A Regioselective Total Synthesis of the Fungal Sesquiterpene (±)-Lagopodin A

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Abstract: A highly regiocontrolled total synthesis of fungal sesquiterpene lagopodin A, employing a combination of Claisen rearrangement–intramolecular diazoketone cyclopropanation and a highly regioselective cyclopropane ring cleavage, is described.

Key words: natural products, total synthesis, rearrangement, ring closure, ring cleavage

Helicobasidium mompa Tanaka is a noxious pathogenic fungus for plants found in Japan and infects subterranean organs of many plants, causing the 'violet root rot'. In 1962, Nishikawa reported[1] isolation of two colouring matters, helicobasidin (**1**, Figure 1) and mompain (**2**) from the mycelium cultures of *Helicobasidium mompa* Tanaka grown in malt medium during his phytopathological investigations on this fungus. Almost at the same time, Takai[2] also reported the isolation of orange-yellow pigment from the steam distillate of the culture and identified as helicobasidin (**1**). In 1967 Natori et al.[3] reported the isolation and structural elucidation of mompain (**2**) and a minor constituent deoxyhelicobasidin (**3**) from the mycelium cultures of *Helicobasidium mompa* Tanaka. In 1965 Bollinger reported[4] the isolation of lagopodin A (**4**) and lagopodin B (**5**) from the cultures of *Coprinus lagopus*. In 1975 Bottom and Siehr reported[5] the isolation of hydroxylagopodin B (**6**) from single mutant of the basidomycete *Coprinus macrorhizus* var. *microsporus* extracts into the liquid culture medium. Later, Bulock and Darbyshire reported[6] the isolation of lagopodins A and B (**4** and **5**), and the dimeric quinone lagopodin C (**7**) from *Coprinus lagopus* Fr. and *Coprinus macrorhizus* var. *microsporus*. Most of the lagopodins exhibited significant antibiotic activity.[4,6]

Lagopodins 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. Recently, we have reported the first total synthesis of lagopodin A[7] (**4**), employing an RCM reaction of the diene **8** as the key step. However, hydroboration–oxidation of the cyclopentene **9** generated a regiochemical mixture of the cyclopentanones **10** and **11** (Scheme 1). Herein, we report a highly regioselective total synthesis of (±)-lagopodin A (**4**).

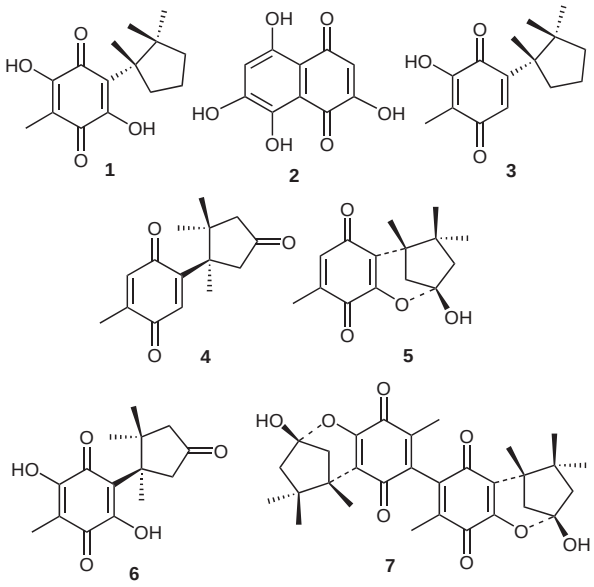
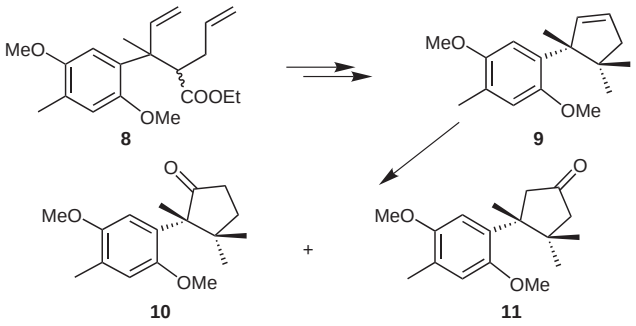


