# Synthesis of Lycopodium Alkaloids of the Lycopodine Structure Type

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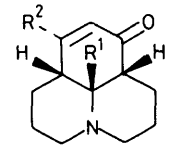
The total syntheses of the Lycopodium alkaloids lycopodine, deacetylfawcettiine, acetylfawcettiine, clavolonine, and annofoline by the elaboration of a hydrojulolidine, prepared earlier from dimethyl quinolinate, in few steps are described.

Some time ago there was developed a facile, short route of synthesis of the hydrojulolidine ring skeleton common to many Lycopodium alkaloids.[1] It involved the transformation of dimethyl quinolinate into tricycle (**1a**) *inter alia*. The present communication describes the conversion of (**1a**) into the alkaloids lycopodine (**2a**),[2] deacetylfawcettiine (**2b**),[3] acetylfawcettiine (**2c**),[3] clavolonine (**2d**),[3] and annofoline (**3**)[4] in racemic form.

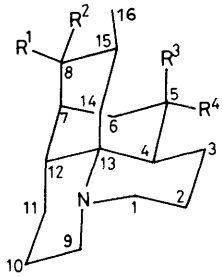
Reduction of ester (**1a**) with lithium aluminium hydride in diethyl ether, followed by exposure of the crude product to aqueous acid, led to alcohol (**1b**) [76% yield; m.p. 148—150 °C; $\lambda_{max}$ (EtOH) 229 nm (log ε 3.84); ν ($CHCl_3$) 3620m, 1670s, 1640w $cm^{-1}$; $\delta_H$ ($CDCl_3$) 1.3—3.2 (m, 15H, methylenes, methines), 4.20 (q, 2H, *J* 10 Hz, $OCH_2$), 6.10 (dd, 1H, *J* 9, 3 Hz, olefinic α-keto H), 6.65 (dd, 1H, *J* 9, 2 Hz, olefinic β-keto H)]. Interaction of the latter in tetrahydrofuran solution with 3 equiv. of 2-ethyl-2-lithio-1,3-dithian and 6.6 equiv. of hexamethylphosphoramide[5] at −78 °C yielded adduct (**4a**) [70%; m.p. 188—189 °C; ν 3450w, 1690s $cm^{-1}$; $\delta_H$ 0.95 (t, 3H, *J* 7 Hz, Me), 1.2—3.5 (m, 26H, methylenes, methines), 4.10 (s, 2, $OCH_2$)], whose Pfitzner–Moffatt oxidation[6] gave aldehyde (**4b**) [86%; m.p. 131—133 °C; ν 2935m, 1720s, 1700s $cm^{-1}$; $\delta_H$ 1.00 (t, 3H, *J* 7 Hz, Me), 1.2—3.6 (m, 25H, methylenes, methines), 9.90 (s, 1H, CHO)]. Hydrolysis [2 equiv. of mercury(II) chloride, 1.1 equiv. of yellow mercury(II) oxide in refluxing 9:1 MeOH–$H_2O$] of (**4b**) afforded ketoaldehyde (**4c**) [52%; liquid; ν 2930m, 1705s $cm^{-1}$; $\delta_H$ 1.00 (t, 3H, *J* 7 Hz, Me), 1.2—3.8 (m, 19H, methylenes, methines), 10.05 (s, 1H, CHO)]. Acid-induced cyclization (9:1 HOAc–HCl, refluxed, 3.5 h) of the latter furnished tetracyclic diketone (**5a**) [83%; m.p. 137—138 °C; $\lambda_{max}$ 230 nm (log ε 3.94); ν 1715s, 1685s, 1655m $cm^{-1}$; $\delta_H$ ($CCl_4$) 1.2—3.6 (m, 17H, methylenes, methines), 1.70 (s, 3H, Me), 7.10 (s, 1H, 14-H)].

Hydrogenation ($H_2$, 5% Pd–C, EtOAc, atmospheric pressure) of enone (**5a**) and isomerization (NaOMe–benzene, room temp., 20 min) of the product yielded diketone (**2e**) [99%; liquid; ν 1710s $cm^{-1}$; $\delta_H$ 1.05 (d, 3H, *J* 6 Hz, Me), 0.8—3.2 (m, 20H, methylenes, methines)]. Conversion {$HS[CH_2]_3SH$, HCl gas in glacial HOAc, 1 h} of the latter into thioacetal (**2f**) [58%; m.p. 181—184 °C; ν 1695s $cm^{-1}$; $\delta_H$ 1.20 (d, 3H, *J* 6 Hz, Me), 1.2—3.3 (m, 26H, methylenes, methines)] and reduction (Raney Ni, refluxing EtOH, 18 h) of the derivative gave (±)-lycopodine (**2a**) (60%; m.p. 129—130 °C; spectroscopically identical with natural material).[7,8]

