NEW APPROACHES TO THE SYNTHESIS OF SPERMINE AND SPERMIDINE ALKALOIDS

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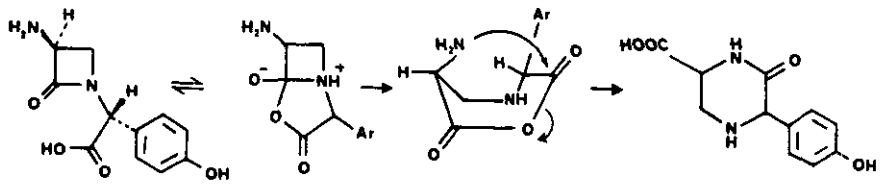
Abstract — New approaches to the formation of macrocyclic lactams are described involving successive ring expansion of β-lactams and other heterocyclic systems. These methods have been used in the synthesis of a number of spermine and spermidine alkaloids including homaline, celacinnine, dihydroperiphylline, chaenorhine and verbascenine.

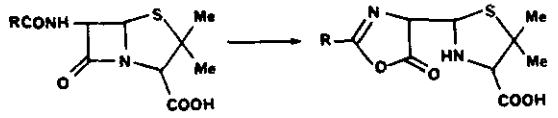
In recent years, there has been striking progress in the development of efficient methods for the formation of azetidinones, as a consequence of the intense activity in the synthesis of the β-lactam antibiotics. Our own work in this area has led to several new procedures for β-lactam synthesis, from cyclopropanone precursors,[1] from azetidine carboxylic acids[2] and from β-halopropionamides.[3] Examples of the application of these methods are found in syntheses of (±)-3-aminonocardicinic acid (3-ANA)(1).[4]

During the course of the above synthetic work, we became aware of a special aspect of β-lactam chemistry which had previously received little attention. In our studies on 3-ANA, we observed an interesting rearrangement of this material in d_5-pyridine/D_2O to form the piperazone carboxylic acid (3). This transformation, previously reported by Kamiya during silica gel chromatography of 3-ANA,[5] was viewed by us as shown in Scheme 1. Here, intramolecular attack of the β-lactam carbonyl by the carboxylate group yields an intermediate 7-membered cyclic anhydride (2) which undergoes further transformation to (3) the product of intramolecular acylation.



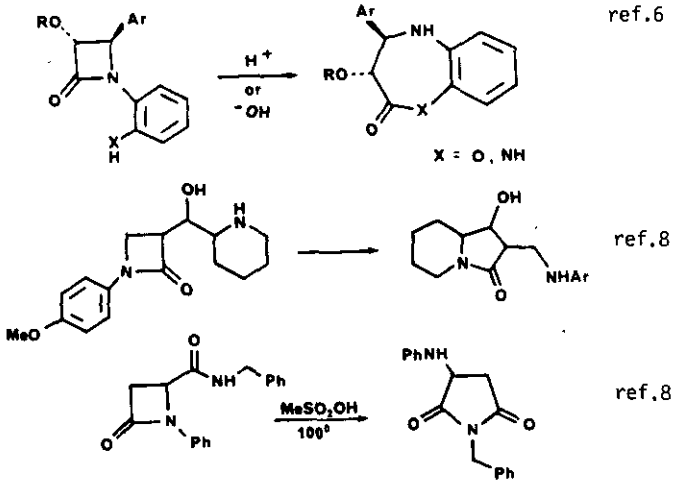
1 2 3 Scheme 1

The rearrangement of 3-ANA(1) to (3) is by no means the first example of the reactivity of β-lactams toward intramolecular ring expansion. In fact, as pointed out by Bose,[6] some of the early confusion over the structure of penicillin-G (4) was due, in part, to its facile



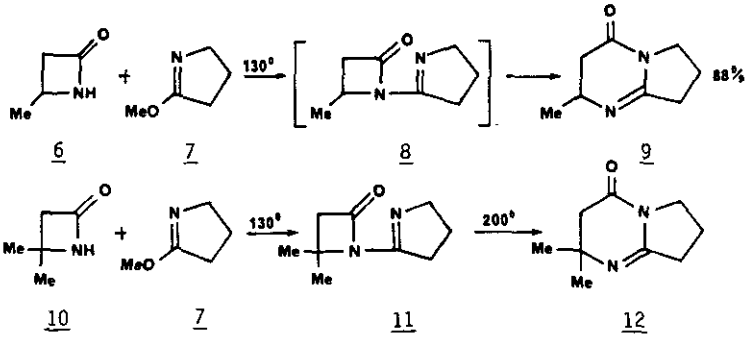
4 5

rearrangement to the oxazolone (5) by an intramolecular attack of the amide side chain.[7] A number of other, more recent examples of this type of reaction [6,8] are shown in Scheme 2. In these reactions, five and six-membered transition states leading to six and seven-membered heterocyclic products are most common.



