THE TOTAL SYNTHESIS OF MACROCYCLIC SPERMINE AND SPERMIDINE ALKALOIDS†

Harry H. Wasserman* and James S. Wu

Department of Chemistry, Yale University
New Haven, Connecticut

Abstract-Useful new synthetic methods for the preparation of macrocyclic spermine and spermidine lactam alkaloids have recently been developed. This review describes work which has led to the total synthesis of a number of compounds in this series.

Table of Contents

I. Introduction
II. Individual syntheses
A. Celacinnine, celallocinnine, celabenzine, and celafurine
B. Dihydroperiphylline and tetrahydroperiphylline
C. Lunarine and lunaridine
D. Codonocarpine
E. Homaline
F. Dihydropalustrine
G. Oncinotine, neooncinotine, isooncinotine, and pseudooncinotine

I. Introduction

The group of macrocyclic lactams containing the biogenetic bases spermine (1) and spermidine (2) represents a new class of polyamine alkaloids which are of particular interest as synthetic targets for the organic chemist in view of the broad activity which has been established for spermine and spermidine-containing compounds in biological systems and because of the structural complexity of the molecules themselves.[1,2] Generally, the spermine and spermidine macrocycles represent a wide variety of structural types which have as their most salient feature a macrocyclic lactam formed from the polyamine base.

$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$ (1)

$H_2N(CH_2)_3NH(CH_2)_4NH_2$ (2)

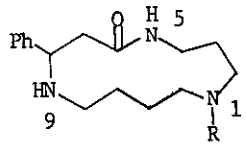
†*The authors take great pleasure in dedicating this paper to Professor Kyosuke Tsuda on the occassion of his 75th birthday.*

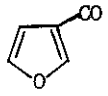
Among the naturally occurring spermine and spermidine macrocycles currently known, both monocyclic and bicyclic compounds containing 8-22 members are represented. The reviews available to date dealing with the chemistry of these macrocyclic alkaloids have been confined primarily to their isolation and structural elucidation.[2] In this survey, we are reporting details of the total syntheses of spermine and spermidine macrocycles bringing into focus special problems associated with the construction of these complex molecules.

II. Individual syntheses

A. Celacinnine, celallocinnine, celabenzine, and celafurine

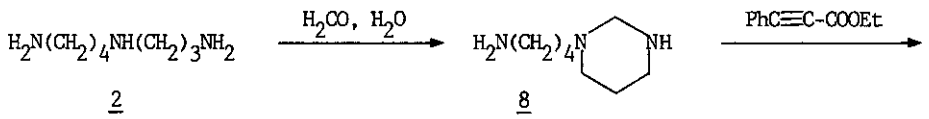
The macrocyclic alkaloids celacinnine (3), celallocinnine (4), celabenzine (5), and celafurine (6) were isolated in 1974 by Kupchan and co-workers[3] from Maytenus arbutifolia and Tripterygium wilfordii, members of the plant family Celastraceae. Their structures have in common a 13-membered ring composed of a spermidine and a beta-phenylpropionate precursor. The compounds differ only with respect to the acyl function attached to N-1, and all may be prepared by reaction of the macrocyclic amine (7) with an appropriate acid chloride. The selective acylation at N-1 appears to be a consequence of steric hinderance at N-9 due to the neighboring phenyl group.



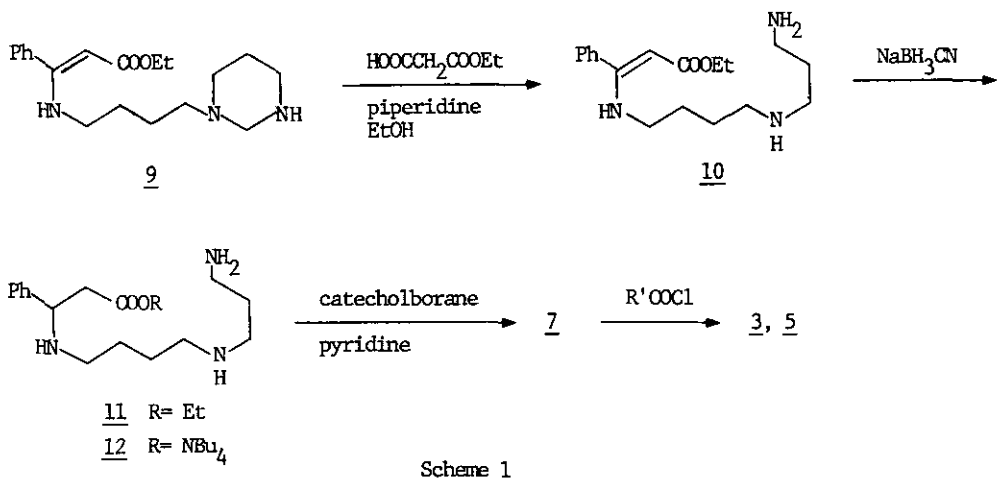
3 R= PhCH=CHCO (trans)
4 R= PhCH=CHCO (cis)
5 R= PhCO
6 R= 

7 R= H

Three syntheses of (7) have appeared in the recent literature. The first synthesis reported by Ganem and McManis[4] involved initial preparation of the N^1, N^2 protected spermidine (8) from equivalent amounts of spermidine and aqueous formalin (87%). Conjugate addition of (8) to ethyl phenylpropiolate gave the enamino ester (9) which was converted to the triamino derivative (10) and then reduced with $NaBH_3CN$ to give the ester (11) [43% overall yield from (8)]. Hydrolysis of the ester with tetrabutylammonium hydroxide afforded triamino-carboxylate (12) which was cyclized in 61-66% yield by exposure to catecholborane in pyridine at 80°C. Acylation with either cinnamoyl chloride or benzoyl chloride gave (±)-celacinnine (40%) and (±)-celabenzine (40%) respectively. The route is summarized in Scheme 1.

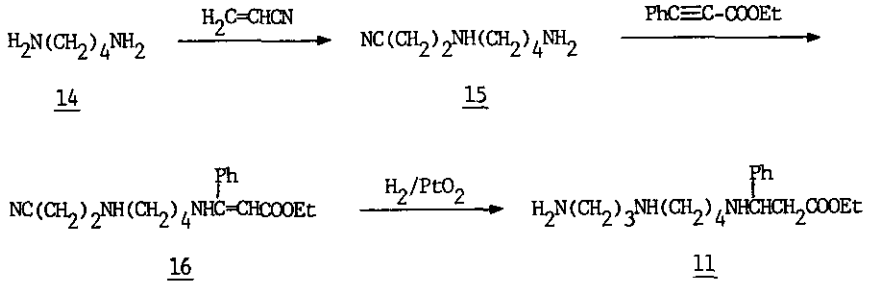


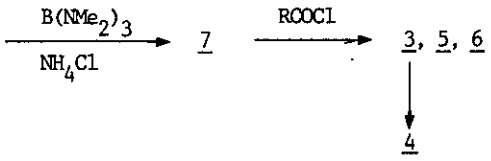
2 8



Scheme 1

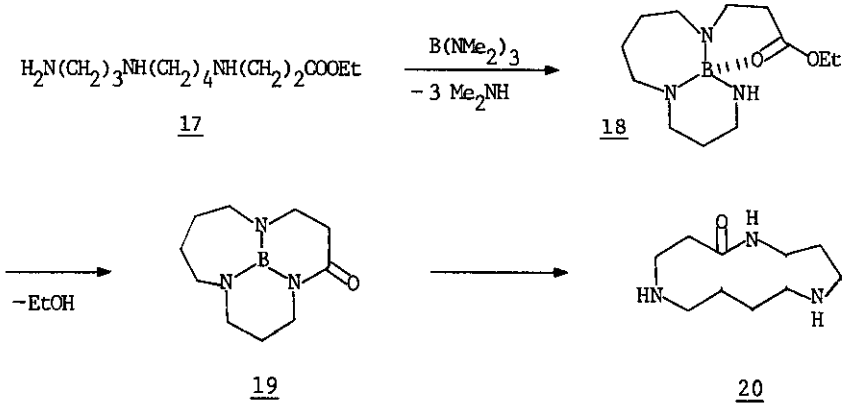
A second synthesis of (7), reported by Yamamoto and Maruoka[5], is notable for the boron-templated macrolactamization of the triaminoester (11) to give (7). The required (11) was prepared in three steps starting from 1,4-diaminobutane (14). Conjugate addition of (14) to acrylonitrile gave amine (15) (68%) which was then converted to cyano ester (16) (92%) by reaction with ethyl phenylpropiolate. Hydrogenation of the cyano group over platinum oxide yielded the desired triaminoester (13) (82%) which was then treated with tris(dimethylamino)borane in freshly distilled xylene to give the macrocyclic (7) (90%) following silica gel chromatography of the crude reaction mixture. Acylation of (7) with the corresponding acid chlorides in the presence of 4-(dimethylamino)pyridine at low temperature gave (±)-celacinnine, (±)-celabezine, and (±)-celafurine in almost quantitative yield. Irradiation of (±)-celacinnine in benzene afforded a mixture of the cis isomer (±)-celallocinnine (50%) and recovered starting material (30%). The detailed reaction pathway leading to (7) from (14) is shown in Scheme 2.





