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TRANSAMIDATION REACTIONS USING β-LACTAMS. THE SYNTHESIS OF HOMALINE

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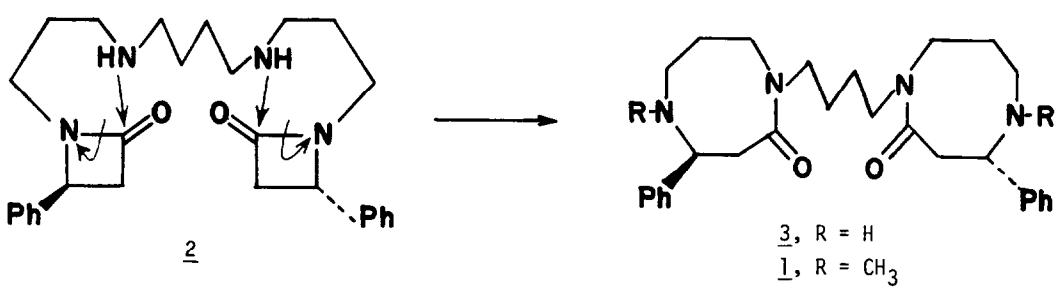
Summary: The synthesis of the plant product, homaline, by a translactamization process involving the β-lactam, (-)-4-phenyl-2-azetidinone, is described.

Homaline,[1,2] (1) isolated from the leaves of Homalium pronyense, has a structure incorporating the naturally occurring polyamine, spermine, along with two cinnamic acid residues. At the time of its isolation, the bis-eight-membered lactam system was unique among natural products, although three other related alkaloids[1] have since been found. Our interest in the synthesis of homaline stemmed from the possibility that this substance, containing β-phenyl-β-aminopropionamide residues might be readily constituted by transamidation of a suitable bis-β-lactam precursor. We have recently shown[3,4] that other macrocyclic polyamine alkaloids such as celacinnine and dihydroperiphylline can be formed by related expansions of small heterocyclic rings.

β-Lactams are remarkably stable to hydrolysis considering the strain in the four-membered ring. They do, however, undergo ready ring opening when subjected to intramolecular attack by nucleophiles through a favorable transition state.[4,5,6] It therefore appeared likely that intramolecular aminolysis of a suitably functionalized β-lactam precursor such as (2) could lead to desdimethylhomaline (3), dimethylation of which would give the natural product (1). We now wish to report the total synthesis of homaline according to this transamidation process.