Scheme 2

In related work, Bormann has reported an unusual azetidinone ring expansion which yields fused bicyclic heterocyclic systems.[9] For example, the reaction of 2-methoxypyrroline (7) *with 4-methylazetidin-2-one* (6) at 130°C gave the bicyclic 4-oxo-tetrahydropyrimidine (9), presumably via the acyl amidine[9] (8) (Scheme 3). Support for the intermediacy of 8 was provided by the reaction of 4,4-disubstituted lactams with lactim ethers. Thus, at 130°C the condensation of 4,4-dimethylazetidin-2-one (10) *with 2-methoxypyrroline* (7) furnished the stable and isolable acyl amidine (11). On raising the temperature to 180-200°C, 11 underwent rearrangement to form the fused bicyclic product (12).



6 7 8 9

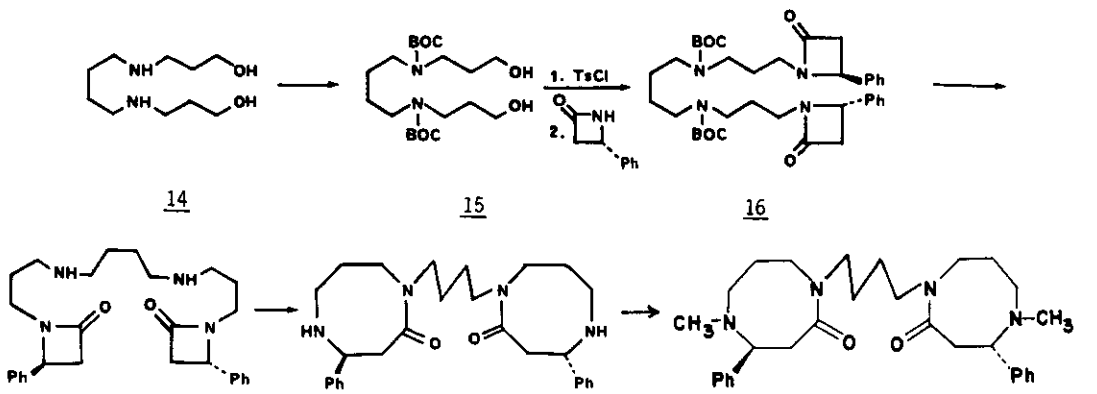
10 7 11 12

Scheme 3

The above examples show that β-lactams represent latent sources of β-amino-propionyl groups of potential use in synthetic application. In particular, one may note the possibility of using these systems in the formation of large ring lactams incorporating β-amino propionamide residues. Among naturally occurring macrocyclic systems, the spermine and spermidine alkaloids include a large number of compounds in which such residues form part of the macrocyclic backbone,[10] and we therefore chose several representatives of this group of compounds as synthetic objectives for the β-lactam ring expansion studies. As is outlined in the following discussion, we used the azetidinone-transamidation reaction in key phases of our synthesis of homaline (13),[11] celacinnine (22),[12] dihydroperiphylline (30),[13] and verbascenine (46).[14] In the formation of chaenorhine (37)[15], a variation of the Bormann coupling reaction was devised in which a β-amino ester served as a β-lactam equivalent.

(-)-Homaline

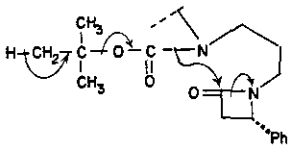
Our first demonstration of the use of ring-expansion methodology in the formation of a naturally occurring spermine alkaloid was the synthesis of (-)-homaline (13),[11] a bis-lactam isolated from the Homalium genus of plants.[16] Since β-lactams were previously known to undergo intramolecular attack by nucleophiles to form larger, less strained heterocycles, it seemed likely that the bis-8-membered system of homaline could be constructed by a double β-lactam transamidation reaction (Scheme 4).



