Tetrahedron Vol. 39, No. 15, pp 2459 to 2464, 1983
Printed in Great Britain

0040 4020/83 $3.00 + 00

THE USE OF β-LACTAMS IN THE SYNTHESIS OF SPERMINE AND SPERMIDINE ALKALOIDS

TOTAL SYNTHESIS OF HOMALINE

HARRY H. WASSERMAN and GREGORY D. BERGER
Department of Chemistry, Yale University, New Haven, CT 06511, U.S.A.

(*Received in USA 4 January* 1983)

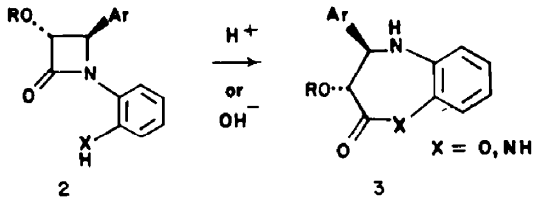
Abstract—The optically active plant product homaline (**6**) has been synthesized in a convergent sequence starting with β-phenyl-β-alanine and putrescine (**14**). The key transformation in this sequence is the ring expansion by transamidation of a functionalized chiral β-lactam precursor.

The macrocyclic polyamine lactams, recently isolated from plant sources, incorporate spermine and spermidine residues along with derivatives of cinnamic acid in a large family of natural products, including lactam systems with rings varying from 8 to 22 members. Because of the biological activity found in certain naturally occurring polyamines,[1] there is special interest in general routes for the preparation of macrocyclic systems containing these components.[2] In the work reported below we discuss a method for the synthesis of members of this class which promises to have wide applicability to the formation of natural products in this series.

There have been a number of approaches to the synthesis of macrocyclic lactams including (a) cyclization of terminally difunctionalized linear precursors, as exemplified by the work of Ganem[3], Quick[4] and Fujita[5]: (b) use of boron-templated macrolactamization as reported by Yamamoto,[6] (c) transamidation reactions as reported by Schmid *et al.*[7]

Our synthetic approach, involving the use of β-lactams as a means of introducing aminopropyl units for stepwise expansion of 5-, 9- and 13-membered lactams, stemmed from an earlier observation made during work on the synthesis of 3-ANA.[8] While attempting to purify this β-lactam we noted its ready conversion to a piperazone carboxylic acid, an observation which had earlier been reported by Kamiya.[9] This transformation appears to take place by the process shown in Scheme 1 in which the carboxyl group takes part in an intramolecular nucleophilic attack on the CO of the lactam leading to ring opening and intramolecular acetylation. A similar rearrangement has been reported during Raney Ni desulfurization of 6-aminopenicillanic (**1**) acid by Mall and Hannick.[10] Here again, a ketopiperazone is obtained. Further examples of intramolecular β-lactam ring-opening can be found in the studies of Bose[11] (conversion of **2** to **3**) and in the earlier work of Testa.[12]

The above reactions, disclosing the susceptibility of the β-lactam ring to intramolecular nucleophilic attack suggested the possibility of using β-lactams in synthetically useful transamidation reactions.

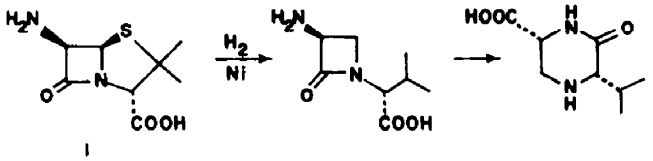


2 3

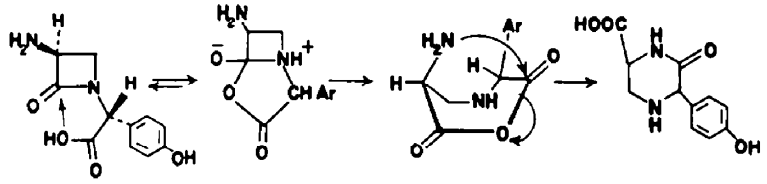
Application of β-lactam transamidations to a synthesis of homaline. We were attracted to the possibility of using transamidation of β-lactams as a key step in the synthesis of spermine and spermidine alkaloids because of the presence of β-aminopropionamide residues in many of these macrocyclic systems. Among these plant products, homaline (**6**) appeared to be of special interest, since β-lactam opening offered a ready means of generating the two 8-membered rings. Earlier work by Pais and members of the Gif group[13] resulted in the preparation of an optically active bis-dihydrodeoxo derivative identical with the corresponding reduction product, but the parent bis-lactam had not been previously synthesized. We noted that an intramolecular transamidation through a favorable 6-membered transition state (Scheme 2) could provide an effective method of generating the desired ring structure, thus avoiding the problems associated with the cyclization of an amino acid precursor to form an 8-membered ring.

Another problem to be addressed in the synthesis involves the introduction of two chiral centers into the molecule. The remoteness of these sites precluded the possibility of asymmetric induction, so an absolute asymmetric synthesis was needed. The symmetry of the system allowed this to be done conveniently.