Scheme 2

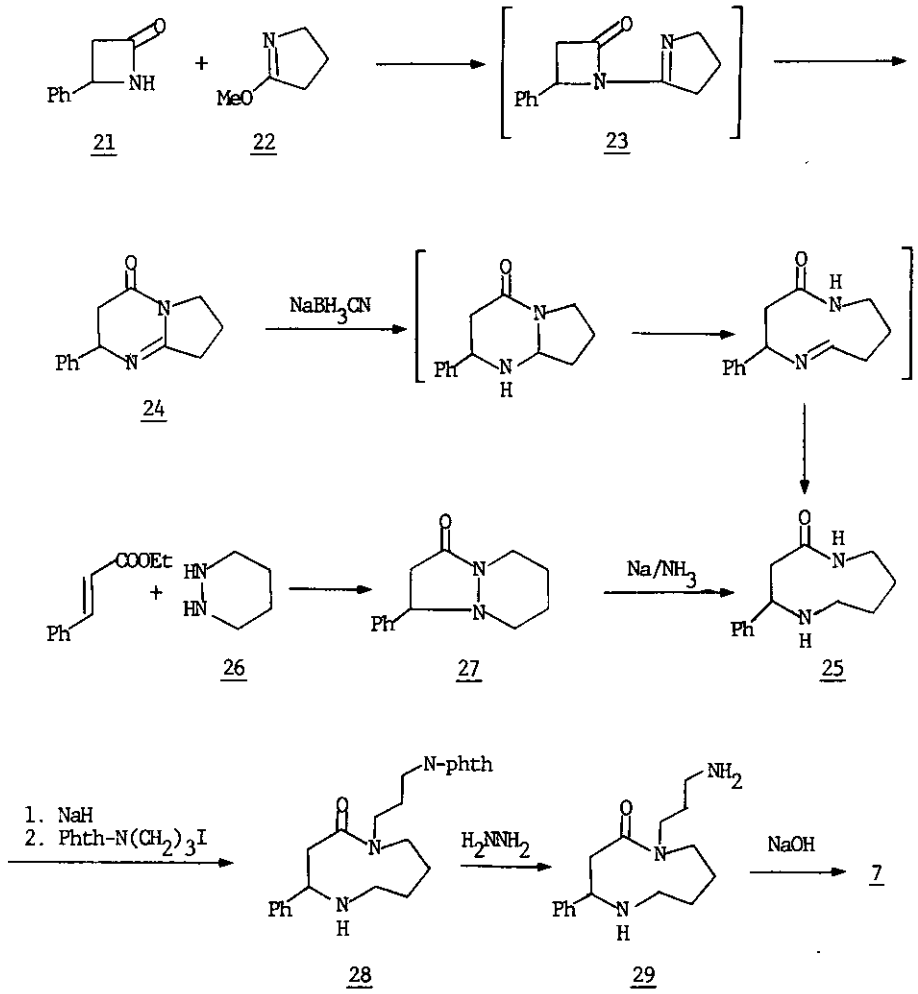
As illustrated in Scheme 3 for triaminoester (17), the proposed mechanism for the crucial macrocyclization step involves initial boronation to intermediate (18) followed by lactamization to boron complex (19), and finally, deboronation to give macrocycle (20).



Scheme 3

A third synthesis of (7) is due to Wasserman et. al.[6] who prepared the 13-membered ring system by a sequence involving successive expansion of smaller heterocyclic rings, This synthesis, shown in Scheme 4, starts with 4-phenyl-2-azetidinone (21) which upon reaction with 2-methoxypyrroline (22) gave bicyclic 4-oxotetrahydropyrimidine (24) presumably via (23). Reductive cleavage of (24) with excess $NaBH_3CN$ in the presence of acetic acid followed by workup in aqueous sodium hydroxide gave the nine-membered lactam (25) (31%). An alternative route to (25) started with the reaction between ethyl cinnamate and piperidazine (26) to give the bicyclic diazanonane (27) (71%). Reductive fission of the N-N bond with Na/NH_3 afforded lactam (25) in 80% yield. Treatment of (25) with sodium hydride followed by addition of N-(3-iodopropyl)phthalimide gave the tertiary amide (28). Removal of the phthalimide function with ethanolic hydrazine generated the N-(3-aminopropyl)lactam (29) which upon warming with dilute sodium hydroxide underwent transannular ring expansion to (7) in 70% overall yield from (28).

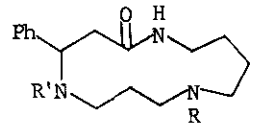
Synthetic (±)-celacinnine was obtained by regioselective acylation with cinnamoyl chloride according to the method of Ganem.[4]



Scheme 4

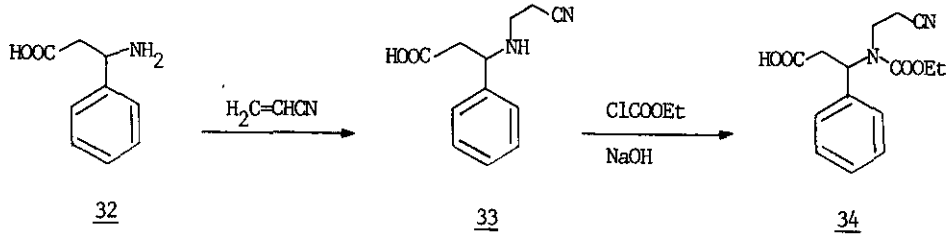
B. Dihydroperiphylline and tetrahydroperiphylline

Dihydroperiphylline (30) and tetrahydroperiphylline (31), isolated from the leaves of Peripterygia marginata, are 13-membered lactams derived from dicinnamoylspermidine.[7] The two compounds are structurally related to celacinnine, differing only with respect to the arrangement of the spermidine within the lactam ring.

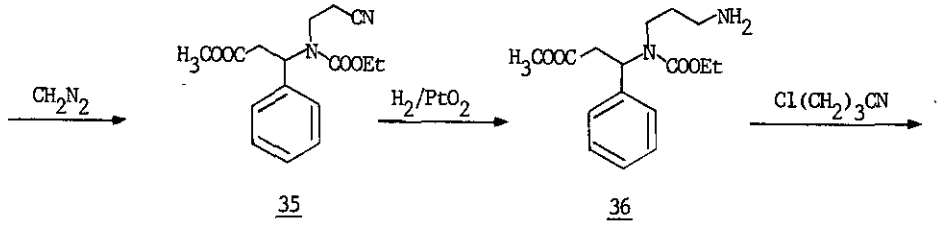


30 R= PhCH=CHCO (trans), R'= H
31 R= $PhCH_2CH_2CO$, R'= H
31a R= $PhCH_2CH_2CO$, R'= COOEt

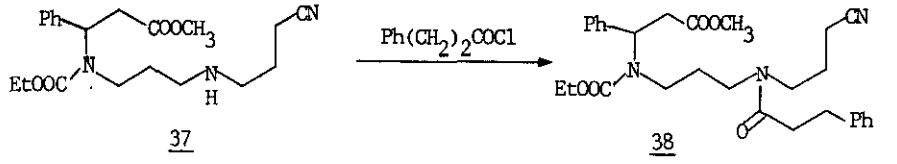
(±)-Tetrahydroperiphylline (31) was first synthesized by the Gif group.[8] The synthesis, depicted in Scheme 5, involves the sequential addition of a spermidine unit to β-phenyl-β-alanine (32) followed by direct cyclization to the natural product. Treatment of (32) with acrylonitrile afforded amine (33) which was acylated (68%) to (34) with ethyl chloroformate in dilute sodium hydroxide. Following conversion of (34) to the methyl ester (35), the nitrile function was reduced by hydrogenation over platinum oxide to amine (36) (86%). Monoalkylation of (36) with 4-chlorobutyronitrile in HMPT afforded (37) (55%) which was acylated with beta-phenylpropionyl chloride to afford nitrile (38). Catalytic reduction of the nitrile function gave the amino ester (39) (97%) which underwent saponification with methanolic sodium hydroxide to the acyclic amino acid (40). Macrocyclization by sequential treatment of (40) with pyridine, ethyl chloroformate, and triethylamine in DMF solution at -15°C afforded the urethane derivative of (±)-tetrahydroperiphylline (5.4%) which was identical to material obtained by direct acylation of an authentic sample of the natural product.



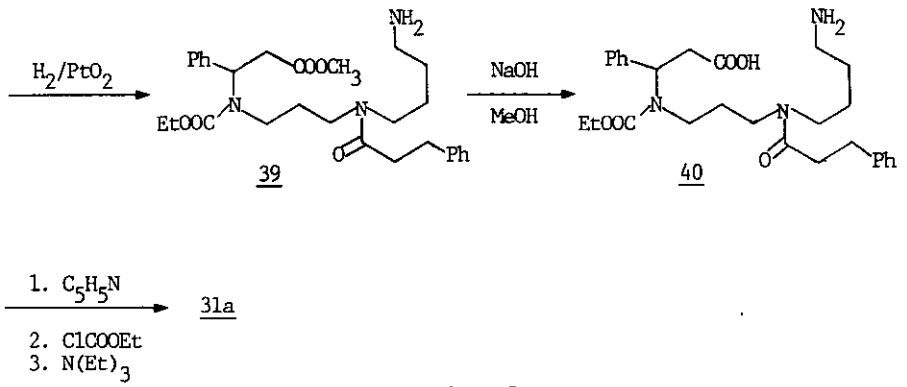
32 33 34



35 36



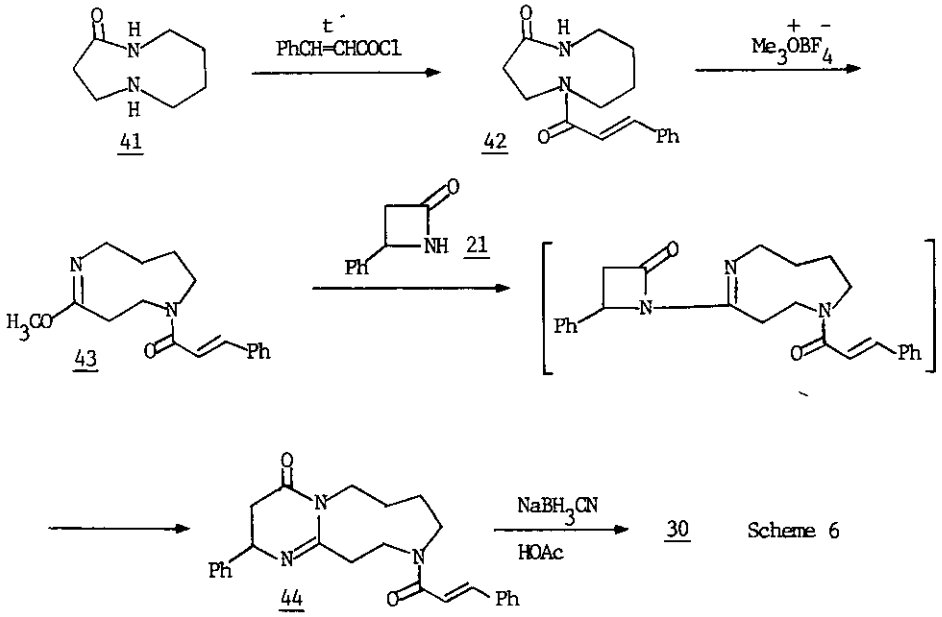
37 38



Scheme 5

The total synthesis of (±)-dihydroperiphylline (30) was recently accomplished by Wasserman and Matsuyama.[9] The strategy for this synthesis was based on procedures previously reported in the preparation of (±)-celacinnine[6] whereby the macrocyclic ring is formed by successive ring expansions of smaller heterocyclic units. The outline of this synthesis is shown is Scheme 6.

