Synthesis of Homaline and *epi*-Homaline

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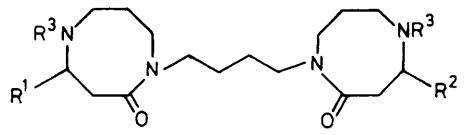
5-Methyl-4-phenyl-1,5-diazacyclo-octan-2-one has been prepared by cyclisation of an acyclic precursor or by transamidation from 4-phenylazetidin-2-one, and converted into natural (−)-homaline and *epi*-homaline: the approach is applicable to the synthesis of unsymmetrical alkaloids.

Homaline, (*SS*)-(−)-(**1a**), isolated from the leaves of *Homalium pronyense* (Flacourtiaceae) is the parent alkaloid of a group of four natural products (**1a**—**d**) containing the unusual bis-eight-membered lactam structure,[1] and is based biogenetic-



(1)

a; $R^1 = R^2 = Ph$, $R^3 = Me$ (Homaline)
b; $R^1 = [CH_2]_4Me$, $R^2 = [CH_2]_6Me$, $R^3 = Me$ (Hopromine)
c; $R^1 = Ph$, $R^2 = CH_2CH(OH)[CH_2]_4Me$, $R^3 = Me$ (Hopromalinol)
d; $R^1 = [CH_2]_4Me$, $R^2 = CH_2CH(OH)[CH_2]_4Me$, $R^3 = Me$ (Hoprominol)
e; $R^1 = R^2 = Ph$, $R^3 = H$

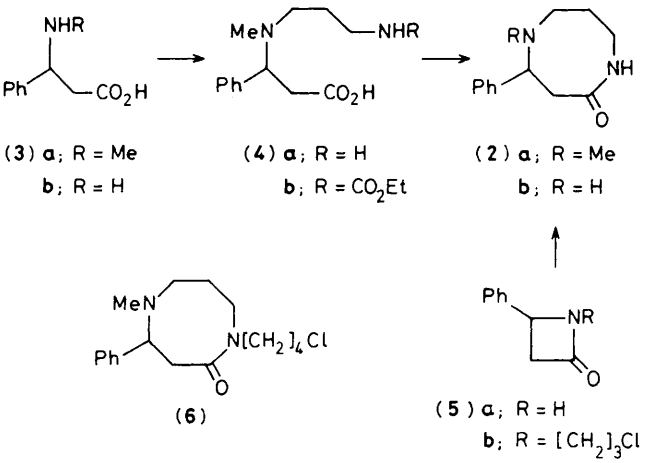
ally on the physiologically significant polyamine spermine together with two cinnamic acid residues. We report here a short and efficient synthesis of natural (*SS*)-(−)-homaline, and separately of the (*RS*)-diastereoisomer *epi*-homaline, that is adaptable for synthesis of the unsymmetrical alkaloids (**1b—d**).[2]

Our strategy required the eight-membered azalactam (**2a**) and was developed initially on racemic material. In our first approach, (±)-3-methylamino-3-phenylpropionic acid (**3a**), readily available from benzylidenemethylamine and malonic acid,[3] was converted as previously reported,[2a] by cyanoethylation and hydrogenation of the nitrile group, into the diamino-acid (**4a**). Using the reported[2a] mixed anhydride procedure (EtO_2CCl, Et_3N, *N*,*N*-dimethylformamide; −15 °C) cyclisation to (**2a**) was inefficient (22%), with the *N*-ethoxycarbonyl-amino-acid (**4b**)† as the major product, but treatment of diamino-acid (**4a**) with di-2-pyridyl disulphide and triphenylphosphine (MeCN, reflux) afforded the (±)-azalactam (**2a**) in 94% yield.