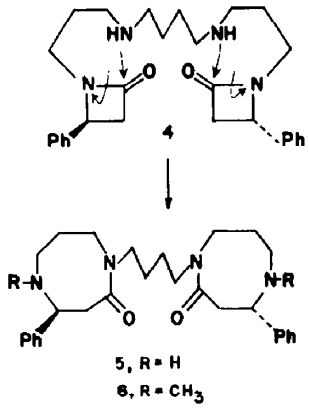
The synthesis of homaline[14] outlined below was developed with the above goals in mind. We chose the bis-β-lactam (**4**) as the source of the β-amino-β-propionic acid residues with the aim of introducing



1



Scheme 1.

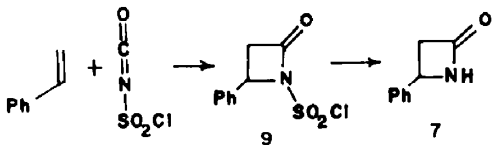


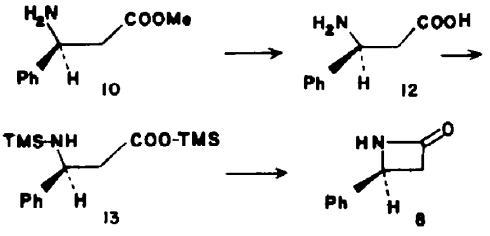
Scheme 2.

the Me groups subsequent to ring expansion. While other transamidations could take place from this amino lactam, all possible side reactions would involve transition states larger than 6-membered.

The synthesis of (−)-*4-phenyl-2-azetidinone.* In studies directed toward the synthesis of homaline (**6**), both racemic 4-phenyl-2-azetidinone (**7**) and the optically active lactam (**8**) corresponding to an *S*-configuration were required. The racemic mixture was conveniently produced by first generating N-chlorosulfonyl-4-phenyl-2-azetidinone (**9**) from chlorosulfonyl isocyanate and styrene according to the procedure of Graf.[15] While the reduction procedure described by Graf using potassium iodide gave a mixture of products, chromatographically homogeneous β-lactam could be obtained conveniently in a buffered modification of the sodium sulfite procedure reported by Durst.[16] The product possessed the characteristic 1760 cm^{-1} CO absorption in the IR. In the NMR, each of the methylene protons existed as a doublet of doublets at 2.84 and 3.43 δ, respectively.

The enantiomerically pure β-lactam (**8**) was synthesized from β-phenyl-β-alanine. The latter could be produced in large quantities by condensing benzaldehyde, ammonium acetate and malonic acid in n-butanol. Fischer esterification in methanolic hydrogen chloride yielded the amino ester hydrochloride from which the amino ester (**10**; 85%) was liberated with sodium hydroxide. The amino ester (**10**) was resolved by recrystallization of its L-(+)-tartrate salt (**11**). Typically, either two or three recrystallizations provided a white salt which possessed a constant m.p.