Scheme 4

The key bis-lactam intermediate was synthesized starting from the known diol (14) which was converted (BOC-ON/Et_3N) to the diurethane diol (15) to protect the secondary amino groups. Tosylation (TsCl/py) of the hydroxyl groups and subsequent displacement with the sodium salt of (S)-4-phenylazetidin-2-one provided the adduct (16) in 24% overall yield from 15. Compound (16) was then treated with HCO_2H to remove the BOC protecting groups, forming 17. Refluxing 17 in quinoline for 10 hours brought about the desired transamidation reaction to yield the homaline ring system (18)(25%). More efficiently, pyrolysis of the diurethane 16 gave the bis-lactam (18)

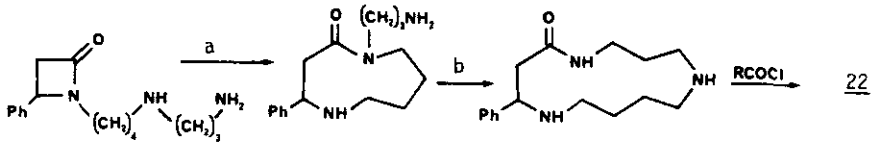
directly (36%) by the fragmentation sequence shown (Scheme 5). The synthesis of (-)-homaline (13) was finally completed by Eschweiler-Clarke methylation (CH_2O/HCOOH) of 18.



(±)-Celacinnine

Scheme 5

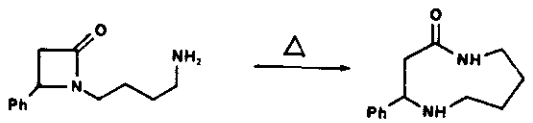
For the synthesis of celacinnine (22)[12] the route depicted in Scheme 6 was first considered. As in the "zip" reaction reported by Hesse et al,[17] this pathway would involve stepwise expansion of smaller ring lactam systems by transamidation. The formation of the 13-membered lactam (21) would be promoted by irreversible deprotonation of the secondary amide function. Furthermore, 21 would be thermodynamically favored over the more strained β-lactam and medium ring lactam precursors.



19 20 21 22

Scheme 6

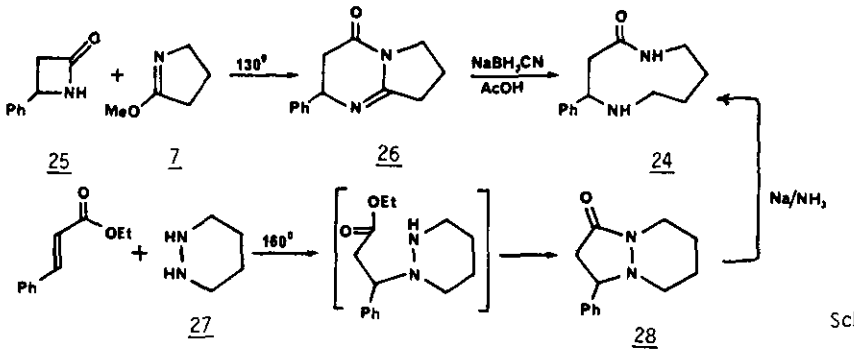
Step b (Scheme 6) is analogous to the "zip" reaction[17] in which 6-membered transition states are involved. Step a, designed to form the amino lactam (20), would have to proceed through a 7-membered transition state. We hoped that the β-lactam (19) might be sufficiently reactive to compensate for the relatively unfavorable 7-membered transition state. However, in studies on model systems, we found that while the primary amino group in 23 took part in transamidation to form 24, other systems containing secondary amino groups and/or larger ring lactams did not appear



