, we report the first total synthesis of (±)-lagopodin A **1a** and a formal total synthesis of enokipodins A and B **2a** and **3a**.

The retrosynthetic analysis is depicted in Scheme 1. It was readily identified that hydroboration and oxidation of arylcyclopentene **6** would lead to lagopodin A **1a**. It was conceived that cyclopentene **6** could be obtained from cyclopentene carboxylate **7**.

The cyclopentene ester **7**, which was employed as a key intermediate in the total synthesis of the cuparenoids HM-1 and HM-2, could readily be obtained[8] from acetophenone **8** employing a combination of orthoester Claisen rearrangement[9] and ring-closing metathesis[10] (RCM) as key steps.

To begin, acetophenone **8** was converted into cyclopentene carboxylate **7** in six steps in 50% overall yield (Scheme 2). Thus, Horner–Wadsworth–Emmons reaction of acetophenone **8** followed by regioselective

* Corresponding author. Tel.: +91 80 22932215; fax: +91 80 23600529; e-mail: ask@orgchem.iisc.ernet.in

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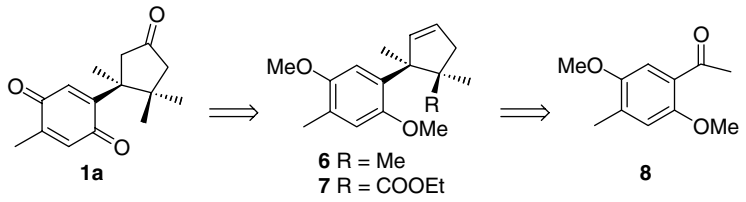
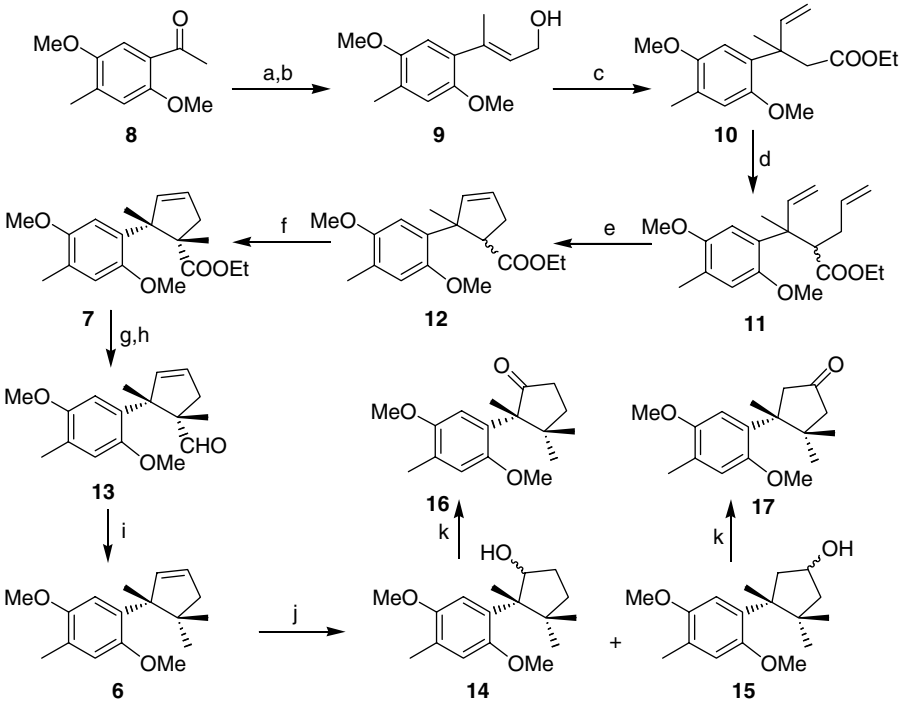
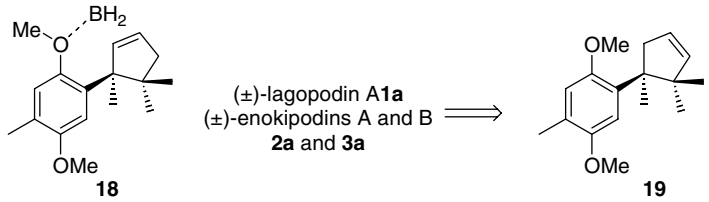


Scheme 1.



Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, rt, 8 h, 100%; (b) LAH, Et_2O, −50 °C, 1 h, 95%; (c) $CH_3C(OEt)_3$, EtCOOH, sealed tube, 180 °C, 48 h, 78%; (d) LDA, THF, allyl bromide, −70 °C→rt, 8 h, 80%; (e) $Cl_2Ru(PCy_3)_2$=CHPh (5 mol %), CH_2Cl_2, rt, 5 h, 100%; (f) LDA, THF, HMPA, MeI, −30 °C→rt, 12 h, 85%; (g) LAH, Et_2O, 0 °C→rt, 2 h, 96%; (h) PCC, silica gel, CH_2Cl_2, rt, 0.5 h, 90%; (i) $N_2H_4{\cdot}H_2O$, KOH, digol, 120→160 °C, 10 h, 73%; (j) $BH_3{\cdot}Me_2S$, hexane, 0 °C→rt, 1 h; 3 N NaOH, 30% H_2O_2, 0 °C→rt, 5 h; 100%; **14/15** 3:1; (k) PCC, silica gel, CH_2Cl_2, rt, 2 h, 95%.



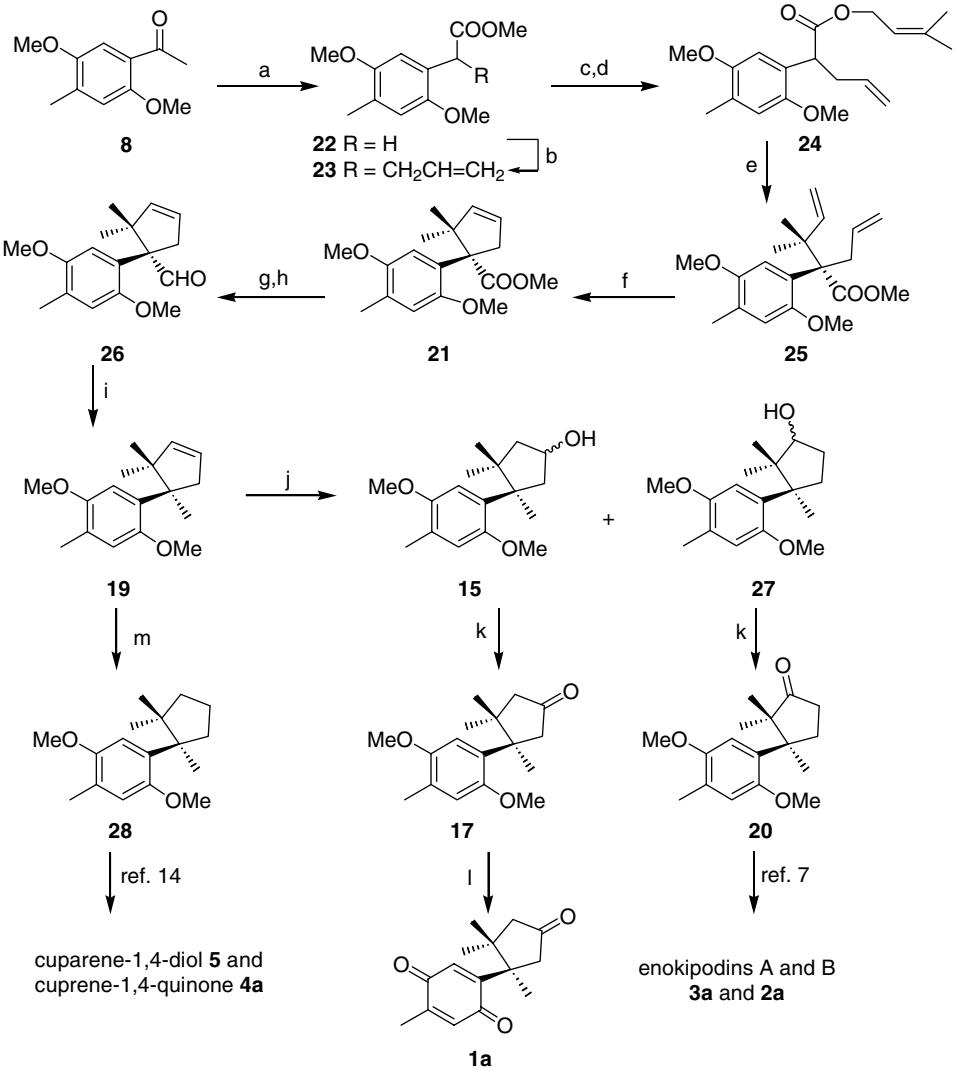
1,2-reduction of the resultant cinnamate with lithium aluminium hydride (LAH) generated cinnamyl alcohol **9**, which on Johnson orthoester Claisen rearrangement with triethyl orthoacetate and propanoic acid gave 4-pentenoate **10**. Allylation of pentenoate **10** with LDA and allyl bromide, followed by RCM of the resultant heptadiene **11** furnished cyclopentene ester **12**. Alkylation of ester **12** with LDA and methyl iodide in THF and hexamethylphosphoramide (HMPA) stereoselectively generated cyclopentene carboxylate **7**. Next, the ester group in **7** was converted into a methyl group via the corresponding aldehyde. Reduction of ester **7** with LAH followed by oxidation of the resultant primary alcohol furnished aldehyde **13**. Wolff–Kishner reduction