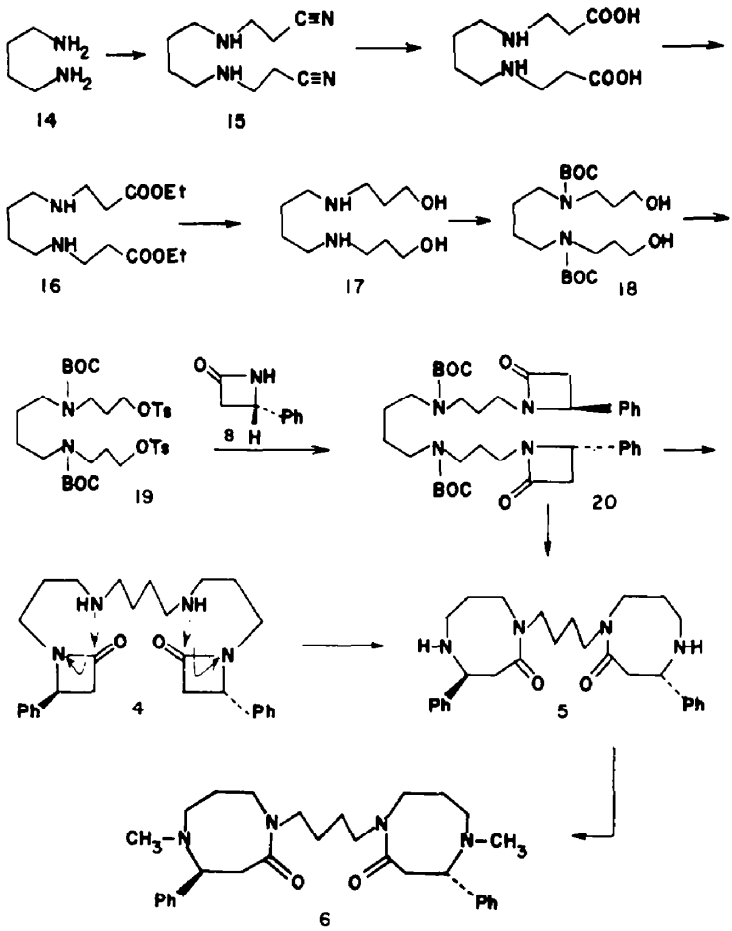


and a constant rotation. The optically active amino ester (**10a**), obtained upon treatment of the tartrate with sodium hydroxide, was shown to be optically pure by the absence of the diastereomeric Eu(hfc)$_3$ complex in the 90 MHz NMR spectrum, monitoring the methyl ester singlet. The optically active ester was saponified in 40% sodium hydroxide to form the β-amino acid (**12**; 98%). Reaction of **12** as the hydrochloride with chlorotrimethylsilane and triethylamine according to the procedure of Birkofer[17] produced the bis-trimethylsilylamino ester (**13**; 99%). This unstable oil, characterized by NMR, was carried on directly to the next step which involved treatment with ethylmagnesium bromide followed by desilylation to yield the chiral β-lactam (**8**).

In the synthesis of the homaline precursor (**5**; Scheme 3) the known N,N′-bis(3-hydroxypropyl)-1,4-diaminobutane (**17**) appeared to be an ideal starting material for introducing the spermine backbone. This compound, previously synthesized by Tabor,[18] was prepared in our laboratories with only slight modifications.

The dinitrile (**15**) formed by Michael addition of putrescine (**14**) to acrylonitrile at 0°, was hydrolzed to the diacid (dihydrochloride) and the product esterified in hydrogen chloride–ethanol. Lithium aluminum hydride reduction of the diester (**16**) in refluxing tetrahydrofuran generated (**17**) the dioxo analog of spermine (36%). The diaminodiol (**17**) exhibited spectroscopic and physical properties identical to those described by Tabor. Prior to activation of the alcohols for displacement, the amines were protected as butoxy urethanes (**18**) using BOC–ON in water–dioxane.

Early attempts to activate the alcohols (**18**) as their methanesulfonate esters according to the procedure of Crossland[19] were unsuccessful. On the other hand reaction of **18** with *p*-toluenesulfonyl chloride in pyridine generated the ditosylate (**19**) in moderate yield (40%). The sodium salt of (−)-4-phenyl-2-azetidinone, formed upon reaction of **8** with sodium hydride in N,N-dimethylformamide, was than added to the ditosylate in one portion and the reaction was heated at 90° for 16 hr. After workup, the BOC-β-lactam (**20**) was obtained in 63% yield. Deprotection of **20** in 1 N HCl–dioxane gave the dihydrochloride of the desired diamine (**4**) as an

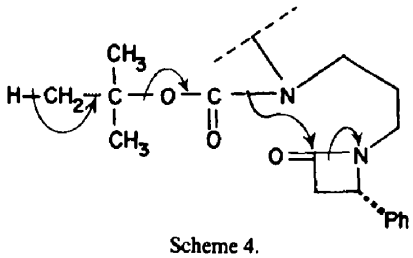


Scheme 3.

extremely hygroscopic yellow solid. Isolation of **4** (47%) from basic media gave an oil which was fully characterized by its 90 MHz NMR spectrum.

In carrying out the transamidation reaction to form the *bis*-β-lactam we studied conditions of acid and base catalysis as well as purely thermal processes. Among these procedures, pyrolysis proved to be the most fruitful. In our early attempts, the free amino bis-β-lactam (**4**) was heated in quinoline for 10 hr, or in diphenyl ether for 3 hr to form the ring-expanded product (**5**; 25%). We found, subsequently, that a more suitable method for the ring expansion involved refluxing the optically active bis-BOC-β-lactam (**20**) for 3 hr in diphenyl ether which had been charged with dry air. These conditions, leading to the fragmentation sequence shown in Scheme 4, produced the optically active homaline precursor (**5**) in 36% yield. Similar pyrolysis of the diastereomeric BOC-β-lactam for 2 1/4 hr gave the 8-membered lactams in 28% yield. Not only were these conditions more reproducible, but they also provided a mixture which was more conveniently purified than the mixture obtained from quinoline pyrolysis of the free amine (**4**).

Eschweiler–Clark methylation of the homaline precursor (**5**) generated pure optically active homaline (**6**) in 33% yield. This compound was identical in all respects (m.p., m.m.p., FTIR, 270 MHz, NMR) to the naturally-isolated sample of homaline including the specific rotation, $(\alpha)_D^{24} = -35°$.



Scheme 4.