23 24

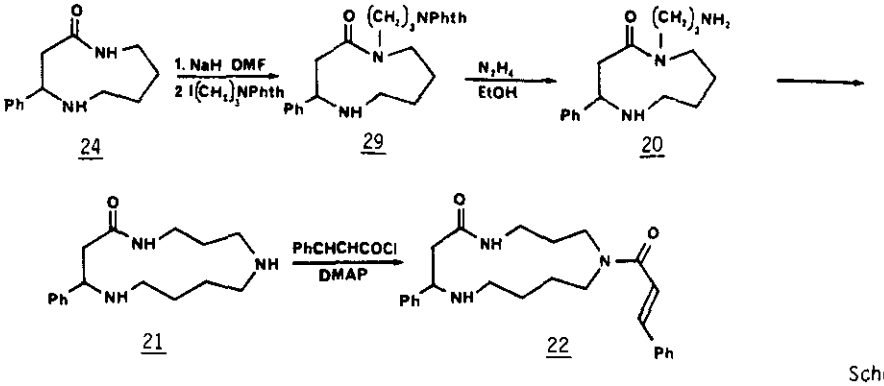
to undergo transamidation through seven-membered transition states. Accordingly, the intermediate amino lactam (20) which would have been formed in step a was prepared by an alternative route involving alkylation of the 9-membered lactam (24) with a 3-amino propyl equivalent. We also found two additional procedures for preparing 24.

Using the Bormann procedure,[9] 4-phenylazetidinone (25) was heated with 2-methoxypyrroline (7) yielding 4-oxo-tetrahydropyrimidine (26), which could be reduced with excess $NaBH_3CN$ in the presence of HOAc to form 24(31%) (Scheme 7). Better results were obtained by heating ethyl cinnamate with piperidazine (27) forming 2-oxo-4-phenyl-1,5-diazabicyclo[4·3·0] nonane (28) (80%). Fission of the N-N bond in 28 (Na/NH_3)[18] yielded 24(80%).



Scheme 7

Selective alkylation of the amide NH group (25%) was achieved by treatment of 24 with NaH in DMF followed by addition of N-(3-iodopropyl)- phthalimide (Scheme 8). The product 29 was heated in ethanol with $H_2N-NH_2\cdot H_2O$ followed by warming in 1N NaOH to yield 21 (50%). Lactam (21) was then converted to celacinnine (22)(85%) by acylation with trans-cinnamoyl chloride as reported by Ganem[19] and by Yamamoto.[20]

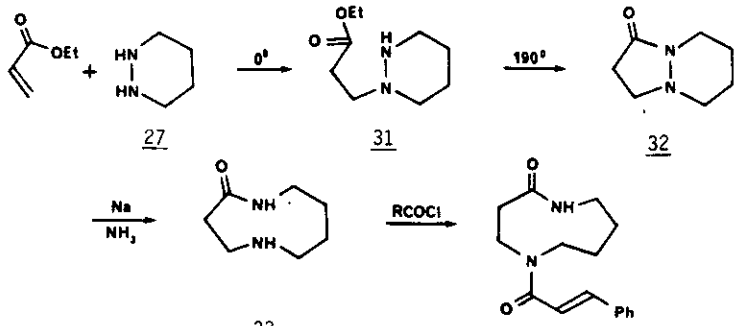


Scheme 8

(±)-Dihydroperiphylline

The synthesis of (±)-dihydroperiphylline (30) was achieved in an efficient 6-step sequence making use of internal N-N and C-N bond cleavage reactions of the type previously employed in the celacinnine work.[13] An important aspect of the synthesis is that, in contrast to the celacinnine route, the trans-cinnamoyl group was specifically introduced at an early stage, eliminating the need for selective acylation in the last step.

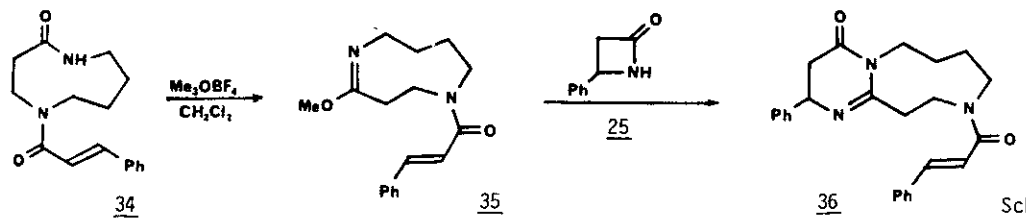
2,7-Diazacyclononanone (33) was obtained in a manner entirely analogous to the preparation of the 8-phenyl derivative (24) used in the synthesis of celacinnine (Scheme 9). Slow addition of ethyl acrylate to piperidazine (27) at 0°C led to formation of the Michael adduct (31), which, on heating to 190°C underwent cyclization with loss of ethanol to give the bicyclic acyl hydrazine (32)(85%). The 9-membered lactam (33) was then obtained by Na/NH_3 reduction of 32 (87%). This material was then treated with trans-cinnamoyl chloride in the presence of DMAP to provide the acylamino lactam (34)(95%).