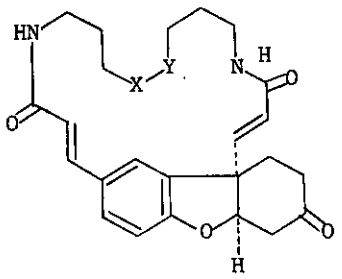
Acylation of (41) with trans-cinnamoyl chloride in the presence of 4-(dimethylamino)pyridine gave diamide (42) (95%) which was converted to the imino ether (43) with Meerwein's reagent (83%). The subsequent addition-ring expansion[6,10] of (43) with 4-phenyl-2-azetidinone (21) afforded the bicyclic ring-enlarged product (44) (67%). Final reduction of (44) with $NaBH_3CN$ in acetic acid resulted in the formation of (±)-dihydroperiphylline (30) (93%).



Scheme 6

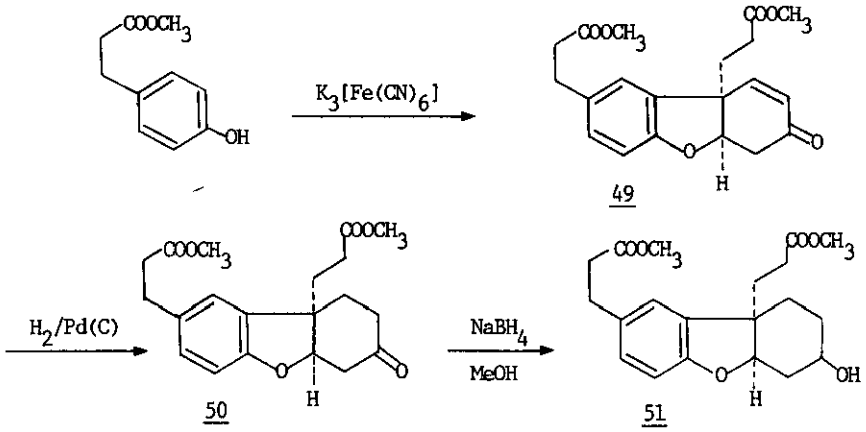
C. Lunarine, lunaridine, and tetrahydrolunaridine

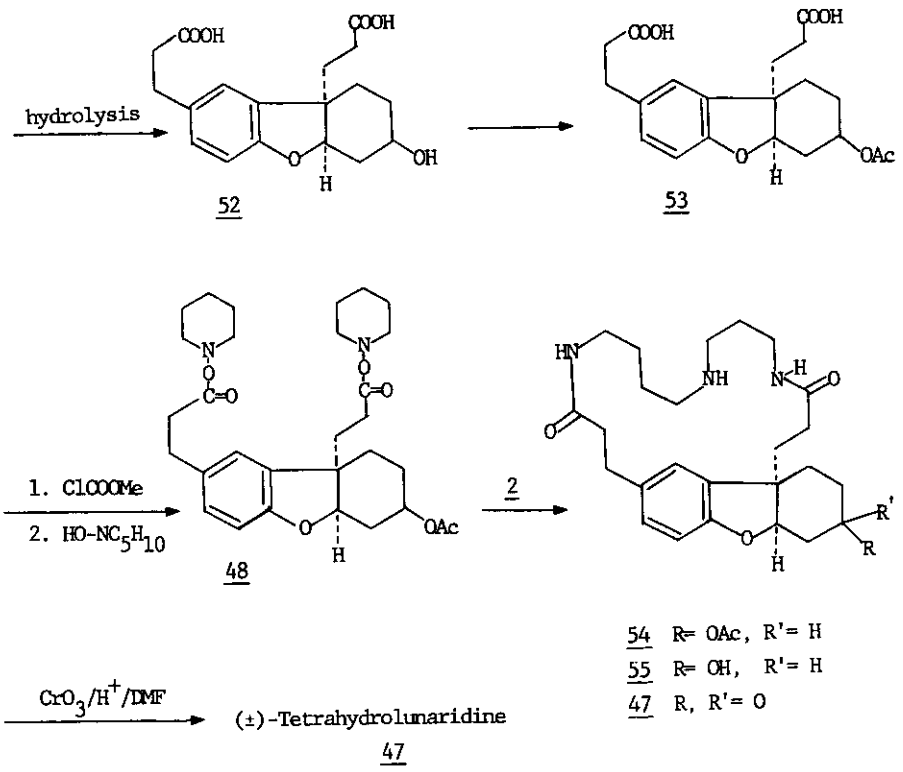
Lunarine (45) and lunaridine (46), isolated from Lunaria biennis (Cruciferae) by Potier and co-workers in 1972,[11] are 20-membered lactams which are structurally derivable from spermidine and p-hydroxycinnamic acid. The two molecules differ only with respect to the arrangement of the spermidine residue in the lactam ring.



45 X= NH, Y= CH_2
46 X= CH_2, Y= NH

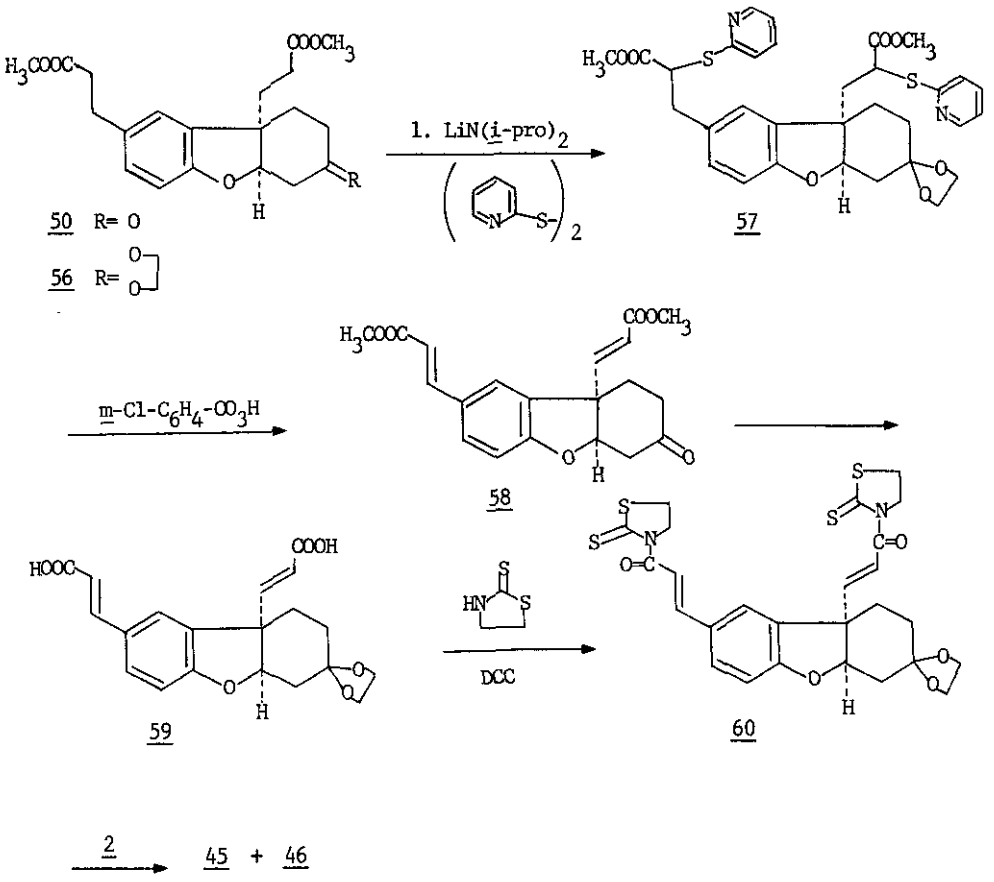
In an early synthesis, tetrahydrolunaridine (47) was prepared in its racemic form by the Potier group[12] following a route which featured the stereoselective addition of spermidine to the "doubly activated" diacyl intermediate (48) in the macrolactamization step. The synthesis proceeds according to Scheme 7. The Pummerer ketone-like compound (49) was prepared in 14% yield by oxidative coupling of methyl 3-(p-hydroxyphenyl)proionate with potassium ferricyanide. Catalytic reduction of the enone double bond gave ketone (50) which was converted to the alcohol (51) following treatment with sodium borohydride in methanol. Hydrolysis of (51) gave diacid (52) which after conversion to the acetate (53) underwent successive reactions with methyl chloroformate and then N-hydroxypiperidine to afford the N, N'-diacylhydroxyamine (48). Condensation of (48) with spermidine in refluxing THF gave, regiospecifically, macrocyclic lactam (54) (12%). Following saponification of the acetate, the resulting alcohol (55) was oxidized to (±)-tetrahydrolunaridine (47) upon treatment with chromium trioxide in acidic DMF.





Scheme 7

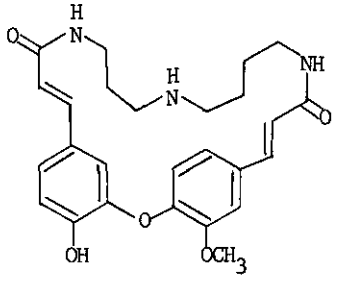
Following a similar synthetic strategy, Fujita and co-workers[13] prepared (±)-lunarine (45) and (±)-lunaridine (46) starting from Potier's ketone (50). Protection of (50) resulted in the formation of ketal (56) which upon sequential treatment with lithium diisopropylamide in THF at -78°C and di-2-pyridyl disulphide afforded sulfide (57). After oxidation of (57) with excess m-chloroperbenzoic acid in benzene, the reaction mixture was heated to afford the α,β-unsaturated diester (58) in 46% yield from (50). Regeneration of the ethylene ketal followed by ester hydrolysis with lithium hydroxide in aqueous THF afforded the diacid (59) [89% from (58)]. Activation of the carboxylic acids with thiazolidine-2-thione in the presence of dicyclohexylcarbodiimde and 4-(dimethylamino)pyridine yielded the diamide intermediate (60). Simultaneous slow addition of dilute solutions of (60) and spermidine to a large volume of methylene chloride furnished an oily substance from which was isolated (±)-lunarine (45) [18% from (59)] and (±)-lunaridine (46) [19.6% from (59)] following preparative layer chromatography on silica gel. The synthesis is summarized in Scheme 8.