EXPERIMENTAL

M.ps were determined on either a mel-Temp or a Thomas-Hoover m.p. apparatus. All m.ps and b.ps are uncorrected. Continuous wave IR spectra were obtained on a Perkin–Elmer 700 A spectrophotometer. Fourier transform IR (FTIR) spectra were recorded on a Nicolet 7000 spectrophotometer with 4 cm^{-1} resolution. IR samples were prepared as neat liquids, as $CHCl_3$ or CH_2Cl_2 solns, as KBr pellets or as mineral oil mulls. FTIR samples were obtained in $CHCl_3$ solns. Proton NMR spectra were obtained in the indicated solvents on a Perkin–Elmer R-32, a Variant EM-390 or a Jeol FX-90Q spectrometer at 90 MHz, or on a Bruker HX-270 spectrometer at 270 MHz. Unless otherwise noted, TMS was employed as an internal reference in $CDCl_3$ and Na, 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was the internal reference in D_2O. Optical rotations were obtained at the D-line of sodium on a Perkin-Elmer 241 polarimeter in a 1 dm pathlength, temp-jacketed cell. Elemental analyses were performed by Dr. Robert Rittner, Olin Laboratories, New Haven, Connecticut.

(+)-(3S)-Methyl-3-amino-3-phenylpropionate-L-tartrate salt (**11**)

A soln of 17.75 g (99 mmol) of (±)- **10** in 100 mL of MeOH was added in one portion to a refluxing soln of 14.90 g (99 mmol) of L-(+)-tartaric acid in 100 mL MeOH. The product crystallized overnight at − 20° and was filtered off, m.p. 168–169.5°, $(\alpha)_D^{24} \times +18°$ ($c = 7.6$, water). Recrystallization from 100 mL MeOH gave 6.8 g (42%) white needles, m.p. 171.5–172°, $(\alpha)_D^{24} = +18°$ ($c = 7.6$, water): lit m.p. 170–171°, $(\alpha)_D^{24} = +20.8°$ ($c = 3$, water): IR (mull) 3540, 3400, 3300–2300, 1735 cm^{-1}; NMR (D_2O δ 3.12 (dd, J = 1 Hz, J = 7 Hz, 2H), 3.63 (s, 3H), 4.45 (s, 2H), 7.43 (s, 5H).

Further crystallization of the salt from 200 mL MeOH afforded 1 g white needles whose physical and spectroscopic properties were unchanged. The mother liquor was evaporated and the solid materials were combined for use in the next step.

(+)-(3S)-Methyl-3-amino-3-phenyl-propionate (**10a**)

A soln of 42.6 g (1229 mmol) of **11** in 260 mL 1 N NaOH was extracted three times with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated. Distillation afforded 19.4 g (84%) of a colorless oil, bp 85° C/0.3 mm Hg, $(\alpha)_D^{24} = +12.9$ (neat). The product was otherwise spectroscopically identical to the racemic amino ester (**10**).

(+)-(3S)-3-Amino-3-phenylpropionic acid hydrochloride

The hydrochloride of (**12**). A mixture of 5.7 g (32 mmol) of **10a**, 90 mL MeOH and 25 mL 40% NaOHaq was stirred for 16 hr at room temp. The resulting white mixture was acidified to pH 2 with conc HCl followed by solvent evaporation. The resulting solid mixture was extracted three times with hot $CHCl_3$–EtOH (85 : 15). Concentration of the organic layer left a white solid which was dried in a vacuum oven at 60° for 16 hr in the presence of P_2O_5, yielding 6.3 g (98%) of the hydrochloride of **12**, m.p. 181–185°, $(\alpha)_D^{24} = +3.3°$ ($c = 2.95$, MeOH): IR (KBr) 3400, 3300–2300, 1720 cm; NMR (D_2O) δ 3.12 (dd, J = 1 Hz, J = 7 Hz, 2 H), 7.49 (s, 5H).

(−)-4-Phenyl-2-azetidinone (**8**). To a mechanically stirred suspension of 9.4 g (47 mmol) of **12** in 100 mL benzene was added 13 mL (11.2 g; 103 mmol) of chlorotrimethylsilane in one portion under N_2. After stirring for 30 min, a soln of 23 mL (16.5 g; 165 mmol) Et_3N in 50 mL benzene was added dropwise to the mixture. The resulting thick, white suspension was heated for 4 hr at 80° and then allowed to stand overnight at room temp. The mixture was diluted with benzene and filtered. Solvent evaporation left 14.3 g (99%) of **13** as a clear oil. NMR ($CDCl_3$; ref. CH_2Cl_2) δ 0.03 (s, 3H), 0.30 (s, 3H), 2.80 (complex m, 2H), 4.40 (ddd, J = 6Hz, J = 8Hz, J = 11Hz, 1H), 7.35 (broad m, 5H). The above silyl ester could be (Kugelrohr) distilled with no apparent improvement in purity, bp 85° C/0.03 mm Hg. Typically, the crude oil was used directly in the next step.

