# Synthesis of (±)-Septicine and (±)-Tylophorine by Regioselective [3 + 2] Cycloaddition

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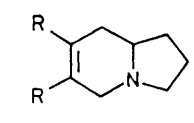
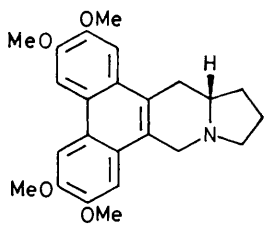
The synthesis of (±)-septicine and (±)-tylophorine, using 1,3-dipolar cycloaddition and intramolecular photocyclisation reactions as key steps, is described.

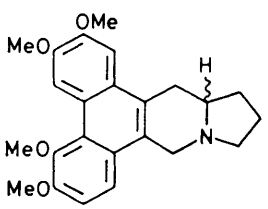
Tylophorine (**2**) and its positional isomers, tylocrebrine (**3**) and isotylocrebrine (**4**), are part of a small group of alkaloids[1] that possess antitumour activity and have as a common parent system the phenanthroindolizidine nucleus. Tylophorine has been synthesised by six independent groups.[2] These syntheses were accomplished mostly *via* phenanthrene derivatives, but two methods[2d,f] involve oxidative coupling. Here we report a new, efficient synthesis of (**2**) and its biogenetic congener, septicine (**1**), through 1,3-dipolar cycloaddition and intramolecular photocyclisation as key steps.



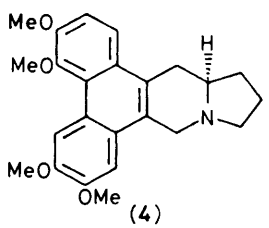
(**1**) R = 3,4-$(MeO)_2C_6H_3$–



(**2**)

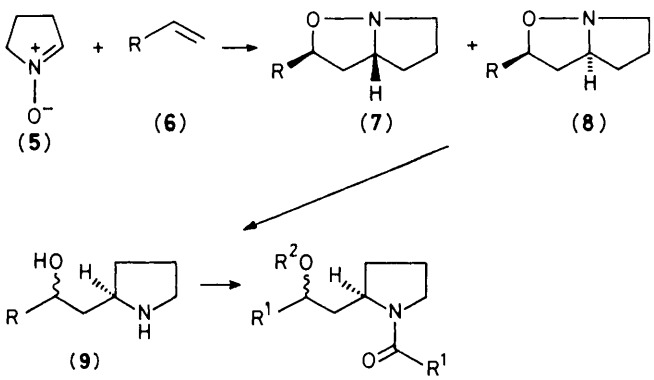


(**3**)



(**4**)

Our strategy, based on retrosynthetic analysis, utilised a 2-substituted pyrroloisoxazole as key intermediate. Thus the regioselective [3 + 2] cycloaddition was performed between the pyrroline oxide (**5**) and 3,4-dimethoxystyrene (**6**) in boiling toluene for 3 h to give an inseparable diastereoisomeric mixture of the adducts† (**7**) and (**8**) in nearly quantitative yield with preferential formation of (**7**). These adducts were then



(**5**) (**6**) (**7**) (**8**) (**9**)