Scheme 8

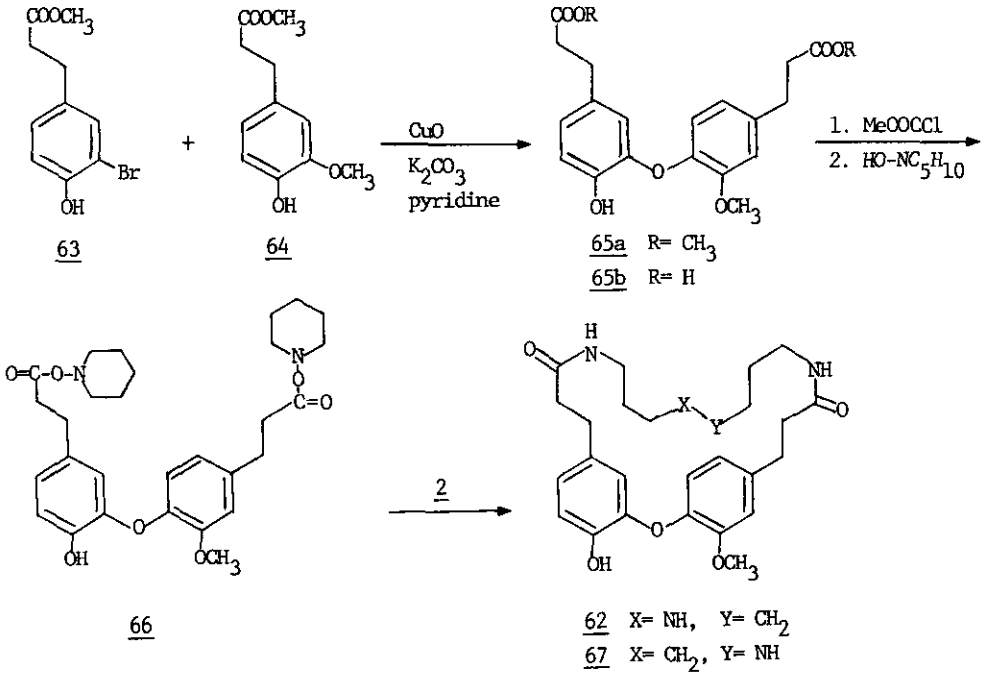
D. Codonocarpine

The 24-membered macrolactam codonocarpine (61) was isolated from the bark of Codonocarpus australis (Phytolaccaceae) in 1972.[14] Similar to the Lunaria class of alkaloids, codonocarpine is structurally derived from di-p-hydroxycinnamoyl-spermidine.



61

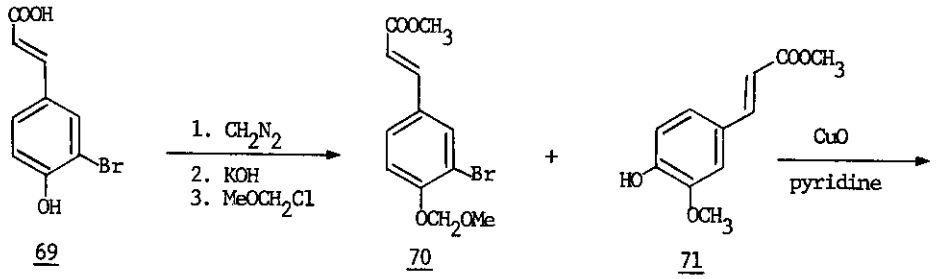
Poupat's synthesis of tetrahydrocodonocarpine (62) in 1976[15] introduced a general strategy for construction of the complex macrocyclic ring system. This synthesis, summarized in Scheme 9, involves initial preparation of the key biphenyl ether fragment (65a) by Ulmann coupling of the 3-(p-hydroxyphenyl)-propionic acid derivatives (63) and (64) (26%). Hydrolysis of the ester groups furnished diacid (65b) which upon successive reaction with methyl chloroformate and then N-hydroxypiperidine in the presence of triethylamine afforded a mixture of the diesters containing (66) (34%). Final reaction of (66) with spermidine provided tetrahydrocodonocarpine (62) which was identical to the product obtained from catalytic hydrogenation of natural codonocarpine. The isomeric lactam (67) was also obtained as a significant reaction side product.



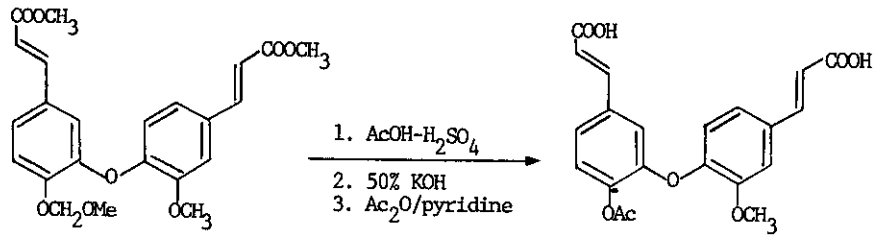
Scheme 9

Two total syntheses of codonocarpine (61) were reported in 1980. A synthesis by Fujita and co-workers[16] shown in Scheme 10 accomplished the macrocycle formation by aminolysis of the dicarboxylic acid thiazolidine-2-thione diamide (68). Protection of the acid and phenol functions of m-bromo-p-hydroxycinnamic acid (69) gave bromide (70) (87%) which underwent Ulmann coupling with methyl furulate (71) to form the biphenyl ether (72) (15%). Sequential acid cleavage of the methoxymethyl ether protecting group, saponification of the methyl esters, and acylation of the liberated phenol gave diacid (73) in 72% overall yield from (72). The acid chloride of (73) was then treated with four equivalents of the thallium (I) salt of thiazolidine-2-thione in THF at 25°C to yield the doubly activated diamide

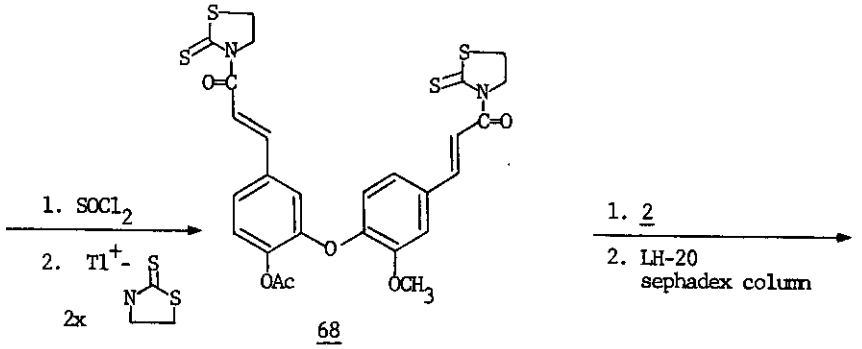
intermediate (68) in 84% overall yield from (73). In the key macrolactamization step, dilute methylene chloride solutions of (68) and spermidine were slowly mixed at room temperature. Sephadex chromatography of the reaction mixture gave a substance from which was crystallized codonocarpine (61) and isomeric (75). The two compounds were separated by repeated droplet countercurrent chromatography to give pure codonocarpine (61) and isomeric (75) in 25% and 59% yields respectively.