of aldehyde **13** with hydrazine hydrate, potassium hydroxide and digol furnished arylcyclopentene† **6**. A hydroboration sequence was chosen for oxidation of olefin **6**. However, reaction of arylcyclopentene **6** with freshly generated borane–THF, followed by oxidation with hydrogen peroxide and sodium hydroxide furnished predominantly neopentyl alcohol **14**. On the other hand, reaction of olefin **6** with borane–dimethyl sulfide complex followed by oxidation gave a 3:1 mixture of the regioisomers **14** and **15**. Oxidation of alcohols **14** and **15** with pyridinium chlorochromate (PCC) and silica gel furnished cyclopentanones† **16** and **17**, whose structures were established from their spectral data. The preferred formation of the unwanted regioisomer in the hydroboration reaction is probably due to complexation of the borane with the aromatic methoxy group, cf. **18**, and thereby delivering the borane to the nearest carbon of the olefin in an intramolecular manner.

In order to overcome the intramolecular delivery of borane, the regioisomeric arylcyclopentene **19** was considered as an alternative precursor for lagopodin A **1a**. It was also readily identified that the two possible regioisomeric cyclopentanones **17** and **20** that could be generated from the arylcyclopentene would serve as precursors for lagopodin A **1a** and enokipodins A and B **2a** and **3a** (Scheme 3). Accordingly, synthesis of arylcyclopentene **19** was addressed via cyclopentene carboxylate **21**, which was prepared starting from acetophenone **8** in six steps in 47% overall yield, employing an Ireland ester Claisen rearrangement and RCM reaction based sequence as described earlier.[11] Thus, acetophenone **8** was converted into ester **22** using iodine and trimethyl orthoformate. Allylation of ester **22** with LDA and allyl bromide furnished pentenoate **23**, which on hydrolysis with aqueous sodium hydroxide in methanol followed by coupling of the resultant acid with dimethylallyl alcohol employing DCC and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) generated ester **24**. Generation of the TMS enol ether of ester **24** with LDA, trimethylsilyl chloride and triethylamine in THF at −70 °C followed by refluxing the reaction mixture for 3 h resulted in the Ireland ester Claisen rearrangement.[12] Hydrolysis of the reaction mixture with dilute hydrochloric acid followed by esterification with ethereal diazomethane furnished ester **25**, which on RCM reaction with 5 mol % of Grubbs' first generation catalyst [$Cl_2Ru(PCy_3)_2$=CHPh] cleanly furnished cyclopentene carboxylate **21**. Reduction of the ester in **21** with LAH followed by oxidation of the resultant alcohol generated aldehyde **26**, which on Wolff–Kishner reduction furnished arylcyclopentene† **19**. Reaction of olefin **19** with freshly generated borane–THF followed by oxidation with hydrogen peroxide and sodium hydroxide furnished a 3:1 regioisomeric mixture of alcohols **15** and **27**, which were separated by column chromatography on silica gel.[13] Oxidation of alcohols **15** and **27** with PCC and silica gel furnished cyclopentanones **17** and **20**. Cyclopentanone **20** exhibited spectral data identical to that of an authentic sample. Since, conversion of cyclopentanone **20** to enokipodins A **3a** and B **2a** has already been described,[7] the present synthesis of **20** constitutes a formal synthesis of enokipodins A and B. Oxidation of cyclopentanone **17** with ceric ammonium nitrate (CAN) furnished lagopodin A **1a**, which exhibited a ^{1}H NMR spectrum identical to that reported for the natural product.† On the other hand, catalytic hydrogenation of arylcyclopentene **19** furnished arylcyclopentane **28**, the conversion of which to cuparenediol **5** and cuparenequinone **4a** is known.[14]