To a soln of 14.3 g (46.2 mmol) of **13** in 100 mL ether at 0°, under N_2 was added, dropwise, 17.0 mL (51 mmol) of a solution of EtMgBr in ether (3 M; Aldrich) with gas evolution. The soln was stirred at room temp for 3 hr and allowed to stand overnight. Upon cooling to − 10°, the mixture was acidified to pH 3 with ammonium chloride-satd 2 N HCl. The organic layer was separated and the aqueous layer was extracted five times with ether. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (60 mm × 6") eluted with EtOAc–hexane (3 : 2) gave a yellow solid. Recrystallization from hexane–$CHCl_3$ afforded **8a** 2.7 g (39% overall from **13**) as a yellow fibrous solid, m.p. 115.5–116°, $(\alpha)_D^{25} = -132°$ ($c = 1$, MeOH); lit m.p. 115–117°, $(\alpha)_D^{20} = -131.6°$ ($c = 1$, MeOH).

N,N'-Bis(2-cyanoethyl)-1,4-diaminobutane (**15**)

To 49.6 g (0.565 mol) of **14** at 0° under N_2 was added 59.9 g (1.13 mol) acrylonitrile (freshly distilled) dropwise over 20 min with stirring. The cooling bath was allowed to warm to room temp over 2 hr. After cooling, the undesired volatile byproducts were evaporated from the mixture at 130 (0.1 mm Hg), leaving **15** as a pale yellow oil, 106.6 g (97%): IR ($CDCl_3$) 3320, 2220 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 1.33 (broad, 2H), 1.54 (m, 4H), 2.52 (t, J = 6.5 Hz, 4H), 2.66 (m, 4H), 2.93 (t, J = 6.5Hz, 4H).

N,N'-Bis(2-carbethoxyethyl)-1-4-diaminobutane dihydrochloride (**16**)

A soln of 96.8 g (498 mmol) of **15** in 6N HCl (750 mL) was refluxed for 10 hr. The mixture was concentrated to dryness leaving the diacid dihydrochloride as an off-white solid which was used directly for esterification. Dry HCl gas was bubbled for 15 min through a mechanically stirred mixture of the hydrolysis residue and abs EtOH, 1 L. Complete dissolution of the solid did not occur if the sample was very dry. Refluxing the mixture for 12 hr followed by hot filtration through a steam-jacketed course-sintered glass funnel provided **16** which crystallized upon cooling the filtrate to room temp. The solid was filtered off, washed with EtOH and dried in a vacuum over at 80° for 10 hr leaving 122.4 g (68%) of **16** as a white powder, m.p. 237–238° (dec): IR (KBr) 2450, 1730 cm^{-1}; NMR (D_2O) δ 1.25 (t, J = 8Hz, 6H), 1.78 (m, 4H), 2.82 (t, J = 6Hz, 4H), 3.12 (m, 4H), 3.33 (t, J = 6Hz, 4H), 4.17 (q, J = 8Hz, 4H). Recrystallization from abs EtOH afforded an analytical sample as white platelets mp 236.5–238° (dec).

(Found: C, 46.56; H, 8.31; N, 7.65. Calcd. for $C_{14}H_{30}N_2O_4Cl_2$: C, 46.54; H, 8.37; N, 7.76%).

N,N'-Bis(3-hydroxypropyl)-1,4-diaminobutane (**17**)

A soln of LAH, 30.8 g (812 mmol), in 1.4 L THF was prepared by refluxing the mechanically stirred mixture for 1 hr under N_2. To this soln was added 45.6 g (126 mmol) of **16** portionwise over 30 min with ice bath cooling. The reaction was stirred again at room temp for 3 hr, refluxed for 1 hr, and then stirred again at room temp for 12 hr. Cautiously, 31 mL water, then 31 mL 15% NaOHaq and then 95 mL water were added dropwise over a 2 hr period. The mixture was stirred vigorously until the Al-salts coagulated, (*ca.* 2 hr). After filtering off the salts, the filtrate was concentrated and the residue was dissolved in water. Continuous extraction with $CHCl_3$ for 3 days followed by drying the organic layer over Na_2SO_4 and concentration left 9.40 g (36%) of **17** as an off-white solid, m.p. 75–76°; lit m.p. 78–79°: IR ($CDCl_3$) 3200 cm^{-1}; NMR ($CDCl_3$) δ 1.5 (m, 4H), 1.66 (p, J = 6Hz, 4H), 2.59 (m, 4H), 2.82 (t, J = 6Hz, 4H), 3.11 (broad s, 4H), 3.73 (t, J = 6Hz, 4H).