27 31 32 33 34

Scheme 9

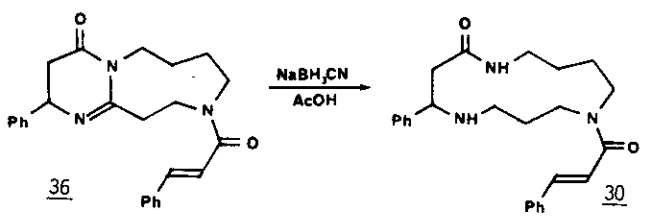
To prepare for the subsequent inclusion of the 3-aminopropionyl unit, the acylamino lactam (34) was activated by reaction with trimethyloxonium tetrafluoroborate followed by basic aqueous workup to give the lactim ether (35)(78%) (Scheme 10). The reaction of the lactim ether (35) with 4-phenylazetidin-2-one (25) provided the first example of the Bormann condensation involving a medium ring lactim ether. After heating the reactants in refluxing chlorobenzene, the 4-oxo-tetrahydropyrimidine (36) was isolated in 67% yield.



34 35 25 36

Scheme 10

The final step in the synthesis involved the treatment of 36 with 3 equivalents of $NaBH_3CN$ in acetic acid (Scheme 11). The yield (93%) of synthetic dihydroperiphylline (30) in this step was a significant improvement over that (31%) for a related reaction (reduction of 26) in the celacinnine synthesis.



36 30

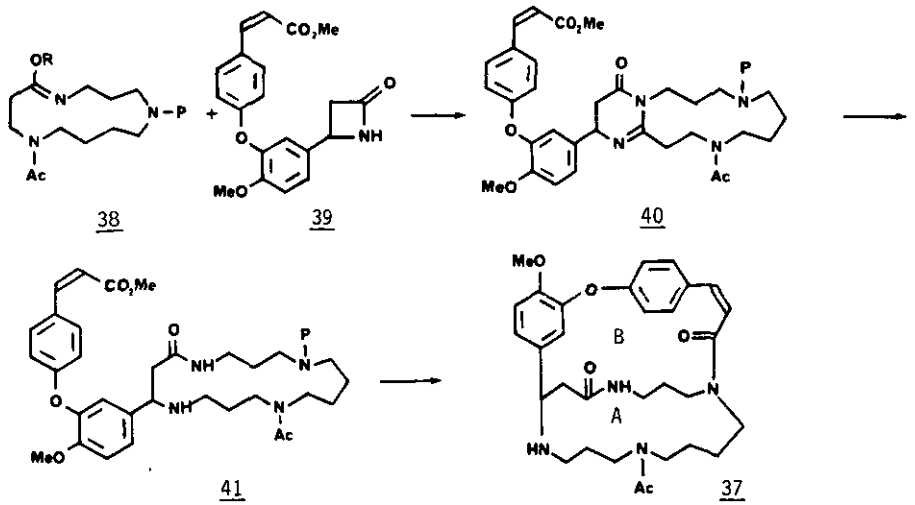
Scheme 11

(±)-Chaenorhine[15]

In considering the synthesis of chaenorhine (37), the problem of forming two fused macrocyclic lactam rings had to be addressed. The aliphatic lactam (ring A), incorporating a 3-amino-3-arylpropionyl group, appeared amenable to preparation via the ring expansion route previously employed in the syntheses of celacinnine and dihydroperiphylline. These procedures

were, however, not applicable to the formation of the second macrocyclic ring (ring B) containing the unsaturated residues. This lactam would have to be generated in a macrocyclization step involving intramolecular amide bond formation.

Leaving the macrocyclization step until the end of the synthesis, an approach to chaenorhine was first envisioned which would involve Bormann reaction of a suitably protected lactim ether (38, R=Me or Et, P=protecting group) with a β-lactam component (39). The aromatic portion of the molecule could then be introduced as part of this coupling step (Scheme 12). Reductive opening of the 4-oxo-tetrahydropyrimidine ring (40) would then produce the mono-macrocyclic system (41) as a fully functionalized intermediate designed to generate 37 in the final macrolactamization.