In summary, we have accomplished the first total synthesis of (±)-lagopodin A **1** and the formal total syntheses of the antifungal sesquiterpenes (±)-enokipodins A and B, starting from 2,5-dimethoxy-4-methylacetophenone in 12 steps, in a combined overall yield of ~26%.

† Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^{1}H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data for 3,4,4-trimethyl-3-(2,5-dimethoxy-4-methylphenyl)cyclopentene **6**: IR (neat): ν_{max}/cm^{-1} 1502, 1211. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.72 (1H, s), 6.61 (1H, s), 5.83 (1H, br d, *J* 6.0 Hz), 5.63 (1H, dt, *J* 6.0 and 2.5 Hz), 3.75 (3H, s), 3.74 (3H, s), 2.33 (1H, dt, *J* 15.9 and 2.5 Hz), 2.17 (3H, s), 2.13 (1H, ddd, *J* 15.9, 2.5 and 1.5 Hz), 1.37 (3H, s), 1.24 (3H, s), 0.57 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.5 (C), 151.1 (C), 141.4 (CH), 132.1 (C), 126.0 (CH), 124.6 (C), 114.8 (CH), 112.1 (CH), 57.3 (C), 55.9 (CH_3), 55.5 (CH_3), 49.0 (CH_2), 44.2 (C), 28.8 (CH_3), 25.3 (CH_3), 22.7 (CH_3), 16.1 (CH_3). Mass: *m*/*z* 260 (M^+, 76%), 245 (16), 217 (15), 205 (25), 187 (100), 175 (13). HRMS: *m*/*z* Calcd for $C_{17}H_{25}O_2$ (M+1): 261.1854. Found: 261.1859. 2-(2,5-Dimethoxy-4-methylphenyl)-2,3,3-trimethylcyclopentanone **16**: IR (neat): ν_{max}/cm^{-1} 1738, 1506, 1209. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.66 (1H, s), 6.61 (1H, s), 3.78 (3H, s), 3.60 (3H, s), 2.64 (1H, dt, *J* 18.0 and 9.0 Hz), 2.34 (1H, ddd, *J* 18.0, 7.8 and 4.5 Hz), 2.17 (3H, s), 1.90–1.65 (2H, m), 1.28 (3H, s), 1.04 (3H, s), 0.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 220.7 (C), 152.2 (C), 150.5 (C), 129.9 (C), 126.2 (C), 116.6 (CH), 111.4 (CH), 56.6 (C), 56.2 (CH_3), 56.0 (CH_3), 43.7 (C), 36.5 (CH_2), 35.3 (CH_2), 26.2 (CH_3), 25.6 (CH_3), 20.6 (CH_3), 16.1 (CH_3). HRMS: *m*/*z* Calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623. Found: 299.1626. 3,3,4-Trimethyl-4-(2,5-dimethoxy-4-methylphenyl)cyclopentene **19**: IR (neat): ν_{max}/cm^{-1} 1505, 1213. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.82 (1H, s), 6.63 (1H, s), 5.54–5.65 (1H, m), 5.36 (1H, dd, *J* 6.0 and 3.0 Hz), 3.77 (3H, s), 3.75 (3H, s), 3.29 (1H, br d, *J* 15.3 Hz), 2.27 (1H, dd, *J* 15.3 and 3.0 Hz), 2.18 (3H, s), 1.30 (3H, s), 1.29 (3H, s), 0.69 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.2 (C), 151.3 (C), 142.7 (CH), 133.9 (C), 124.6 (C), 124.5 (CH), 114.6 (CH), 112.7 (CH), 56.1 (CH_3), 55.2 (CH_3), 52.6 (C), 49.6 (C), 46.5 (CH_2), 25.4 (CH_3), 25.1 (CH_3), 23.7 (CH_3), 16.0 (CH_3). HRMS: *m*/*z* Calcd for $C_{17}H_{25}O_2$ (M+1): 261.1854. Found: 261.1856. 4-(2,5-Dimethoxy-4-methylphenyl)-4,3,3-trimethylcyclopentanone **17**: IR (neat): ν_{max}/cm^{-1} 1741, 1655, 1507, 1213. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.71 (1H, s), 6.66 (1H, s), 3.77 (3H, s), 3.67 (3H, s), 3.20 (1H, d, *J* 18.3 Hz), 2.34 (1H, d, *J* 18.3 Hz), 2.33 (1H, d, *J* 18.3 Hz), 2.18 (3H, s), 2.10 (1H, d, *J* 18.3 Hz), 1.50 (3H, s), 1.18 (3H, s), 0.82 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 217.4 (C), 151.7 (C), 151.4 (C), 131.2 (C), 126.0 (C), 115.7 (CH), 112.6 (CH), 56.0 (CH_3), 55.5 (CH_3), 53.3 (CH_2), 52.4 (CH_2), 48.4 (C), 43.0 (C), 26.1 (2C, CH_3), 25.2 (CH_3), 16.0 (CH_3). HRMS: *m*/*z* Calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623. Found: 299.1632. Lagopodin A **1a**: IR (neat): ν_{max}/cm^{-1}: 1744, 1654; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.66 (1H, s), 6.56 (1H, q, *J* 1.5 Hz), 3.13 and 2.25 (2H, 2 × d, *J* 18.0 Hz), 2.33 and 2.25 (2H, 2 × d, *J* 18.6 Hz), 2.04 (3H, d, *J* 1.5 Hz), 1.39 (3H, s), 1.22 (3H, s), 0.93 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 215.6 (C), 188.1 (C), 188.0 (C), 151.6 (C), 144.4 (C), 135.4 (CH), 134.9 (CH), 52.6 (CH_2), 50.8 (CH_2), 48.4 (C), 42.0 (C), 27.0 (CH_3), 25.2 (CH_3), 23.8 (CH_3), 14.8 (CH_3). HRMS: *m*/*z* Calcd for $C_{15}H_{19}O_3$ (M+1): 247.1334. Found: 247.1340.