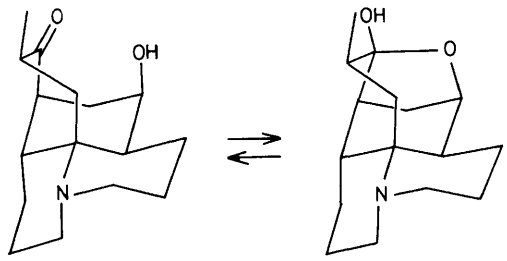
Reduction ($LiAlH_4$–$Et_2O$) of diketone (**2e**) produced (±)-deacetylfawcettiine (**2b**) [88%; m.p. 217—219 °C; ν 3600w, 3400w (br.) $cm^{-1}$; $\delta_H$ 1.05 (d, 3H, *J* 6 Hz, Me), 1.1—1.3 (m, 21H, methylenes, methines), 3.3—3.4 (m, 2H, H of $NCH_2$, 8-H), 3.8—4.0 (m, 1H, 5-H)].† Acetylation (MeLi–THF, 0 °C and then $Ac_2O$ at 20 °C) of the latter yielded (±)-acetylfawcettiine (**2c**) [99%; m.p. 134—136 °C; ν 1735s $cm^{-1}$; $\delta_H$ 0.97 (d, 3H, *J* 6 Hz, Me), 1.2—3.5 (m, 20H, methylenes, methines), 2.10, 2.15 (s, 3H each, 2 COMe), 4.70 (dd, 1H, *J* 10, 4 Hz, 8-H), 5.10 (m, 1H, 5-H)].† By following a published procedure[3] for the conversion of natural deacetyl-



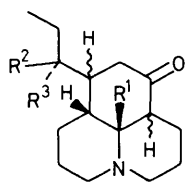
(**1**) **a**; $R^1 = CO_2Me$, $R^2 = OMe$
**b**; $R^1 = CH_2OH$, $R^2 = H$



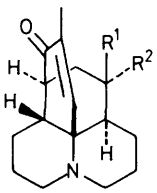
(**2**)**a**; $R^1 = R^2 = H$, $R^3 + R^4 = O$
**b**; $R^1 = R^4 = H$, $R^2 = R^3 = OH$
**c**; $R^1 = R^4 = H$, $R^2 = R^3 = OAc$
**d**; $R^1 = H$, $R^2 = OH$, $R^3 + R^4 = O$
**e**; $R^1 + R^2 = R^3 + R^4 = O$
**f**; $R^1 + R^2 = S[CH_2]_3S$, $R^3 + R^4 = O$
**g**; $R^1 = R^4 = H$, $R^2 = OAc$, $R^3 = OH$
**h**; $R^1 = H$, $R^2 = OAc$, $R^3 + R^4 = O$



(**3**)



(**4**) **a**; $R^1 = CH_2OH$, $R^2 + R^3 = S[CH_2]_3S$
**b**; $R^1 = CHO$, $R^2 + R^3 + = S[CH_2]_3S$
**c**; $R^1 = CHO$, $R^2 + R^3 = O$



(**5**) **a**; $R^1 + R^2 = O$
**b**; $R^1 = OH$, $R^2 = H$

† The $^{13}C$ n.m.r. spectrum was identical with that of an authentic alkaloid sample.

fawcettiine (**2b**) into natural clavolonine (**2d**), racemic (**2b**) was acetylated and the resultant monoacetate (**2g**) [95%; liquid; ν 1725s $cm^{-1}$; $\delta_H$ 0.90 (d, 3H, *J* 6 Hz, Me), 1.0—3.5 (m, 21H, methylenes, methines), 2.05 (s, 3H, COMe), 3.8—4.0 (m, 1H, 5-H), 4.55 (dd, 1H, *J* 10, 5 Hz, 8-H)] oxidized, leading to ketoester (**2h**) [70%; liquid; ν 1730s, 1705s $cm^{-1}$; $\delta_H$ 0.85 (d, 3H, *J* 6 Hz, Me), 1.2—3.5 (m, 19H, methylenes, methines), 2.05 (s, 3H, COMe), 4.60 (dd, 1H, *J* 11, 3 Hz, 8-H)], whose hydrolysis yielded (±)-clavolonine (**2d**) [95%; m.p. 192—194 °C; ν 3400w, 1695s $cm^{-1}$; $\delta_H$ 0.95 (d, 3H, *J* 6 Hz, Me), 1.0—3.5 (m, 22H, methylenes, methines)].[8]

For the construction of the final base, diketone (**5a**) was reduced ($KBBu^s_3H$–THF, −78 °C, 4 h) and the resultant alcohol (**5b**) [72%; m.p. 176—177 °C; u.v. absorption at 240 nm; ν 3400w, 1670s $cm^{-1}$; $\delta_H$ ($CCl_4$) 1.2—3.5 (m, 18H, methylenes, methines), 1.70 (s, 3H, Me), 3.7—3.9 (m, 1H, 5-H), 7.10 (s, 1H, 14-H)]‡ hydrogenated ($H_2$, 10% Pd–C, HOAc, atmospheric pressure), yielding (±)-annofoline (**3**) [85%; m.p. 191—193 °C; ν 3600w, 1700s $cm^{-1}$; $\delta_H$ 1.05, 1.10 (d, total of 3H, *J* 6 Hz, Me), 1.2—3.3 (m, 21H, methylenes, methines), 3.6—3.8, 3.8—4.0 (m, total of 1H, 5-H)].†

The above preparations of the four bases (**2b—d**) and (**3**) constitute the first total syntheses of 5,8-dioxygenated Lycopodium alkaloids of the lycopodine type.

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‡ The hydride reduction gave also the 14-en-8α-ol-5-one (12%).

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8 The $^{13}C$ n.m.r. spectrum was identical with that recorded by T. T. Nakashima, P. P. Singer, L. M. Browne, and W. A. Ayer, *Can. J. Chem.*, 1975, **53**, 1936.