(**10**) $R^1$ = 3,4-$(MeO)_2C_6H_3$–, $R^2$ = 3,4-$(MeO)_2C_6H_3CH_2CO$

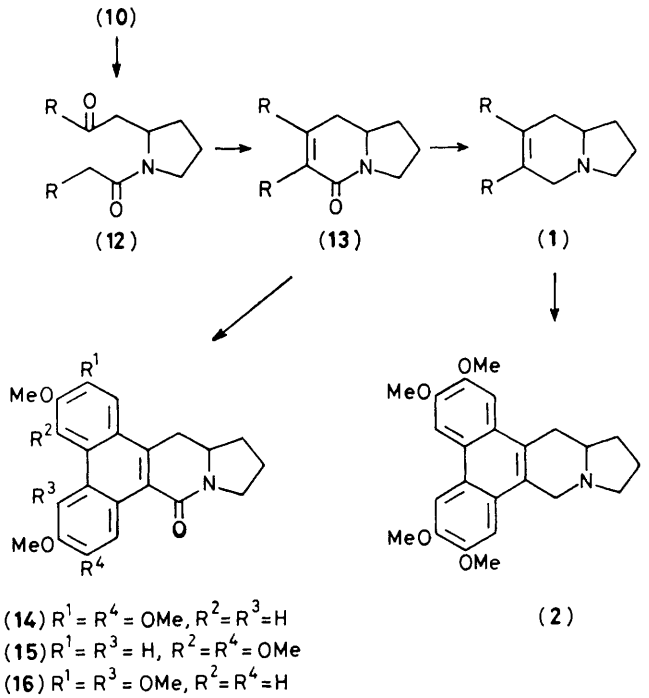
(**11**) $R^1$ = 3,4-$(MeO)_2C_6H_3$–, $R^2$ = H

**Scheme 1.** R = 3,4-$(MeO)_2C_6H_3$–

† All new compounds gave satisfactory spectroscopic, microanalytical, and/or high-resolution mass spectral data.

hydrogenolysed over 10% Pd–C in methanol to give the amino-alcohol (**9**) (86%) which is substantially a mixture of two isomers [β- and α-OH in (**9**)].

Compound (**9**) was acylated to prevent subsequent oxidation of the amino-group and treated with (3,4-dimethoxyphenyl)acetyl chloride in chloroform in the presence of $K_2CO_3$ to give the amido-ester (**10**). The crude mixture of products was hydrolysed under alkaline conditions for a short time to produce (**11**) [70% from (**9**)] (Scheme 1). Oxidation with Collins reagent converted (**11**) into the keto-amide (**12**) (m.p. 98—99 °C, 87%), which then gave the lactam (**13**) (95%) by intramolecular aldol condensation induced by alcoholic KOH under reflux. Irradiation of (**13**) (Pyrex vessel, $CH_2Cl_2$, $I_2$) followed by preparative t.l.c. [silica gel, EtOAc–benzene (6:1)] yielded 9-oxotylophorine (**14**) (m.p. 237—238 °C decomp., 55%), 9-oxoisotylocrebrine (**15**) (m.p. 237—238 °C, 24%), and 9-oxotylocrebrine (**16**) (m.p. 207 °C decomp., 4.3%). Reduction of (**14**) with $LiAlH_4$ or diborane resulted in only the recovery of the starting material or a low yield of (**2**).




(**14**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**15**) $R^1 = R^3 = H$, $R^2 = R^4 = OMe$
(**16**) $R^1 = R^3 = OMe$, $R^2 = R^4 = H$

**Scheme 2.** R = 3,4-$(MeO)_2C_6H_3$–

We considered next the use of (**1**) as a photochemical precursor to (**2**). Thus the lactam (**13**) was reduced with the mixed hydride reagent prepared from $LiAlH_4$ and $AlCl_3$ (3:1) in ether–tetrahydrofuran to give (±)-septicine (**1**) (m.p. 138—139 °C, 88%). The latter was identified by direct comparison (mixed m.p., t.l.c., i.r., and n.m.r.) with an authentic sample. Irradiation of (**1**) in a manner similar to that for (**13**) followed by purification by h.p.l.c. [silica gel, $CHCl_3$–EtOH (50:1)] produced (±)-(**2**) as the major product‡ (43%) (Scheme 2). (±)-Tylophorine thus obtained was found to be identical with natural tylophorine by i.r., n.m.r., and mass spectra as well as by its t.l.c. behaviour.

We are grateful to Dr. Richard B. Herbert for a sample of synthetic septicine and a copy of its n.m.r. spectrum, and also to Dr. Tuticorin R. Govindachari for a sample of natural tylophorine.

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## References

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‡ H.p.l.c. of the photo-products gave a minor amount of a less polar component which is considered to be a mixture of tylocrebrine (**3**) and isotylocrebrine (**4**).