Total Synthesis of the Macrocyclic Spermidine Alkaloids (±)-Lunarine and (±)-Lunaridine

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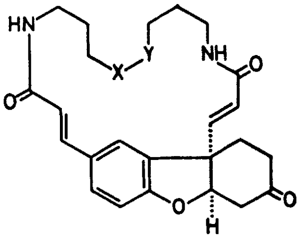
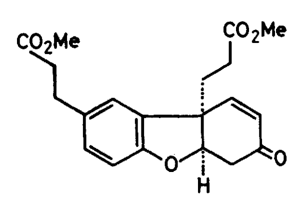
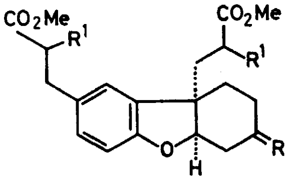
Summary Total syntheses of (±)-lunarine (**1**) and (±)-lunaridine (**2**) have been performed *via* aminolysis of the thiazolidine-2-thione diamide derivative (**10**) with spermidine (**11**).

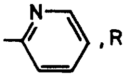


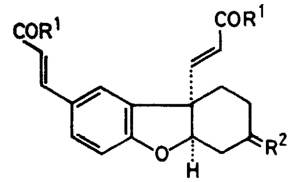
(1) X = NH, Y = CH_2
(2) X = CH_2, Y = NH

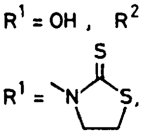


(3)

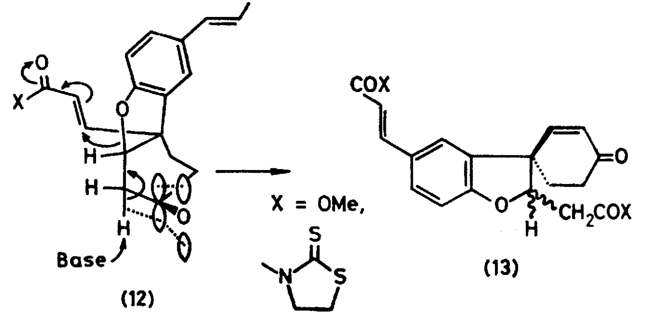


(4) $R^1 = H$, $R^2 = O$
(5) $R^1 = H$, $R^2 = {}^{-O}_{-O}]$
(6) $R^1 = -S-$  , $R^2 = O$



(7) $R^1 = OMe$, $R^2 = O$
(8) $R^1 = OMe$, $R^2 = {}^{-O}_{-O}]$
(9) $R^1 = OH$, $R^2 = {}^{-O}_{-O}]$
(10) $R^1 =$  , $R^2 = {}^{-O}_{-O}]$

$H_2N-[CH_2]_3-NH-[CH_2]_4-NH_2$
(11)



RECENTLY we developed a new cyclization method for macrocyclic diamides through the aminolysis of dicarboxylic acid thiazolidine-2-thione diamides with diamines, spermidine, and spermine.[1] We now report a new application of this cyclization procedure as a key step in the first total synthesis of two macrocyclic spermidine alkaloids, lunarine (**1**) and lunaridine (**2**), which were isolated from *Lunaria biennis* (Cruciferae) by Potier and his co-workers.[2]

The Pummerer ketone-like compound (**3**), prepared through their route,[3] on hydrogenation (H_2/Pd-C) gave the saturated keto-ester (**4**) (67%). The ketone (**4**) was protected as its ethylene acetal (**5**) which was treated with lithium di-isopropylamide (LDA) (2·2 mol. equiv.) in tetrahydrofuran (THF) at −78 °C with stirring under N_2, and then a solution of di-2-pyridyl disulphide (2·2 mol. equiv.) in THF was added dropwise under the same conditions.[4] The mixture was stirred at −78 °C for 10 min and at −25 °C for 20 min. After being stirred at room temperature for 1 h, the mixture was treated as usual to give an oily product (**6**) which, after oxidation with *m*-chloroperbenzoic acid (3 mol. equiv.) to give the sulphoxide, was heated in benzene to afford the desired αβ-unsaturated ester (**7**) in 46% overall yield from (**4**). Its acetal (**8**) was hydrolysed (LiOH, THF–H_2O) at room temperature and neutralized using Amberlite IR-120B cation exchange resin to yield the dicarboxylic acid (**9**) in 89% overall yield from (**7**). Compound (**9**) was treated with thiazolidine-2-thione in CH_2Cl_2 at room temperature for 30 min in the presence of dicyclohexylcarbodi-imide and 4-dimethylaminopyridine to afford the diamide (**10**). A yellow solution of (**10**) in CH_2Cl_2 and a solution of spermidine (**11**) in CH_2Cl_2–THF (7 : 3) were added dropwise using two mechanically driven syringes (microfeeder) over 5 h into a large amount of CH_2Cl_2 under N_2 with stirring at room temperature. The mixture was then stirred for a further 3 h and was treated as usual to give an oily substance which was subjected to preparative t.l.c. on silica gel plates with $CHCl_3$–EtOH (4 : 1) saturated with NH_3 as eluant to give pure (±)-lunarine (**1**), R_f 0·6, m.p. >300 °C (from EtOH) as colourless plates [18% overall yield from (**9**)] and (±)-lunaridine (**2**), R_f 0·2, decomp. >260 °C (from EtOH–acetone) [19·6% overall yield from (**9**)]. The accomplishment of these total syntheses was confirmed by the identity of ^{1}H n.m.r. data and retention times (h.p.l.c.†) of the synthetic racemates, (**1**) and (**2**), and optically active natural lunarine and lunaridine, respectively.

The cyclohexanone moiety was protected as the 1,3-dioxolan in the synthetic pathway from (**7**) to the diamide (**10**) because the unprotected ketone was easily converted into the spiro compound (**13**) under basic conditions.

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† Analytical conditions: JASCO TRI ROTAR (UV-100), column: Finepak SIL C_{18}, solvent system: MeOH–1% aq. $(NH_4)_2CO_3$ (80:20).

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[2] C. Poupat, H.-P. Husson, B. Rodriguez, A. Husson, P. Potier, and M.-M. Janot, *Tetrahedron*, 1972, **28**, 3087; C. Poupat, H.-P. Husson, B. C. Das, P. Bladon, and P. Potier, *ibid.*, p. 3103.

[3] H.-P. Husson, C. Poupat, B. Rodriguez, and P. Potier, *Tetrahedron*, 1973, **29**, 1405.

[4] *Cf.* Y. Nagao, K. Seno, and E. Fujita, *Tetrahedron Lett.*, 1979, 4403.