Figure 1



Scheme 1

The synthetic sequence starting from 2,5-dimethoxy-4-methylacetophenone[8] (**12**) is depicted in Schemes 2 and 3. An orthoester Claisen rearrangement[9] was employed for the generation of the first quaternary carbon atom. Thus, Horner–Wadsworth–Emmons reaction of the acetophenone **12** with triethyl phosphonopropionate and sodium hydride in refluxing THF generated an *E*/*Z* mixture of the cinnamate **13**, which on reduction with lithium aluminum hydride (LAH) in diethyl ether at –50 °C furnished a mixture of the cinnamyl alcohol **14** in an overall yield of 88%. Although they are separable, since both the isomers will lead to the same product in Claisen rearrangement, the sequence was carried out with a mixture

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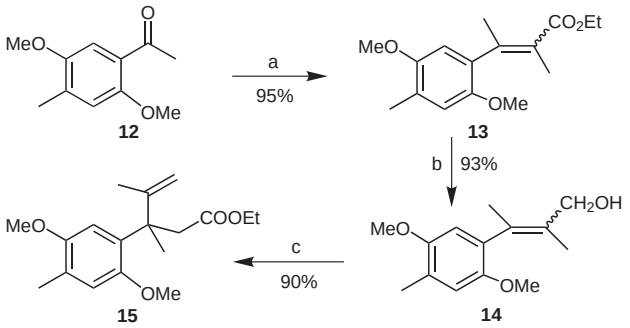
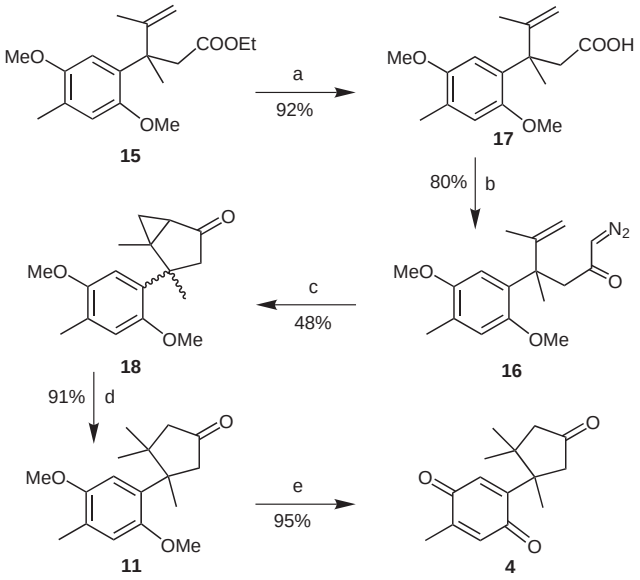
of alcohols **14**. Thermal activation of the cinnamyl alcohol **14** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180 °C for 48 hours furnished the pentenoate **15** in 90% yield.[10]



Scheme 2 *Reagents and conditions*: (a) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, reflux, 8 h; (b) LAH, Et_2O, –50 °C, 2 h; (c) $MeC(OEt)_3$, $EtCO_2H$ (catalytic), sealed tube, 180 °C, 48 h.



Scheme 3 *Reagents and conditions*: (a) 5% NaOH, MeOH–H_2O (1:1), reflux, 4 h; (b) i. $(COCl)_2$, C_6H_6, r.t., 3 h; ii. CH_2N_2, Et_2O, 0 °C, 1 h; (c) Cu, $CuSO_4$, *c*-C_6H_{12}, reflux, 6 h, 48%, (1:2.5); (d) i. Li, liq. NH_3, *t*-BuOH, –33 °C, 15 min; ii. PCC, silica gel, CH_2Cl_2, r.t., 2 h; 91%; (e) CAN, MeCN–H_2O (1:1), r.t., 1 h.