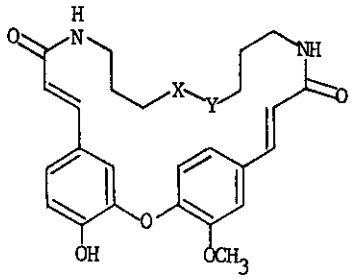
69 70 71



72 73



68

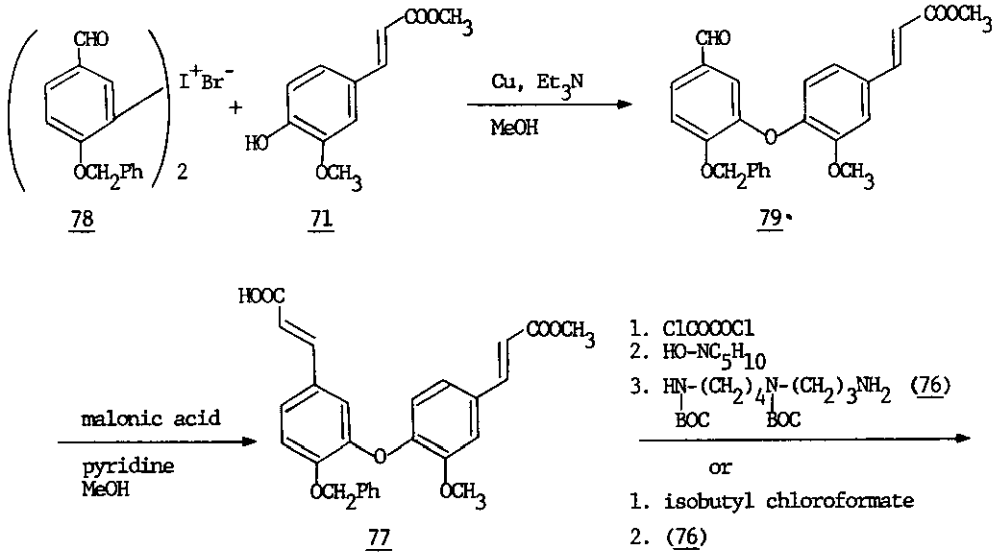


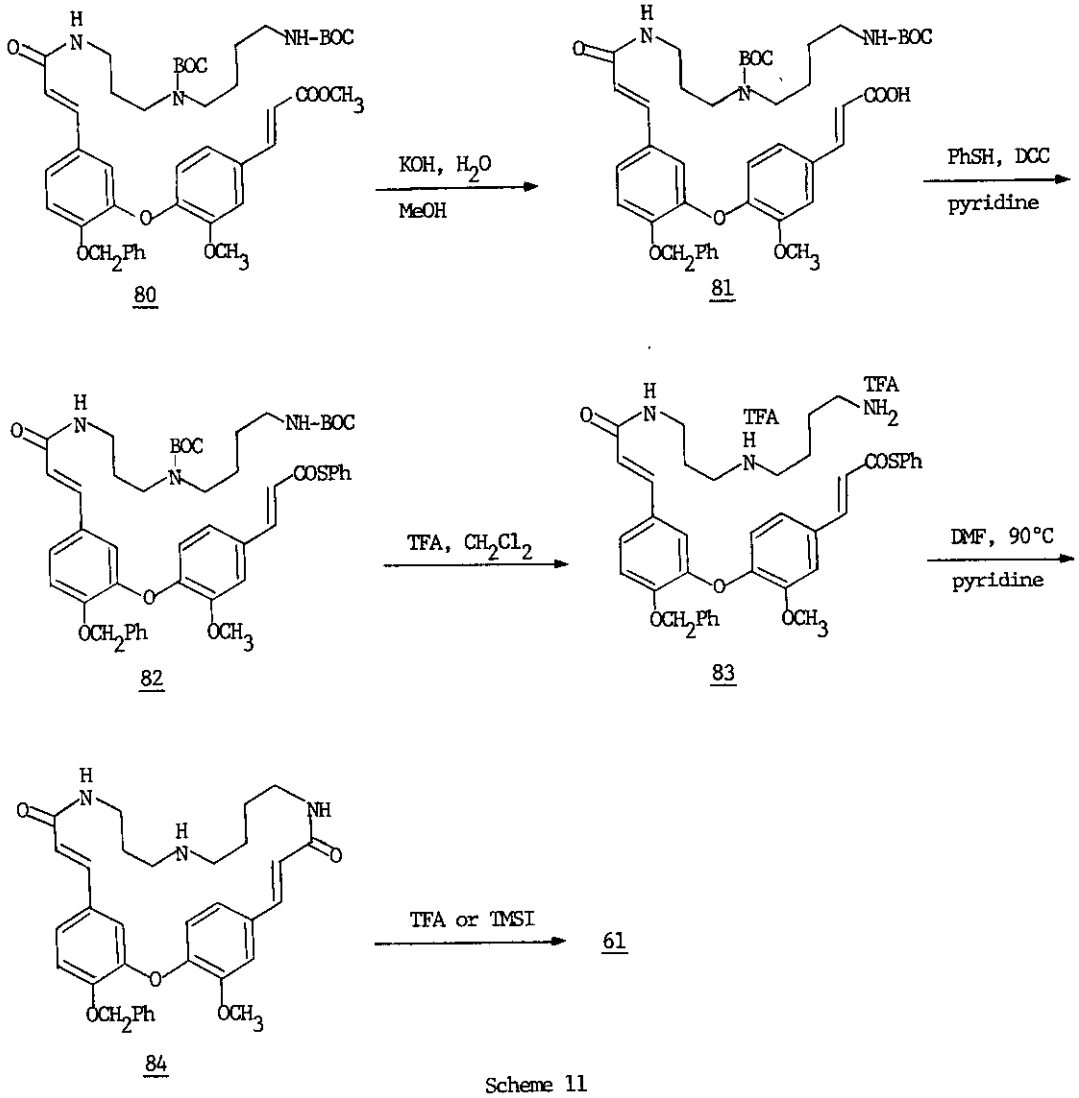
61 X= NH, Y= CH_2
75 X= CH_2, Y= NH

Scheme 10

The synthesis of codonocarpine accomplished by Humora, Seitz, and Quick[17] was the first procedure to report regiocontrolled incorporation of the spermidine fragment of the unsymmetrical bis-lactam ring. The synthesis involves initial preparation of the differentially functionalized spermidine and bis-cinnamoyl building blocks (76) and (77) followed by stepwise, regiospecific formation of the amide linkages. The details of the synthetic route are shown in Scheme 11.

The doubly protected N^2, N^3-di-BOC-spermidine equivalent (76) was prepared in three steps starting from 1,4-diaminobutane.[18] Synthesis of (77) was accomplished from the readily available diphenyliodonium bromide (78)[19] which upon coupling with methyl ferulate (71) afforded the biphenyl ether (79) in 50% yield. Knoevenagel condensation of (79) with malonic acid produced the trans-cinnamic acid derivative (77) (96%) which was coupled with the protected spermidine unit (76) by either of two methods. Treatment of a THF solution of the activated ester derived from N-hydroxypiperidine with (76) at 25°C over 14 days yielded amide (80) (90%). An alternative route to (80) proved to be more convenient. Reaction of the mixed anhydride of (77) (isobutyl chloroformate, -10°C, 20 min) with (76) at -10°C for 10 min furnished the desired amide (80) (79%). Following saponification of the methyl ester, the resulting acid (81) was converted into the thioester (82) by treatment with equimolar amounts of thiophenol, dicyclohexylcarbodiimide, and pyridine. Trifluoroacetic acid cleavage of the BOC groups generated the amine salt (83) which, following solvent removal was cyclized by heating in DMF-pyridine under high dilution conditions to afford after chromatography, a 60% yield of O-benzylcodonocarpine (84). Removal of the benzyl group with either trifluoroacetic acid or trimethylsilyl iodide furnished codonocarpine (61).





80 81 82 83 84

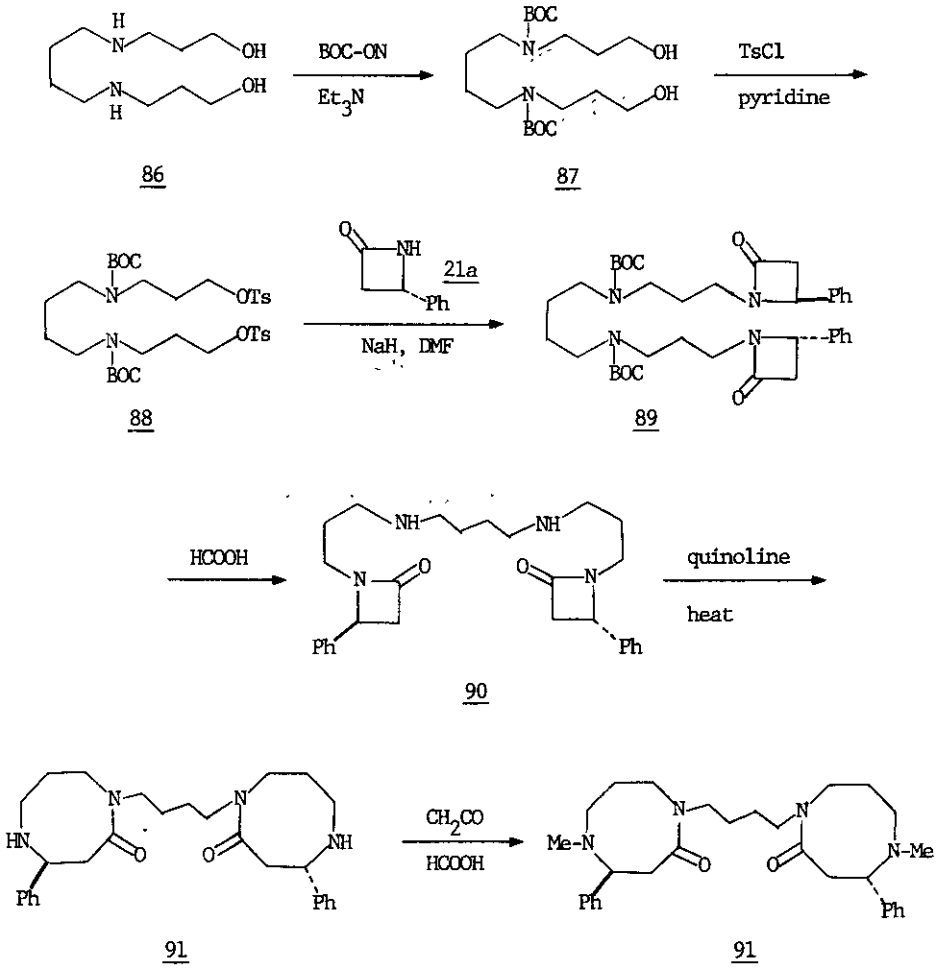
Scheme 11

E. Homaline

Homaline (85) is a naturally occurring alkaloid isolated from the leaves of Homalium pronyense (Homaliaceae)[20] and is structually derivable from spermine and two cinnamic acid units. A recent synthesis of homaline in its natural form was accomplished by the Wasserman group[21] following a route which features a bis-transannular ring expansion procedure for the formation of the two eight membered rings. The synthesis proceeds according to Scheme 12.

Treatment of N,N'-bis-(3-hydroxypropyl)-1,4-diaminobutane (86)[22] with BOC-ON[23] gave urethanediol (87) (91%) which was converted into the ditosylate (88) (41%) following reaction with p-toluenesulfonyl chloride. Intermediate (88) was then

alkylated with the sodium hydride generated anion of (S)-4-phenyl-2-azetidinone (21a)[24] to produce the di-beta-lactam adduct (89) (63%). Formic acid was used to remove the BOC protecting groups, and the symmetrical diamine (90) so obtained was converted into the ring expanded bis-lactam (91) by heating in purified quinoline (25%). Alternatively, pyrolysis of (89) in diphenyl ether directly provided a 28% yield of the ring expanded (91). Finally, Eschweiler-Clark methylation (CH_2O, HCOOH) of (91) gave natural (-)-homaline (85) (25%).