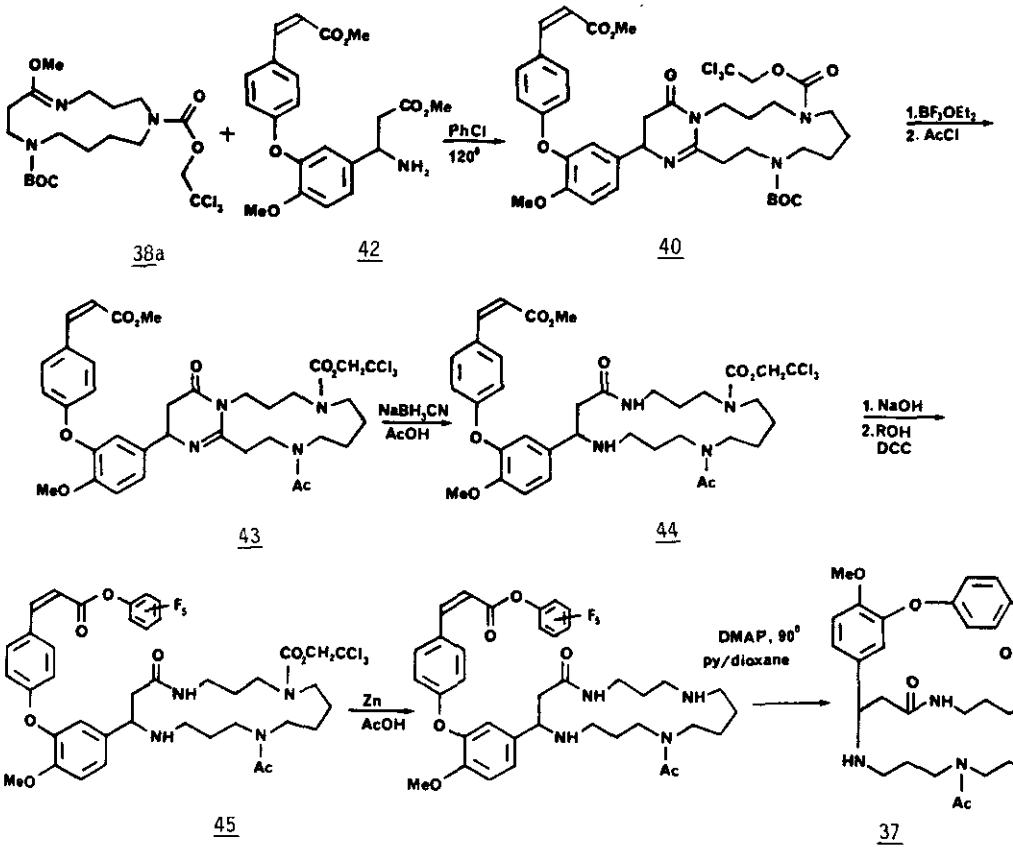


Scheme 12

This approach to chaenorhine appeared to have the distinct advantage over other approaches (requiring two macrocyclization steps) of being highly convergent. Synthetic transformations used in the preparation of each component could thus be carried out with reduced risk of interference with other functionalities and protecting groups. The somewhat acid sensitive cis-cinnamoyl group could be introduced at a relatively late stage in the synthesis, diminishing the opportunities for cis- to trans- isomerization. In practice, we were able to use the above procedure essentially as outlined, except for the use of the β-lactam. We found that the β-amino ester equivalent (42) of this lactam was much more readily available and we therefore chose to use this species even though it was less reactive than the typical β-lactam participant.

The synthesis is summarized in Scheme 13 showing the use of two key fragments, the 13-membered imino ether (38a) and the substituted β-amino ester (42). The imino ether (38a) was prepared by the sequence outlined in Scheme 14; the amino ester (42) was formed by the reaction of methyl cis-p-bromocinnamate with the copper salt shown in Scheme 15. Coupling of the two components was followed by introduction of the acetyl group yielding 43, and then reductive ring

opening to 44, the monocyclic precursor of chaenorhine. The final lactamization was accomplished by hydrolysis of the methyl ester in dilute NaOH, activation of the acid with pentafluorophenol (DCC) forming 45, removal of the trichloroethoxycarbonyl protecting group (Zn,HOAc) and macrocyclization to 37 in pyridine/dioxane in the presence of dimethylaminopyridine.