For the creation of the second quaternary carbon atom, an intramolecular cyclopropanation reaction[11] of the diazoketone **16** and regioselective cyclopropane-ring cleavage was investigated. Thus, hydrolysis of ester **15** with sodium hydroxide in refluxing aqueous methanol furnished acid **17**. Reaction of **17** with oxalyl chloride followed by treatment of the resultant acid chloride with an excess of ethereal diazomethane furnished diazoketone **16**. Copper–anhydrous copper sulfate catalysed reaction of diazoketone **16** resulted in the intramolecular cyclopropanation of the resultant carbenoid to furnish a 5:2 diastereomeric mixture of the bicyclo[3.1.0]hexanones **18** containing the requisite two vicinal quaternary carbon atoms.[10] It is well established[12] that electron-transfer reaction of cyclopropyl ketones will proceed in a highly regioselective manner via cleavage of the cyclopropane bond which has better overlap with the p-orbital of the ketone group. Accordingly, treatment of bicyclic ketone **18** with lithium in liquid ammonia in the presence of tertiary butanol generated cyclopentanone **11** in 91% yield and in a highly regioselective manner.[10,13] Finally, oxidation of compound **11** with ceric ammonium nitrate in aqueous acetonitrile furnished lagopodin A (**4**) in 95% yield, which exhibited spectral data identical to those reported in the literature.[6,7]

In conclusion, we have developed a short and convenient highly regioselective approach for the synthesis of (±)-lagopodin A. A combination of Johnson's orthoester Claisen rearrangement, intramolecular diazoketone cyclopropanation of a diazoketone and a highly regioselective cyclopropane ring cleavage was strategically applied for the generation of the two vicinal quaternary carbon atoms. Currently, we are investigating the extension of this approach for the synthesis of helicobasidins and other lagopodins.

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References and Notes

(1) Nishikawa, H. *Agric. Biol. Chem.* **1962**, *26*, 696.
(2) Takai, S. *Phytopathol. Zeit.* **1962**, *43*, 175.
(3) Natori, S.; Inouye, Y.; Nishikawa, H. *Chem. Pharm. Bull.* **1967**, *15*, 380.
(4) Thomson, R. H. *Naturally Occurring Quinones*; Academic Press: London, **1971**.
(5) Bottom, C. B.; Siehr, D. J. *Phytochemistry* **1975**, *14*, 1433.
(6) Bu'Lock, J. D.; Darbyshire, J. *Phytochemistry* **1976**, *15*, 2004.
(7) Srikrishna, A.; Lakshmi, B. V.; Ravikumar, P. C. *Tetrahedron Lett.* **2006**, *47*, 1277.
(8) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758.
(9) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(10) Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H NMR, ^{13}C NMR, and HRMS) consistent with their structures.
Selected Spectral Data
Ethyl 3-(2,5-Dimethoxy-4-methylphenyl)-3,4-dimethylpent-4-enoate (**15**): IR (neat): ν_{max} = 1732, 1638, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 6.68 (1 H, s), 6.59 (1 H, s), 4.77 (1 H, s), 4.70 (1 H, s), 3.92–3.80 (2 H, m), 3.75 (3 H, s), 3.69 (3 H, s), 3.35 (1 H, d, *J* = 13.2 Hz), 2.63 (1 H, d, *J* = 13.2 Hz), 2.17 (3 H, s), 1.61 (3 H, s), 1.55 (3 H, s), 0.98 (3 H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 171.8 (C), 151.9 (C), 151.7 (C), 151.2 (C), 131.2 (C), 125.2 (C), 114.9 (CH), 111.2 (CH), 108.6 (CH_2), 59.4 (CH_2), 55.8 (CH_3), 55.7 (CH_3), 45.3 (C), 42.8 (CH_2), 25.9 (CH_3), 20.5 (CH_3), 15.9 (CH_3), 14.0 (CH_3). HRMS: *m/z* calcd for $C_{18}H_{26}O_4Na$ [M + Na]: 329.1729; found: 329.1733.