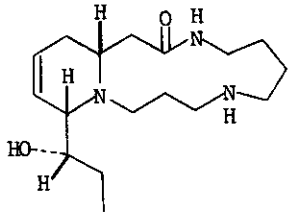


86 87 88 89 90 91 91

Scheme 12

F. Dihydropalustrine

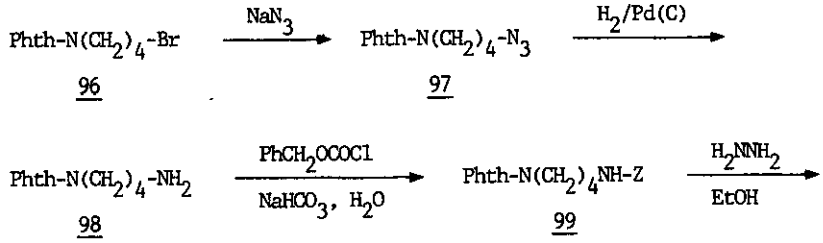
Palustrine (92) is a macrocyclic spermidine alkaloid that has been found in several Equisetum species.[25] Although a synthesis of natural palustrine has not yet appeared in the chemical literature, a recent report by Wälchli-Schaer and Eugster[26] describes the preparation of (±)-threo-cis/threo-trans-dihydropalustrine (93) from the major building blocks methyl (2E)-cis-7,8-epoxy-2-decenoate (94)[27] and the threefold protected spermidine, N^3-benzyloxycarbonyl-N^1-phthaloyl-N^2-tosylspermidine (95). The detailed synthetic pathway is shown in Scheme 13.



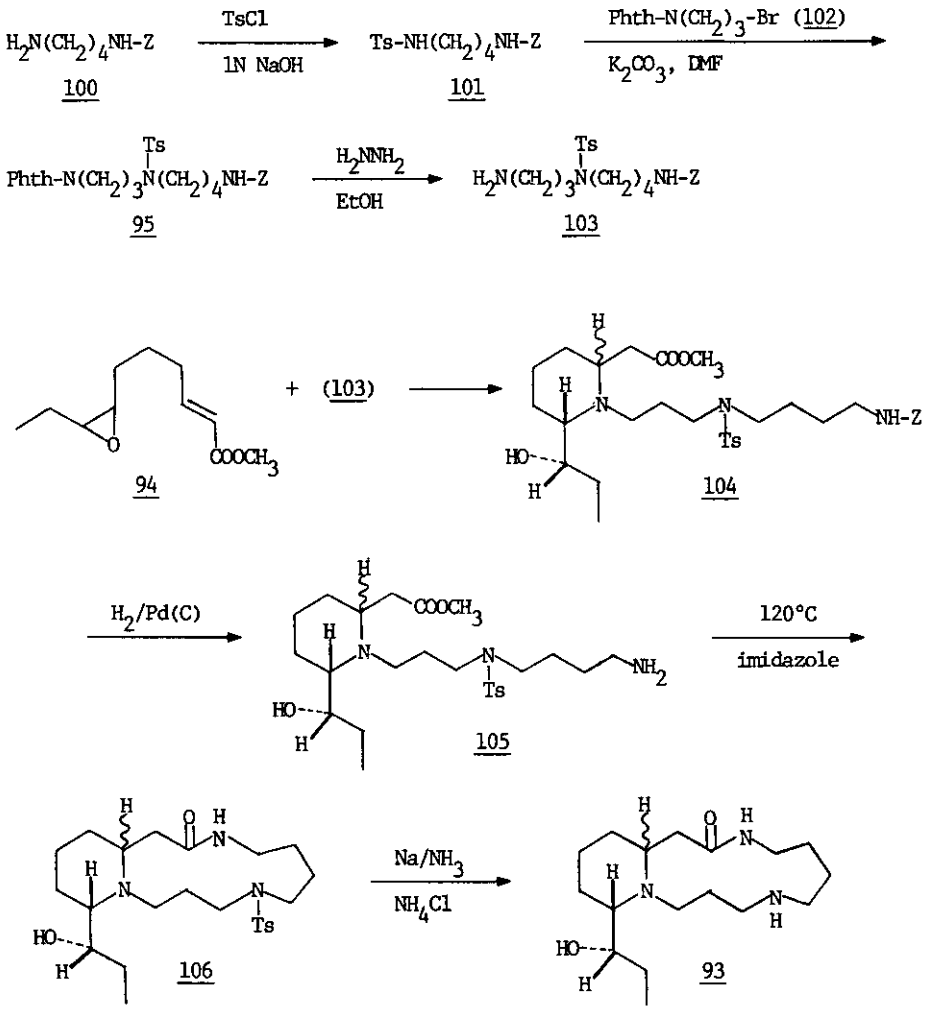
92

The threefold protected spermidine (95) was prepared in six steps from N-(4-bromobutyl)phthalimide (96).[28] Sequential conversion of (96) to azide (97), followed by reduction to amine (98) and treatment with carbobenzyloxy chloride gave intermediate (99) in 55% overall yield. Hydrazinolysis of (99) provided N-(benzyloxycarbonyl)-1,4-diaminobutane (100) which was converted in 88% yield into the doubly-protected diamine (101) following treatment with p-toluenesulfonyl chloride. Heating of (101) with bromide (102) in dry DMF at 80°C over three days in the presence of potassium carbonate produced the desired spermidine equivalent (95).

The amine (103) obtained by selective cleavage of the N^1-phthaloyl protecting group of (95) was successfully condensed with epoxy-unsaturated ester (94) in methanol over two days to afford piperidine (104) in 26% yield. Subsequent removal of the carbobenzyloxy group gave amino ester (105) in 74% yield. The lactam ring closure was effected by heating (105) for 2.5 h at 120°C in the presence of freshly sublimed imidazole to afford macrolactam (106) (quantitative). Finally, detosylation by sodium/ammonia reduction furnished (±)-threo-cis/threo-trans-dihydropalustrine (93) (11%).



96 97 98 99

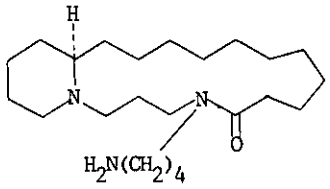


Phth= phthalimido; Z= $PhCH_2OCO$; Ts= p-$CH_3C_6H_4SO_2$

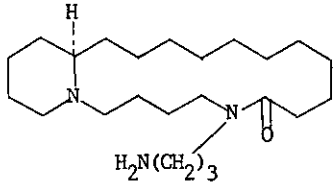
Scheme 13

G. Oncinotine, neooncinotine, isooncinotine, and pseudooncinotine

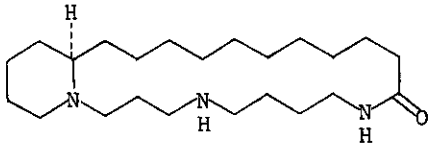
The isomeric macrocyclic spermidine alkaloids oncinotine (107), neooncinotine (108), and isooncinotine (109) have been isolated from Oncinotis nitada Benth. (Apocynaceae).[29] These three alkaloids, along with a fourth unnatural isomer, pseudooncinotine (110), have recently been synthesized in racemic form by Hesse, Schmid and co-workers.[30, 31]