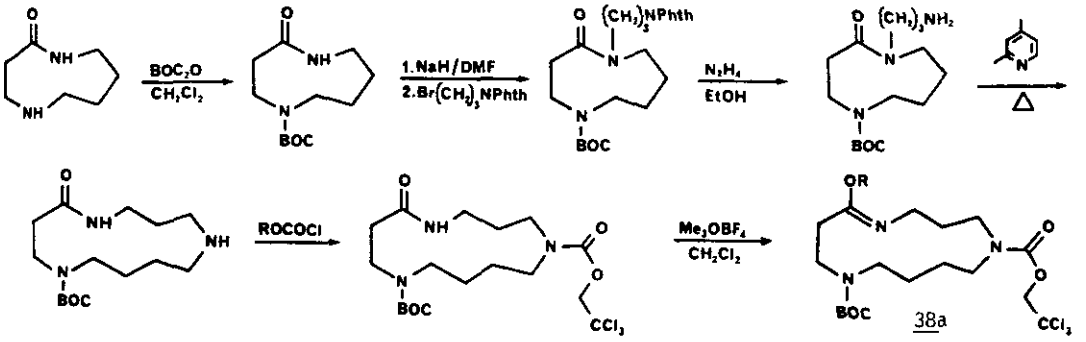


38a 42 40

43 44

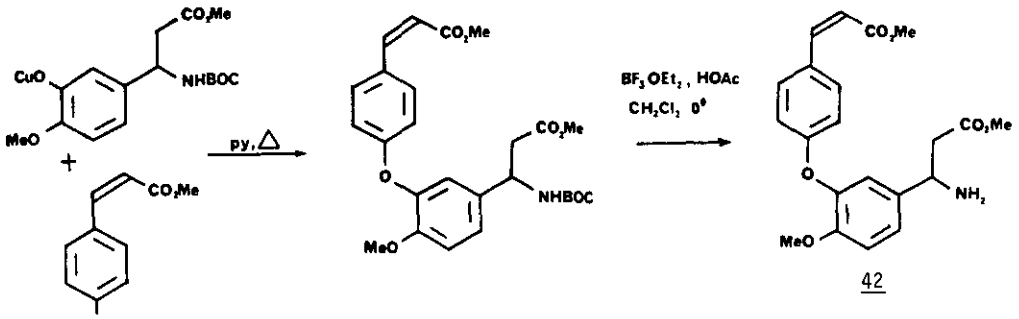
45 37

Scheme 13



38a

Scheme 14



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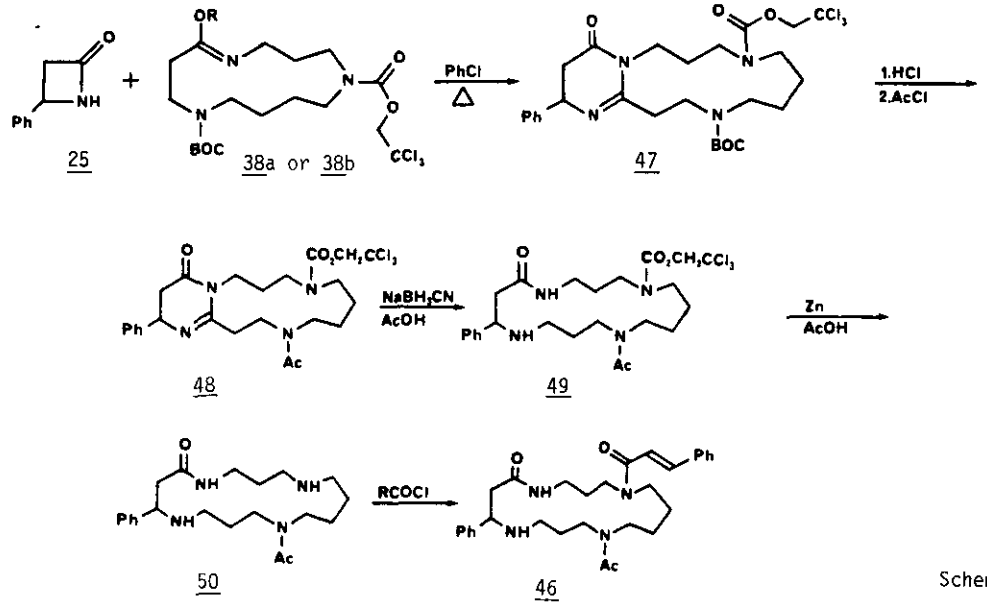
Scheme 15

(±)-Verbascenine[14]

The procedures employed for construction of the non-aromatic 17-membered lactam (ring A) of chaenorhine could be readily applied to the synthesis of related polyamine alkaloids containing the same ring system, for example, the recently isolated alkaloid, verbascenine (46). In the construction of 46, all but one nitrogen atom of the spermine unit could be delivered through the key macrocyclic lactim ether (38).