4-(2,5-Dimethoxy-4-methylphenyl)-4,5-dimethyl-bicyclo[3.1.0]hexan-2-one (**18**) – minor isomer: IR (neat): ν_{max} = 1724, 1674, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 7.05 (1 H, s), 6.65 (1 H, s), 3.81 (3 H, s), 3.74 (3 H, s), 2.60 and 2.07 (2 H, 2 × d, *J* = 18.3 Hz), 2.19 (3 H, s), 1.71 (1 H, dd, *J* = 8.4, 2.7 Hz), 1.51 (3 H, s), 1.50 (2 H, s), 1.45–1.20 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 212.5 (C), 152.0 (C), 151.1 (C), 132.0 (C), 125.3 (C), 114.8 (CH), 110.9 (CH), 56.1 (CH_3), 55.6 (CH_3), 48.5 (CH_2), 44.5 (C), 36.1 (C), 35.4 (CH), 25.2 (CH_3), 23.8 (CH_2), 18.6 (CH_3), 16.1 (CH_3); major isomer: IR (neat): ν_{max} = 1725, 1666, 1511 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 6.78 (1 H, s), 6.65 (1 H, s), 3.80 (3 H, s), 3.66 (3 H, s), 2.29 (1 H, d, *J* = 18.0 Hz), 2.19 (3 H, s), 2.13 (1 H, d, *J* = 18.0 Hz), 1.81 (1 H, dd, *J* = 9.0, 3.0 Hz), 1.56 (3 H, s), 1.20–1.00 (2 H, m), 0.81 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 212.3 (C), 151.6 (C), 151.2 (C), 132.4 (C), 125.7 (C), 114.3 (CH), 110.9 (CH), 56.1 (CH_3), 54.8 (CH_3), 49.4 (CH_2), 44.0 (C), 38.1 (CH), 35.4 (C), 24.1 (CH_3), 19.7 (CH_2), 17.3 (CH_3), 16.0 (CH_3). HRMS: *m/z* calcd for $C_{17}H_{22}O_3Na$ [M + Na]: 297.1467; found: 299.1467.

3-(2,5-Dimethoxy-4-phenyl)-3,4,4-trimethylcyclo-pentanone (**11**): IR (neat): ν_{max} = 1740, 1714, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 6.70 (1 H, s), 6.65 (1 H, s), 3.76 (3 H, s), 3.67 (3 H, s), 3.19 (1 H, d, *J* = 18.3 Hz), 2.34 (1 H, d, *J* = 18.3 Hz), 2.33 (1 H, d, *J* = 18.0 Hz), 2.18 (3 H, s), 2.10 (1 H, d, *J* = 18.0 Hz), 1.50 (3 H, s), 1.18 (3 H, s), 0.82 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 217.1 (C), 151.7 (C), 151.4 (C), 131.1 (C), 125.9 (C), 115.7 (CH), 112.5 (CH), 55.9 (CH_3), 55.4 (CH_3), 53.2 (CH_2), 52.3 (CH_2), 48.3 (C), 43.0 (C), 26.1 (2 C, CH_3), 25.1 (CH_3), 15.9 (CH_3). HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ [M + Na]: 299.1623; found: 299.1615.

(11) (a) Stork, G.; Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678. (b) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.

(12) (a) Norin, T. *Acta Chem. Scand.* **1965**, *19*, 1289. (b) Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 2361. (c) Srikrishna, A.; Krishnan, K.; Yelamaggad, C. V. *Tetrahedron* **1992**, *48*, 9337.

(13) Varying amount of the corresponding cyclopentanol (by over-reduction) was also obtained, which was reoxidised to ketone **11** with PCC and silica gel.