A more convenient alternative route to (**2a**), or the *N*-demethyl compound (**2b**), proceeds from 4-phenylazetidin-2-one (**5a**), easily accessible from styrene and *N*-chlorosulphonyl isocyanate,[4] and utilises our recently developed sequence for transamidation of β-lactams.[5] *N*-Alkylation of (±)-(**5a**) under phase-transfer conditions (powdered KOH, tetrahydrofuran, Bu_4NHSO_4; 20 °C)[6] with 1-bromo-3-chloropropane led to the *N*-(3-chloropropyl) derivative (**5b**)† (94%), ν_{max} 1760 cm^{-1} (film), that was treated with liquid ammonia in a sealed tube (20 °C, 6 days) to afford directly the eight-membered azalactam (±)-(**2b**)† (90%), m.p. 128—130 °C, ν_{max} 1650 cm^{-1} (KBr). Reductive methylation to give (±)-(**2a**) proceeded smoothly (CH_2O, $NaBH_3CN$; 90%).[7]

Synthesis of the bis-lactam framework was completed from either (**2a**) or (**2b**). A double alkylation of (±)-(**2a**) with 1,4-dibromobutane (powdered KOH, dimethyl sulphoxide; 20 °C)[8] gave (**1a**) (62%) as a 1 : 1 mixture of (±)-homaline and *epi*-homaline. Alternatively, and more efficiently, the *N*-demethyl lactam (±)-(**2b**) could be similarly alkylated to give the bis-lactam (**1e**)† (75%) that was reductively methylated (CH_2O, $NaBH_3CN$; 90%) to give the same diastereoisomeric mixture. This mixture could not be efficiently separated chromatographically, but crystallisation from acetone–chloroform afforded the (*RS*)-diastereroisomer *epi*-homaline,† m.p. 210—211 °C, identified by comparison of its ^{13}C n.m.r. spectrum with that of a sample of natural homaline (*SS*)-(−)-(**1a**).[1]

This sequence was repeated with (*S*)-(−)-4-phenylazetidin-2-one (**5a**), $[\alpha]_D^{21}$ −124° (*c* 0.51 in methanol) {lit.,[9] $[\alpha]_D^{20}$ −132°



(3) a; R = Me
b; R = H

(4) a; R = H
b; R = CO_2Et

(2) a; R = Me
b; R = H

(6)

(5) a; R = H
b; R = $[CH_2]_3Cl$

(*c* 1 in methanol)}, prepared by cyclisation (di-2-pyridyl disulphide, Ph_3P, MeCN; 53%)[10] of a sample of (*S*)-(−)-3-phenyl-3-aminopropionic acid (**3b**) obtained from homologation of (*S*)-(−)-phenylglycine.[2a] Alkylation and ring expansion gave the (*S*)-(−)-azalactam (**2b**),† m.p. 166—168 °C, $[\alpha]_D^{22}$ −10.7° (*c* 0.65 in chloroform), that was subjected to the double alkylation with 1,4-dibromobutane and subsequent reductive methylation‡ to afford homaline (*SS*)-(−)-(**1a**), m.p. 134—135 °C, $[\alpha]_D^{22}$ −32° (*c* 0.95 in chloroform) {lit.,[1] m.p. 134 °C, $[\alpha]_D^{20}$ −34° (*c* 1 in chloroform)}. The synthetic material was identical (mixed m.p., t.l.c., i.r., ^1H and ^{13}C n.m.r.) with a sample of the natural product.[1] Our optimum sequence, (**5a**) → (**5b**) → (**2b**) → (**1e**) → (**1a**), constitutes an efficient four-step synthesis of homaline.

To demonstrate the potential of this route for the stepwise construction of the unsymmetrical alkaloids of the homaline group, the (±)-azalactam (**2a**) was alkylated with 1-bromo-4-chlorobutane (powdered KOH, dimethyl sulphoxide) to afford the *N*-(4-chlorobutyl) derivative (**6**) that was further treated with a second molecule of (±)-(**2a**) to give (**1a**) as the same mixture of diastereoisomers outlined above.

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† New compounds gave spectra consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

‡ Wasserman *et al.* report (ref. 2b) partial racemisation during reductive methylation of (*SS*)-(**1e**) with CH_2O–$NaBH_3CN$. We did not observe this.