N - N' - Bis(3-hydroxypropyl)-N,N'-bis(t-butoxycarbonyl)-1,4-diaminobutane (18)

A soln of 9.25 g (45.3 mmol) of **17**, 24.6 g (100 mmol) BOC-ON (Aldrich) and 22 mL (150 mmol) Et_3N in 250 mL water–dioxane (1 : 4) was stirred for 16 hr at room temp. To the resulting yellow soln was added a soln of 1.50 g (20 mmol) glycine in 55 ml Et_3N–water (1 : 10) and stirring was continued for 24 hr. After concentrating the dark orange soln, the residue was dissolved in 500 mL ether. The ether soln was washed 6 times with 1 N NaOH and then with brine. The organic layer was dried over Na_2SO_4 and concentrated to give 17.8 g of **18** as an orange-colored oil. The residue was divided in half and each batch was flash-chromatographed on silica gel (60mm × 6") eluted with 3% MeOH in $CHCl_3$. Evaporation left 16.6 g (91%) of a slightly yellow oil which decomposed on attempted distillation: IR ($CDCl_3$) 3400, 1670 cm^{-1}: NMR ($CDCl_3$) δ 1.44 (s, 18H), 1.5–1.8 (m, 8H), 3.05–3.65 (m, 12H).

(Found: 404.290. Exact mass Calc. for $C_{20}H_{40}N_2O_6$: 404.289.)

(−)-(4S, 4'S)-1, 12-Bis(N-4-phenyl-2-oxoazetidino)-4, 9-bis(tert)-butoxycarbonyl)-4,9-diazododecane (**20**)

To a soln of 7.20 g (17.8 mmol) of **18** in 180 mL pyridine at 0° under N_2 was added with stirring 13.6 g (71.3 mmol) *p*-toluenesulfonyl chloride (recrystallized from hexane) in one portion. After rapid dissolution of the solid, the mixture was stored in a refrigerator at 4° for 36 hr. The reddish-brown soln was added to a 1000 g mixture of ice-water with stirring. The oily mixture was extracted 3 times with ether. The combined organic layer was washed 4 times with an ice-1 N HCl mixture (until the aqueous layer retained an acidic pH) and then twice with an ice-water mixture. The organic layer was dried over a mixture of anhyd K_2CO_3 and anhyd Na_2SO_4. Concentration left 5.20 g (41%) of **19** as a yellow oil: NMR ($CDCl_3$) δ 1.41 (s, 18H), 2.0–2.5 (m, 8H) 2.45 (s, 6H), 3.0–3.4 (m, 8H), 4.05 (t, J = 6.5Hz, 4H), 7.30 (d, J = 8Hz, 4H), 7.78 (d, J = 8Hz, 4H). This material was used directly for the next step.

To a suspension of 1.02 g (25.5 mmol) of a 60% mineral oil dispersion of NaH (pre-washed with hexane) in 100 mL N,N′-DmF at room temp, under N_2 was added 2.5 g (17 mmol) of (−) **-8**. Stirring, aided by a Hirschberg stirrer, served to form the lactam anion in *ca.* 40 min. The ditosylate (**19**) was dissolved in 50 mL N,N′-DmF and was added in one portion to the mixture. After the soln was heated 90° for 16 hr and cooling to room temp, 4 mL water was added with little gas evolution. After concentration of the soln a yellow oil remained. Flash chromatography on silica gel (30 mm × 7″) eluted with hexane–EtOAc (1 : 3) yielded 3.36 g of **20** (63%) as a colorless oil: FTIR ($CDCl_3$) 1731, 1681 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 18H), 1.45 (broad s, 4H), 1.70 (p, J = 8Hz, 4H), 2.67–3.55 (m, 16H), 4.56 (dd, J = 2Hz, J = 6Hz, 2H), 7.35 (broad s, 10H); NMR ($CDCl_3$, 270 MHz, 50°C probe temperature) δ 1.40 (s, 18H), 1.45 (broad s, 4H), 1.66 (p, J = 8Hz, 4H), 2.80 (dd, J = 2 Hz, J = 16 Hz, 2H), 2.85 (dt, J = 6 Hz, J = 12 Hz, 2H), 3.00–3.20 (broad m, 8H), 3.34 (dd, J = 2Hz, 2H), 7.35 (broad m, 10H); $(\alpha)_D^{24} = -57°$ (c = 2.0, $CHCl_3$).

(Found: 561.343. Exact mass Calc. for $C_{33}H_{45}N_4O_4$ (parent $-CO_2-C(CH_3)_3$): 561.344).

1,12((4S,4S′)Bis(N-4-phenyl-2-oxoazetidino))-4,9-diazodecane (**4**)

A soln of 1.40 g 2.11 mmol) of **20** in a mixture of 60 mL 1 N HCl and 80 mL dioxane was stirred at 50° for 20 hr. Concentration left an oil to which dioxane was added and the mixture was reconcentrated. After repeating this procedure once, the residue was dissolved in MeOH (6 mL) and was precipitated into 200 mL ether. Filtration let an extremely hygroscopic yellow solid which was dried *in vacuo* in the presence of P_2O_5. The dihydrochloride thus obtained weighed 850 mg (77%). A soln of 583 mg (1.09 mmol) of the dihydrochloride in water was brought to pH 12 with 1 N NaOH and extracted 3 times with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated to give 311 mg of **4** (61%; 47% overall from 20) as a colorless oil: NMR ($CDCl_3$) δ 1.30–1.85 (m, 8H), 2.36–3.03 (m, 10H), 3.20–3.70 (m, 4H), 4.53 (dd, J = 5Hz, J = 2Hz, 2H), 7.33 (s, 10H).