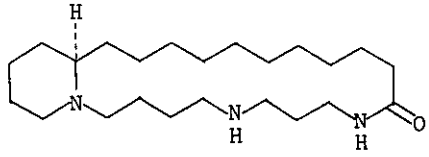
(-)-107: (-)-Oncinotine



(-)-108: (-)-Neooncinotine



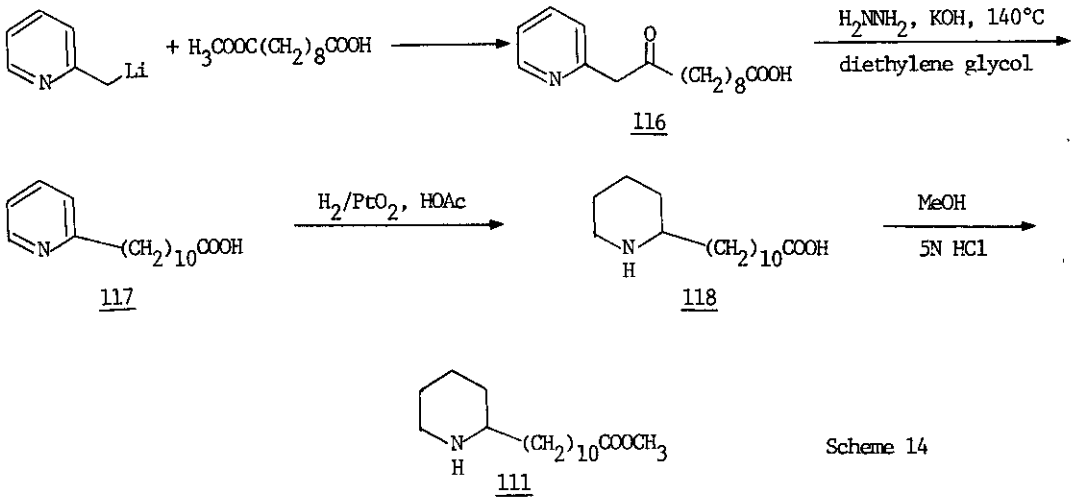
(±)-110: (±)-Pseudooncinotine



(-)-109: (-)-Isooncinotine

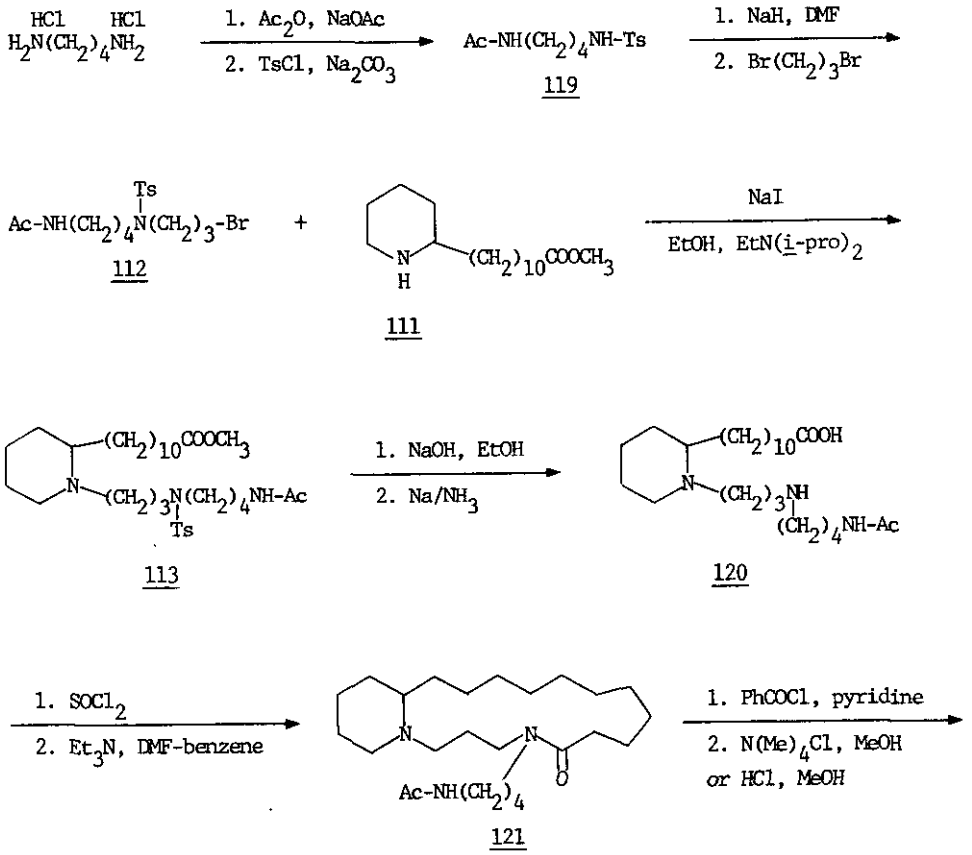
All four of these alkaloids were prepared from the key piperidine derivative (111). Alkylation of (111) with bromide (112) gave intermediate (113) which was transformed into (±)-oncinotine and (±)-pseudooncinotine. Similarly, the reaction of (111) with bromide (114) provided the derivative (115) from which was formed (±)-neooncinotine and (±)-isooncinotine.

The preparation of the pivotal piperidine building block (111) was most conveniently accomplished in four steps as shown in Scheme 14.[30] Treatment of subaric acid monomethyl ester with a threefold excess of 2-methylpyridyl lithium in THF at 20°C gave the keto-acid (116) in 85% yield. Wolff-Kishner reduction of (116) afforded the pyridine-acid (117) (90%) which was catalytically reduced to the piperidine-acid (118) and then esterified to (111) in acidic methanol (quantitative).



Scheme 14

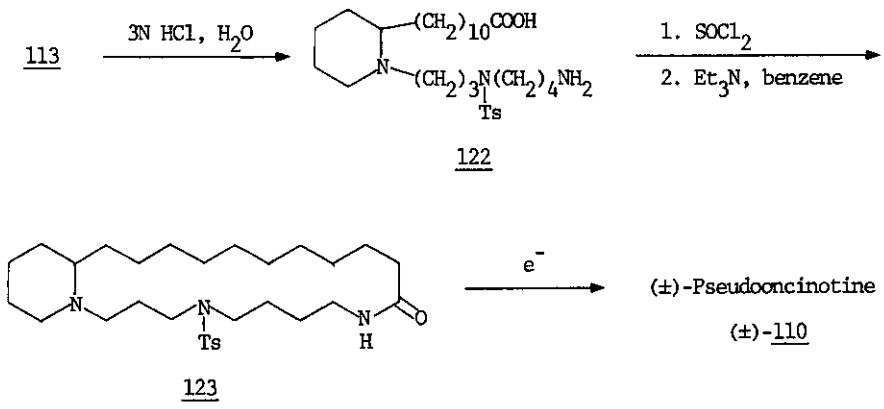
The synthesis of (±)-oncinotine (107) is outlined in Scheme 15. The bromide (112) was prepared from 1,4-diaminobutane dihydrochloride by sequential reaction with acetic anhydride and p-toluenesulfonyl chloride to acetamidosulfonamide (119) in 36% yield. Sodium hydride–induced alkylation of (119) with 1,3-dibromopropane provided (112) (94%). Reaction of (112) with piperidine (111) in ethanolic ethyldiisopropylamine containing one equivalent of sodium iodide gave intermediate (113) in 71% yield. Saponification of the methyl ester and removal of the tosyl group (Na/NH_3) afforded a nearly quantitative yield of the amino acid (120) which was cyclized to N-acetyl-(±)-oncinotine (121) following treatment with thionyl chloride and then triethylamine in dilute benzene-DMF solution (55%). Liberation of (±)-oncinotine (107) was achieved either by direct acid hydrolysis (55%) or by transamidation (57%).



(±)-107: (±)-Oncinotine

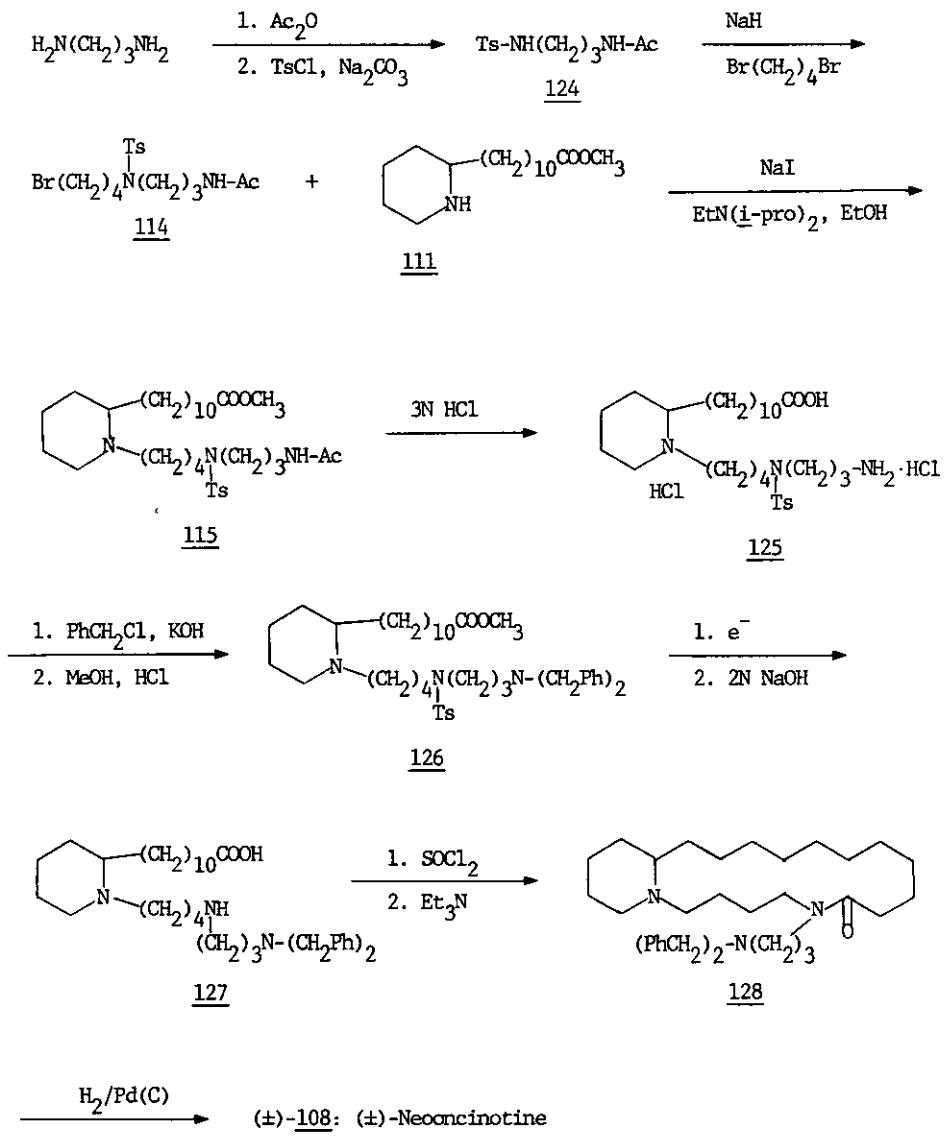
Scheme 15

The synthesis of (±)-pseudooncinotine (110) involved initial preparation of the amino acid (122) which was obtained by acid hydrolysis of the ester and amide functions of intermediate (113) (92%). Successive treatment of (122) with thionyl chloride and then triethylamine (dilute benzene solution) gave N-tosyl-(±)-pseudooncinotine (123) in 47% yield. Finally, electrolytic removal of the tosyl protecting group furnished (±)-pseudooncinotine (110) in quantitative yield. The route is summarized in Scheme 16.



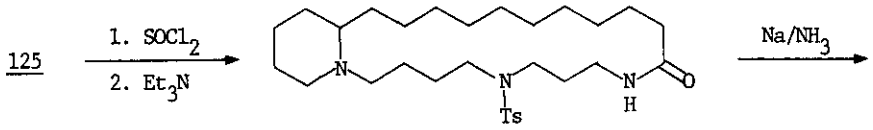
Scheme 16

The synthesis of (±)-neooncinotine (108) is outlined in Scheme 17. Preparation of the required bromide (114) was achieved in three steps. Differential protection of 1,3-trimethylenediamine gave N-(3-acetamidopropyl)-p-toluenesulfonamide (124) (32%) which upon treatment with sodium hydride followed by 1,4-dibromobutane afforded the bromide (114) in 84% yield. The reaction of piperidine (111) with (114) in ethanol containing sodium iodide and ethyldiisopropylamine, produced a 75% yield of intermediate (115) which was converted to the amino acid dihydrochloride (125) following acid hydrolysis (92% yield). The N,N-dibenzylamine-methyl ester (126), obtained by successive benzylation and reesterification, was converted to amino acid (127) following electrolytic removal of the tosyl protecting group and saponification of the methyl ester. Cyclization to N,N-dibenzyl-(±)-neooncinotine (128) was effected in 75% yield by exposure of the acid chloride obtained from (127) to triethylamine in dilute benzene solution. Final catalytic hydrogenation of (128) in acetic acid furnished (±)-neooncinotine (108) in 92% yield.