Scheme 3. Reagents and conditions: (a) I_2 (2 equiv), $HC(OMe)_3$, rt, 6 h, reflux, 6 h, 69%; (b) LDA, THF; $CH_2{=}CHCH_2Br$, −70 °C→rt, 7 h, 89%; (c) 10% NaOH, MeOH–H_2O (1:1), reflux, 7 h, 96%; (d) DCC, DMAP (catalytic), $Me_2C{=}CHCH_2OH$, CH_2Cl_2, rt, 5 h, 95% (e) (i) LDA, THF; TMSCl, Et_3N, −70 °C, 30 min; rt, 6 h; reflux, 3 h; (ii) dil. HCl, 40 min; (iii) CH_2N_2, Et_2O, 0 °C, 30 min, 86%; (f) $Cl_2Ru(PCy_3)_2{=}CHPh$ (5 mol %), CH_2Cl_2, rt, 5 h, 97%; (g) LAH, Et_2O, 0 °C→rt, 2 h, 96%; (h) PCC, silica gel, CH_2Cl_2, rt, 0.5 h, 90%; (i) $N_2H_4{\cdot}H_2O$, KOH, digol, 120→160 °C, 10 h, 73%; (j) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 0 °C→rt, 1 h; 3 N NaOH, 30% H_2O_2, 0 °C→rt, 5 h; 100%; **15**:**27** 3:1; (k) PCC, silica gel, CH_2Cl_2, rt, 2 h, 96%; (l) CAN, CH_3CN, H_2O, rt, 1 h, 94%; (m) H_2, 10% Pd/C, EtOH, 1 atm, 3 h, 100%.

Acknowledgements

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