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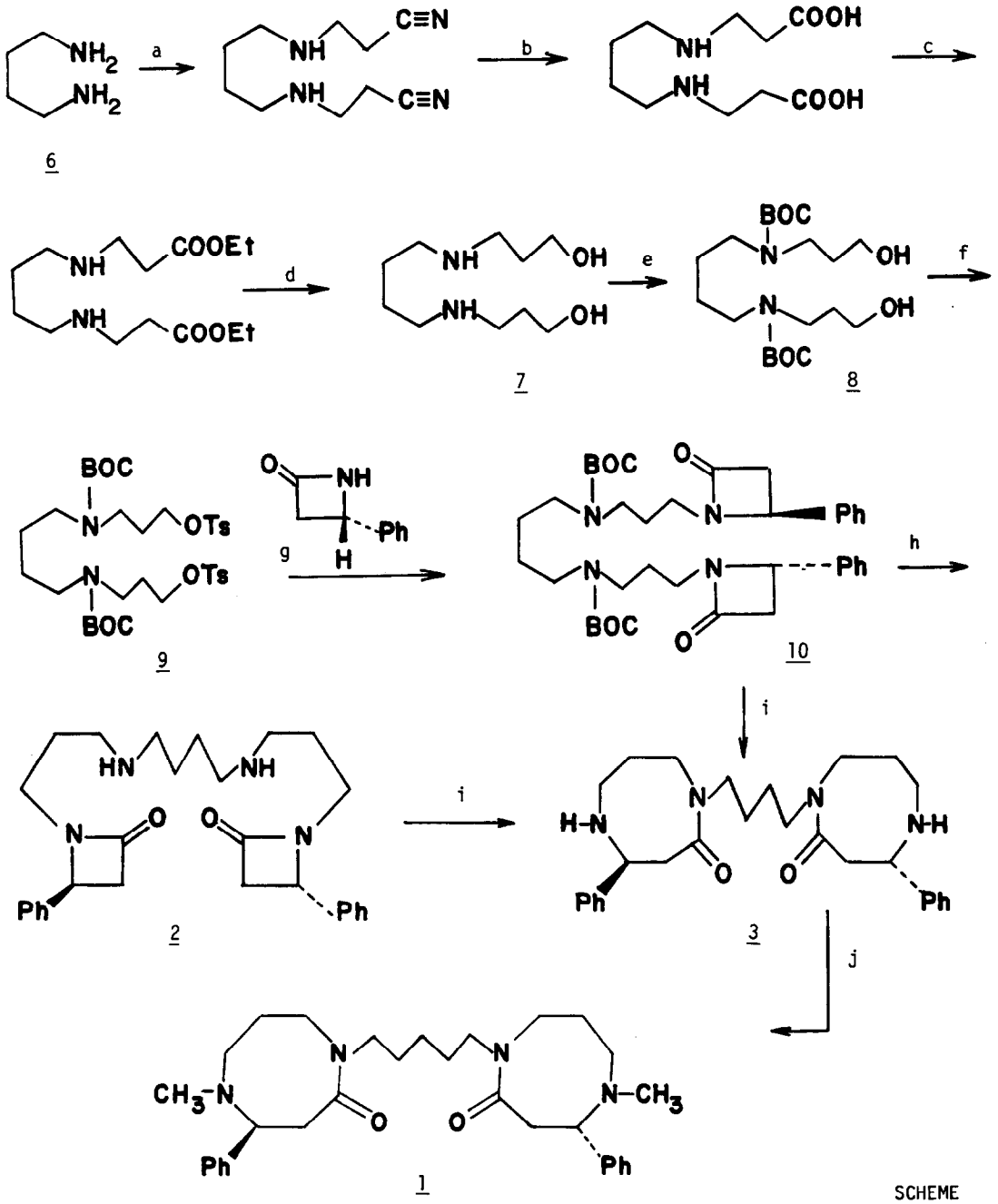
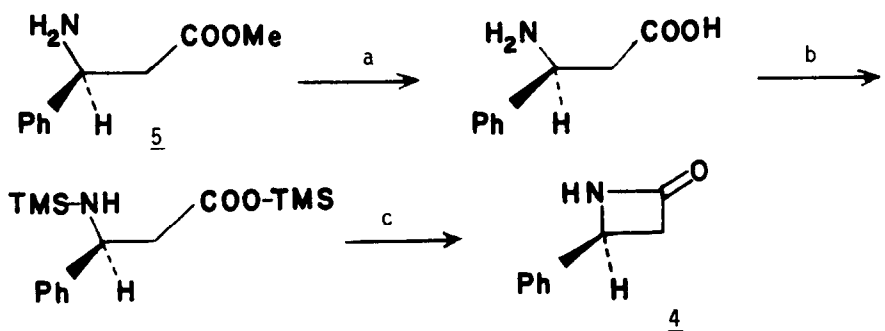
3, R = H
1, R = CH_3

Our synthesis was planned along lines which would allow introduction of the proper stereochemistry at the two benzylic positions. The remoteness of these sites precludes the possibility of asymmetric induction, so a chiral convergent synthesis was developed. Since the benzylic positions are both of the S-configuration, a β-lactam which possesses this chirality would confer the proper stereochemistry to the final product.



(a) CH_2=CH-CN; (b) 6NHCl; (c) EtOH, HCl; (d) $LiAlH_4$, THF, Δ; (e) BOC-ON, Et_3N; (f) pTs-Cl, py; (g) NaH, DMF, 98°, 16hr; (h) HCO_2H, r.t.; (i) Ph_2O, Δ, 3hr; (j) CH_2O, HCO_2H.

A convenient preparation of the desired (-)-4-phenyl-2-azetidinone (4) started with methyl-β-phenyl-β-alanate[7] (5) which could be resolved as its L-(+)-tartarate salt according to the procedure of Pietsch.[8] The optically active amino ester (5) showed satisfactory chiroptical data, $[\alpha]_D^{24}$ = -13.7°, neat; lit $[\alpha]_D^{24}$ = -12.9, neat.[8] Further demonstration of the optical integrity of (5) was provided by the absence of the diastereomeric Eu(hfc)$_3$ complex in the 90 MHz NMR spectrum. Saponification of 5 followed by Grignard-induced ring closure according to the procedure of Birkofer[9] afforded the chiral β-lactam (4), (32% from 5); α_D^{24} = -132°, c = 1 (MeOH); lit[8] α_D^{20} = -132°, c = 1, (MeOH). An alternate (lower yield) method for production of this β-lactam involved the Arndt-Eistert homologation of D-(-)-phenylglycine[2] to give (-)-methyl-β-phenyl-β-alanate (5) followed by similar ring closure to give 4 α_D^{24} = -128°, c = 1, (MeOH).