H2N(CH2)3NH2
1. Ac2O
2. TsCl, Na2CO3
Ts-NH(CH2)3NH-Ac
124
NaH
Br(CH2)4Br
Br(CH2)4N(Ts)(CH2)3NH-Ac
114
(CH2)10COOCH3
NH
111
NaI
EtN(i-pro)2, EtOH
115
3N HCl
125
1. PhCH2Cl, KOH
2. MeOH, HCl
126
1. e−
2. 2N NaOH
127
1. SOCl2
2. Et3N
128
H2/Pd(C)
(±)-108: (±)-Neooncinotine

Scheme 17

As shown in Scheme 18, cyclization of (125), employing the thionyl chloride-triethylamine procedure previously described, provided an 87% yield of N-tosyl-(±)-isooncinotine (129). Reductive cleavage of the tosyl group by sodium in liquid ammonia gave (±)-isooncinotine (109) in 91% yield.

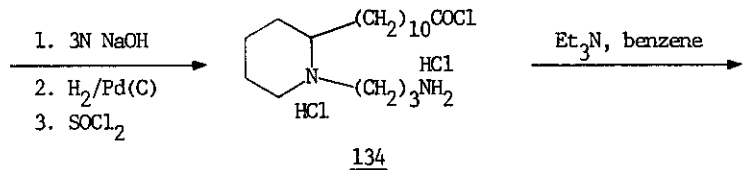


129

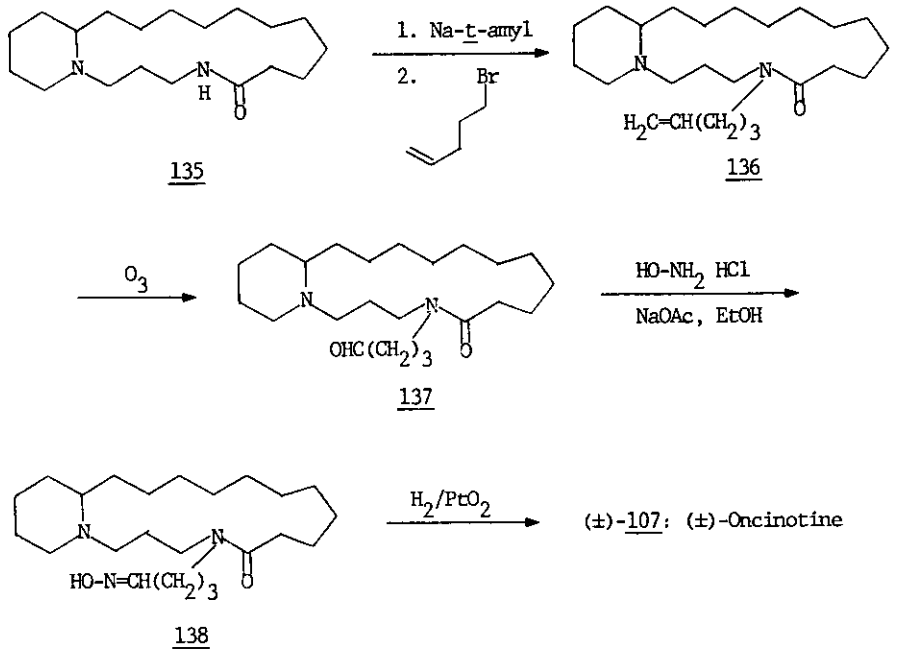
⟶ (±)-109: (±)-Isooncinotine

Scheme 18

In an earlier synthesis,[31] (±)-oncinotine (107) was prepared through the key intermediates (111) and (135). Reaction of (111) with alkyl chloride (132) gave the ester (133) (41%) which was converted into the acid chloride (134) following sequential saponification of the methyl ester, reductive deprotection of the amine function, and treatment with thionyl chloride. Macrocyclization of (134) was effected with triethylamine (dilute benzene solution) to give the 17-membered lactam (135) in 15-30% overall yield from (133). Subsequent alkylation of the lactam (135) with 5-bromo-1-pentene using sodium t-amylate as the base afforded olefin (136) (27%). Ozonolysis of the double bond of (136) provided aldehyde (137) which was converted to oxime (138). Final catalytic hydrogenation of (138) gave (±)-oncinotine (107) in 17% overall yield from (136). The results of this synthesis are depicted in Scheme 19.

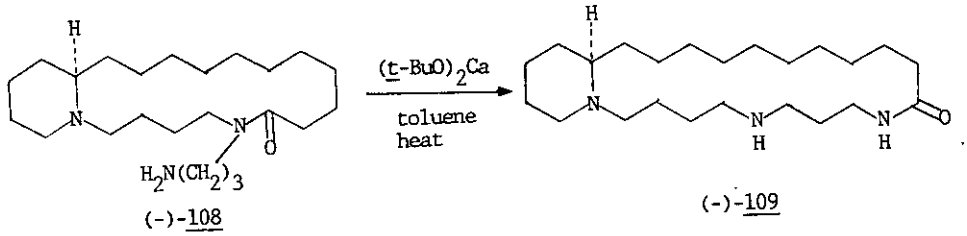


134



Scheme 19

The interconversion of neooncinotine to isooncinotine by intramolecular ring expansion was reported in 1978.[29] The reaction occurs upon heating a toluene solution of neooncinotine in the presence of calcium t-butylate as shown in Scheme 20.



Scheme 20

REFERENCES

1. U. Bachrach, Function of Naturally Occurring Polyamines, Academic Press, New York, 1973.
2. a) M. Hesse and H. Schmid, "Macrocyclic Spermidine and Spermine Alkaloids," from International Review of Science, Series II, Vol. 9, H. D. Hey and K. Wiesner, Eds., Buttersworth, London, 1976, pp. 265-307.
   b) M. M. Badawi, K. Bernauer, P. Van den Broek, D. Groger, A. Guggisberg, S. Johne, I. Kompis, F. Schneider, H.-J. Veith, M. Hesse, and H. Schmid, Pure Appl. Chem., 33, 81 (1973).
3. a) S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. A. Court, and M. Yatagai, J. C. S. Chem. Comm., 329 (1974).
   b) S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. A. Court, and M. Yatagai, J. Org. Chem., 42, 3660 (1977).
4. J. S. McManis and B. Ganem, J. Org. Chem., 45, 2041 (1980).
5. H. Yamamoto and K. Maruoka, J. Am. Chem. Soc., submitted for publication.
6. H. H. Wasserman, R. P. Robinson, and H. Matsuyama, Tetrahedron Lett., 3493 (1980).
7. R. Hocquemiller, M. Leboeuf, B. C. Das, H.-P. Husson, P. Potier, and A. Cave, Compt. Rend. C, 278 525 (1974).
8. R. Hocquemiller, A. Cave, and H.-P. Husson, Tetrahedron, 33, 653 (1977).
9. H. H. Wasserman and H. Matsuyama, J. Am. Chem. Soc., 103, 461 (1981).
10. D. Bormann, Chem. Ber., 103, 1797 (1970).
11. C. Poupat, H.-P. Husson, B. Rodriquez, A. Husson, P. Potier, and M.-M. Janot, Tetrahedron, 28, 3087 (1972); C. Poupat, H.-P. Husson, B. C. Das, P. Bladon, and P. Potier, ibid., p. 3103.
12. H.-P. Husson, C. Poupat, B. Rodriguez, and P. Potier, Tetrahedron Lett., 2697 (1971).
13. Y. Nagao, S. Takao, T. Miyasaka, and E. Fujita, J. C. S. Chem. Comm., 286 (1981).
14. R. W. Doskotch, A. B. Ray, and J. L. Beal, J. C. S. Chem. Comm., 300 (1971).
15. C. Poupat, Tetrahedron Lett., 1669 (1976).
16. Y. Nagao, K. Seno, and E. Fujita, Tetrahedron Lett., 4931 (1980).
17. M. J. Humora, D. E. Seitz, and J. Quick, Tetrahedron Lett., 3971 (1980).
18. M. J. Humora and J. Quick, J. Org. Chem., 44, 1166 (1979).
19. R. W. Doskotch, A. B. Ray, W. Kubelka, E. H. Fairchild, C. D. Hufford, and J. L. Beal, Tetrahedron, 30, 3229 (1974); F. M. Beringer, M. Drexler, E. M. Gindler, and C. C. Lumpkin, J. Am. Chem. Soc., 75, 2705 (1953); F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, ibid., 75, 2708 (1953).
20. M. Pais, R. Sarfati, F.-X. Jarreau, and R. Goutarel, Tetrahedron, 29, 1001 (1973).
21. H. H. Wasserman, G. D. Berger, and K. R. Cho, to be published. See abstracts of the 180th Am. Chem. Soc. meeting, San Franscisco, California, 1980.

22. C. W. Tabor, H. Tabor, and V. Bachrach, J. Biol. Chem., 239, 2194 (1964).
23. M. Itoh, D. Hagiwara, and T. Kamiya, Tetrahedron Lett., 4393 (1975).
24. H. Pietsch, Tetrahedron Lett., 2789 (1972); L. Birkofer and J. L. Schramm, Liebigs Ann. Chem., 2195 (1975).
25. E. Glet, J. Gutschmidt, and P. Glet, Z. Physiol. Chem., 244, 229 (1936); W. Dietsche and C. H. Eugster, Chimia, 14, 353 (1960).
26. E. Wälchli-Schaer and C. H. Eugster, Helv. Chim. Acta, 61 928 (1978).
27. P. C. Wälchli and C. H. Eugster, Helv. Chim. Acta, 61, 885 (1978).
28. Organic Synthesis, Coll. Vol. 1, 119 (1941).
29. M. M. Badawi, A. Guggisberg, P. Van den Broek, M. Hesse, and H. Schmid, Helv. Chim. Acta, 51, 1813 (1968); A. Guggisberg, M. M. Badawi, M. Hesse, and H. Schmid, ibid., 57, 414 (1974).
30. A. Guggisberg, P. Van den Broek, M. Hesse, H. Schmid, F. Schneider, and K. Bernauer, Helv. Chim. Acta, 59, 3013 (1976).
31. F. Schneider, K. Bernauer, A. Guggisberg, P. Van den Broek, M. Hesse, and H. Schmid, Helv. Chim. Acta, 57, 434 (1974).

Acknowledgement:

We wish to thank Mr. Gregory Berger for his generous help in reviewing this manuscript.

Received, 8th September, 1981