(−)-(2S,2′S)-5,5′-(Tetramethylene)bis(2-phenyl-4-oxo-1,5-diazacyclooctane) (**5**)

Method A. Quinoline pyrolysis. Three solns of **20** in quinoline 90.7 mg (0.137 mmol)/7 mL; 79.8 mg (0.120 mmol)/6 mL; 83.1 mg (0.125 mmol)/6 mL) were degassed with argon and refluxed for 10 hr in 25 mL round bottom flasks under argon. After cooling, the combined reaction mixture was evaporated. Flash chromatography on reverse phase silica gel (Whatman LRP-2, 37–53, 15 mm × 6″) eluted with water–MeOH (2 : 3) left 134 mg dark oil. The residue was then flash-chromatographed on silica gel (15 mm × 6″) eluted with 7% MeOH in $CHCl_3$ giving 44 mg of **5** (25%) as a colorless oil, R_f = 0.43 (MeOH–$CHCl_3$; 1 : 9): FTIR ($CDCl_3$) 1620 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 1.44–2.20 (broad m, 8H), 2.37 (ddd, J = 4Hz, J = 12Hz, J = 13Hz, 2H), 2.50 (dd, J = 1Hz, J = 13Hz, 2H), 2.99 (t, J = 12Hz, 2H), 2.90–3.09 (m, 2H), 3.10–3.20 (m, 2H), 3.20–3.30 (m, 2H), 3.20–3.50 (broad, 2H), 3.77–3.94 (m, 2H), 4.01 (dd, J = 1Hz, J = 11Hz, 2H), 7.20–7.40 (broad m, 10H); $(\alpha)_D^{24} = 30°$ (c = 1.34, $CHCl_3$).

Method B. Diphenyl ether pyrolysis. Air was passed through a tube of $CaSO_4$ (indicator: 8 mesh) and bubbled through a soln of 375 mg (0.566 mmol) of **20** in 60 mL diphenyl ether. The soln was refluxed for 3 hr and after cooling, the solvent was evaporated. Flash chromatography on silica gel (30 mm × 7″) eluted with 2% MeOH in $CHCl_3$ for 3 fractions followed by 5% MeOH in $CHCl_3$ yielded 93 mg (37%) of a slightly yellow oil. The material thus obtained was spectroscopically and chromatographically identical to **5** produced in Method A.

(−)-(2S,2′S)-5,5′-(Tetramethylene)bis(1-methyl-2-phenyl-4-oxo-1,5-diazacycloctane) (**7**)

Method A. Eschweiler-Clark methylation. A soln of 89 mg (0.19 mmol) of **5** in 8 mL formic acid-formalin mixture (8.0 : 9.5) was heated to 100° until gas evolution commenced. The heating bath was removed and stirring was continued until the gas evolution ceased. The mixture was then refluxed for 2 hr. After cooling, the mixture was made basic to pH 13 with 1 N NaOH and extracted 6 times with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated to give 95 mg crude oil. Flash chromatography on silica gel (30 mm × 7″) eluted with 5% MeOH in $CHCl_3$ gave several homogeneous fractions of a slightly brown oil, 31 mg (33%), R_f = 0.53 (MeOH–$CHCl_3$; 10 drops: 3 mL) which solidified on standing. Recrystallization from 2 mL benzene–cyclohexane (1 : 9) gave homaline as an off-white powder, m.p. 132–133°. The mixed m.p. with natural homaline was identical to the m.p. of the synthetic material, 132–133°. FTIR ($CDCl_3$) 1622 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 1.54–1.92 (broad m, 8H), 2.26 (s, 6H), 2.46–2.56 (m, 4H), 2.93–3.06 (m, 4H), 3.16 (t, J = 12Hz, 2H), 3.33 (dt, J = 3.5Hz, J = 15Hz, 2H), 3.80–3.90 (m, 4H), 4.00 (dd, J = 3.3Hz, J = 12Hz, 2H), 7.20–7.40 (m, 10H); $(\alpha)_D^{24} = -35°$ (c = 0.92, $CHCl_3$).

Method B. Borch methylation. To a soln of 29.7 mg (0.06 mmol) of **5** in 5.5 mL acetonitrile was added 0.30 mL (0.3 mmol) 37% aqueous formaldehyde followed by 18 mg (3.7 mmol) sodium cyanoborohydride. After stirring at room temp for 30 min, the cloudy mixture was neutralized with 20% AcOH and the stirring was continued for 2.5 hr. Following solvent evaporation, the residue was dissolved in $CHCl_3$ and was washed with 2 N KOH. The aqueous phase was extracted twice with $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and concentrated to give 32.3 mg colorless oil. Flash chromatography on silica gel (10 mm × 5″) eluted with 5% MeOH in $CHCl_3$ yielded 12.7 mg homaline (40%) in two clean fractions. The material obtained was chromatographically and spectroscopically identical to optically active homaline with the exception of the optical rotation, $(\alpha)_D^{24} = -15.4°$ (c = 0.63, $CHCl_3$).