The verbascenine synthesis involved condensation of the lactim ethers (38a) or (38b) with 4-phenylazetidin-2-one (25) to form the 4-oxo-tetrahydropyrimidine (47) (Scheme 16). We found that the yield of (47)(59%) using the ethyl lactim ether (38b) was nearly four times higher than the product resulting from use of the methyl derivative (38a)(16%). It appears that with 38a, regeneration of the 13-membered lactam by demethylation is a serious side reaction.

Exchange of the BOC group for an acetyl group was accomplished by standard means. After treatment of 47 with HCl in methylene chloride, the resulting amine was treated with acetyl



25 38a or 38b 47 48 49 50 46

Scheme 16

chloride in the presence of DMAP to provide pure 48 (80%). The 17-membered lactam (49) was then obtained (88%) by reductive opening of the 4-oxo-tetrahydropyrimidine ring with $NaBH_3CN$. Removal of the trichloroethoxycarbonyl protecting group affording the diaminolactam (50).

Selective cinnamoylation of (50), the final step in the verbascenine synthesis, was carried out under conditions similar to those used for the analogous acylation in the celacinnine synthesis, yielding the racemic alkaloid (46)(58% from 49).

ACKNOWLEDGEMENT This work was supported by Grants GM-07874 and GM-31350 from the National Institutes of Health.

REFERENCES

1. H. H. Wasserman, H. W. Adickes and O. E. Ochoa, J.Am.Chem.Soc., 1971, 93, 5586.
2. H. H. Wasserman, B. H. Lipshutz, A. W. Tremper and J. S. Wu, J.Org.Chem., 1981, 46, 2991.
3. H. H. Wasserman, D. J. Hlasta, A. W. Tremper and J. S. Wu, Tetrahedron Lett., 1979, 549.
4. H. H. Wasserman, D. J. Hlasta, A. W. Tremper and J. S. Wu, J.Org.Chem., 1981, 46, 2999.
5. T. Kamiya, Recent Advances in the Chemistry of β-Lactam Antibiotics, Cambridge University Press, London, 1976.
6. M. S. Manhas, S. G. Amin and A. K. Bose, Heterocycles,1976, 5, 669.
7. A. H. Cook, Quarterly Reviews, 1948, 2, 203.
8. S. Kano, T. Ebata, Y. Denta, S. Hibino and S. Shibuya, Heterocycles, 1977, 8, 411.
9. D. Bormann, Chem.Ber., 1970, 103, 1797.
10. For a review of recent synthetic work in this field, see H. H. Wasserman and J. S. Wu, Heterocycles, 1982, 17, 581
11. H. H. Wasserman and G. Berger, Tetrahedron Lett., 1982, 23, 465.
12. H.H. Wasserman, R. P. Robinson and H. Matsuyama, Tetrahedron Lett., 1980, 3493.
13. H. H. Wasserman and H. Matsuyama, J.Am.Chem.Soc., 1981, 103, 461.
14. H. H. Wasserman and R. P. Robinson, Tetrahedron Lett., 1983, 24, 3669.
15. H. H. Wasserman, R. P. Robinson and C. G. Carter, J.Am.Chem.Soc., 1983, 105, 1697.
16. M. Pais, G. Rattie, R. Sarfati and F. X. Jarreau, C.R. Acad. Sci. Paris, 1968, 267, 82.
17. U. Kramer, A. Gugglsberg, M. Hesse and H. Schmid, Angew.Chem.Int.Ed. Engl., 1977, 16, 861.
18. D. S. Kemp, M. D. Sidell and T. J. Shortridge, J.Org.Chem., 1979, 44, 4473.
19. J. S. McManis and B. Ganem, J.Org.Chem., 1980, 45, 2041.
20. H. Yamamoto and K. Maruoka, J.Am.Chem.Soc., 1981, 103, 6133.