(a) 40% NaOH; (b) $(CH_3)_3Si$-Cl, Et_3N; (c) EtMgBr

Starting with putrescine (6), the known N,N^1-bis-(3-hydroxypropyl)-1,4-diaminobutane (7) was prepared by the procedure of Tabor.[10] (Scheme) The amines were then protected to give the diurethanyldiol (8) (91%)[11]. The alcohols were activated for introduction of the β-lactam (4) by reaction with p-toluenesulfonyl chloride, affording the ditosylate (9) (41%). Displacement of the tosyl groups with the sodium salt of the β-lactam (4) yielded the adduct (10) (63%)[12]. Deprotection of the amines followed by neutralization with 1N NaOH liberated the key intermediate (2).

Among the procedures studied for bringing about the desired transamidation reaction, pyrolysis proved to be the most fruitful. Thus, refluxing 2 in purified quinoline for 10 hr (or, for 3 hr in diphenyl ether saturated with air) afforded the ring-expanded product (3) (25%).[13] Since the BOC protecting group underwent fragmentation at the temperatures required for the transamidation, pyrolysis of the intermediate (10) furnished compound (3) directly (28%). Eschweiler-Clark methylation[14,15] of 3 completed the synthesis of homaline[15]; α_D^{24} = -30°, c = .43 ($CHCl_3$); lit[1] α_D = -34°, c = 1 ($CHCl_3$). In our hands, natural homaline obtained from Dr. Pais showed α_D^{24} = -31°, c = .40 ($CHCl_3$). The synthetic material was identical to natural homaline in all respects (270 MHz NMR, FTIR, TLC behavior).

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References and Notes

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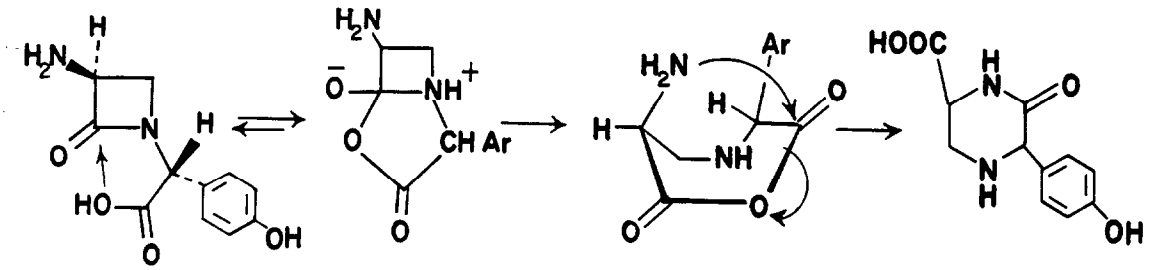
6. T. Kamiya, (Recent Advances in the Chemistry of β-Lactam Antibiotics, Cambridge University Press, London (1976)) has shown that 3-ANA (I) undergoes slow rearrangement on silica gel to the piperazone carboxylic acid (II). We suggest that this rearrangement takes place via an intramolecular attack by the neighboring carboxyl group, followed by acylation as shown.



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11. IR ($CDCl_3$) 3400, 1670 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 3.55 (4H, m, N-CH_2-), 3.33 (4H, t, J = 7, HO-CH_2-), 3.13 (4H, m, N-CH_2-), 1.83-1.40 (8H, m, inner CH_2), 1.43 (18H, s, $C(CH_3)_3$).
12. $(\alpha)_D^{25}$ -57.3°, c = 2 ($CHCl_3$); FTIR ($CDCl_3$) 1731, 1681 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (10H, broad s, Ar-H) δ 4.56 (2H, dd, J = 6,2, N-CH-Ph), 3.55-2.67 (16H, complex m), 1.70 (4H, m, J = 8, (N-CH_2-CH_2-CH_2-N), 1.45 (4H, broad s, (CH_2CH_2-CH_2-CH_2-N), 1.40 (18H, s, $C(CH_3)_3$).
13. $(\alpha)_D^{24}$ -30.0, c = 1.3 ($CHCl_3$); FTIR ($CDCl_3$) 1620 cm^{-1}; NMR ($CDCl_3$) δ 7.60-7.10 (10H, m, Ar-H), 4.30-2.20 (12H, m, N-CH_2), 4.03 (2H, dd, J = 2, 11, N-CH-Ar), 3.00 (2H, t, J = 11, CO-CH_AH_B), 2.50 (2H, dd, J = 2) 11, CO-CH_BH_A), 2.20-1.50 (8H, m, -$CH_2CH_2CH_2$).
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15. While methylation occurs quantitatively with CH_2O and $NaBH_3CN$, some racemization takes place under the reaction conditions; α_D^{24} = -16°, c = 1 ($CHCl_3$). Using CH_2O and HCOOH, optical integrity was preserved, but the yield was only 25%.

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