Acknowledgments—We wish to thank Dr. M. Pais, Institute de Chimie de Substances Naturelles, C.N.R.S., Gif-sur-Yvette for a sample of natural homaline and Dr. Susan Rottschaefer, Smith Kline and Beckman Laboratories for the high resolution mass spectral determinations. This research was supported by Grant GM-07874 from the U.S. Public Health Service. We also acknowledge support of the NSF Regional NMR Facility at Yale University (Grant CHE-7916210).

REFERENCES

[1a] *Advances in Polyamine Research*, (Edited by R. A. Campbell, D. R. Morris, D. Bartos, G. D. Daves and F. Bartos). Vol. 1 and 2, Raven Press, New York (1978); [b] M. M. Badawi, K. Bernauer, P. van den Broeck, D. Groger, A. Guggisberg, S. Johne, I. Kompes, F. Schneider, H.-J. Veith, M. Hesse and H. Schmid, *Pure Appl. Chem.* **33**, 81, (1973).

[2]For a review of recent work on the total synthesis of macrocyclic spermine and spermidine alkaloids see H. H. Wasserman and J. S. Wu, *Heterocycles* **17**, 581 (1982).
[3]J. S. McManus and B. Ganem, *J. Org. Chem.* **45**, 2041 (1980).
[4]M. J. Homora, D. E. Seitz and J. Quick, *Ibid.* **44**, 1166 (1979).
[5]Y. Nageo, S. Takao, T. Miyasaka and E. Fujita, *J. Chem. Soc.* Chem. Commun. 286 (1981).
[6]H. Yamamoto and K. Marouka, *J. Am. Chem. Soc.* **103**, 6133 (1981).
[7]U. Kramer, A. Guggisberg, M. Hesse and H. Schmid, *Angew. Chem.* Int. Ed. Engl. **16**, 861 (1977): [b]U. Kramer, A. Guggisberg, M. Hesse and H. Schmid, *Ibid.* **17**, 200 (1978); [c]A. Guggisberg, B. Dabrowski, U. Kramer, C. Heidelberger, M. Hesse and H. Schmid, *Helv. Chim. Acta* **61**, 1039 (1978); [d]A. Guggisberg, U. Kramer, C. Heidelberger, R. Charubala, E. Stephanou, M. Hesse and H. Schmid, *Ibid.* **61**, 1050 (1978); [e]U. Kramer, A. Guggisberg and M. Hesse, *Ibid.* **61**, 1342 (1978); [f]U. Kramer, H. Schmid, A. Guggisberg and M. Hesse, *Ibid.* **61**, 811 (1979); [g]U. Kramer, A. Guggisberg and M. Hesse, *Ibid.* **62**, 2317 (1979).
[8]H. H. Wasserman and D. J. Hlasta, *J. Am. Chem. Soc.* **100**, 6780 (1978).
[9]T. Kamiya, *Recent Advances in the Chemistry of β-Lactam Antibiotics* Cambridge University Press, London (1976).
[10]F. Moll and M. Hannig, *Arch. Pharmaz.* **303**, 831 (1970).
[11]M. S. Manhas, S. G. Amin and A. K. Bose, *Heterocycles* **5**, 669 (1976).
[12]B. J. Nicolaus, E. Bellasio, G. Pagani, L. Mariani and E. Testa, *Helv. Chim. Acta* **48**, 1867 (1965).
[13a]M. Pais, G. Rattle, R. Sarfati and F. X. Jarreau, *C. R. Acad. Sci., Paris Ser. C*, **267**, 82 (1968); [b]R. Sarfati, M. Pais and F. X. Jarreau, *Bull. Soc. Chim. Fr.* 255 (1971); [c]M. Pais, R. Sarfati, F. X. Jarreau and R. Goutarel, *C.R. Acad. Sci., Paris, Ser. C*, **272**, 1728 (1971); [d]M. Pais, R. Sarfati and F. X. Jarreau, *Bull. Soc. Chim. Fr.* 331 (1973).
[14]For a preliminary report of the homaline synthesis, see H. H. Wasserman, G. D. Berger and K. R. Cho, *Tetrahedron Letters* **23**, 465 (1982).
[15]R. Graf, *Liebigs Ann. Chem.* **661**, 111 (1963).
[16]T. Durst and J. M. O'Sullivan, *J. Org. Chem.* **35**, 2043 (1970).
[17]L. Birkofer and J. Schram, *Liebigs Ann. Chem.* 2195 (1975).
[18]C. W. Tabor, H. Tabor and U. Bachrach, *J. Biol. Chem.* **239**, (1964).
[19]R. K. Crossland and K. L. Servis, *J. Org. Chem.* **35**, 3195 (1970).