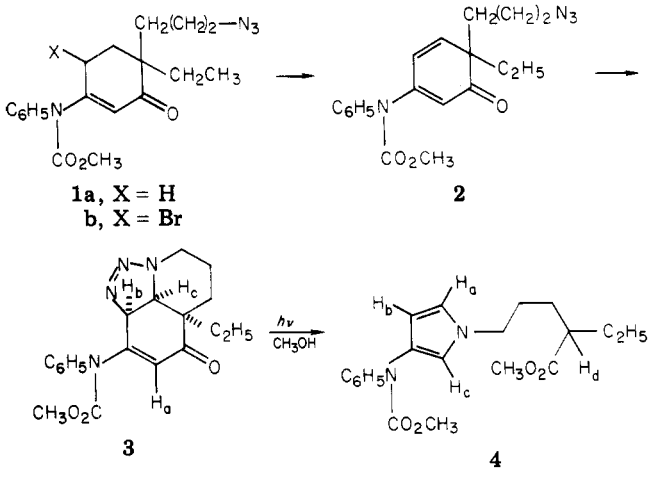
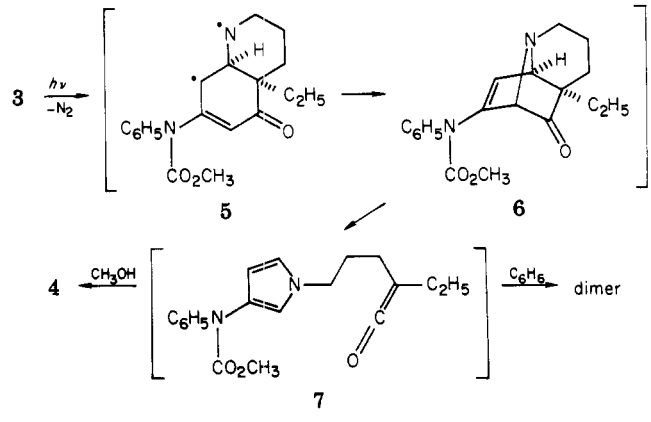
Scheme I



Scheme II



With regard to stereochemical assignment in triazoline **3**, we note that if the mechanism of the rearrangement of **3** → **4** has been correctly interpreted, then formation of **6** demands a *cis*-azaoctalone ring fusion in **3**. The remaining stereochemistry follows from the established cis mode of addition for azide–olefin cycloadditons.[7]

The high efficiency of the photorearrangement of **3** → **4** suggests that this reaction may have synthetic value, and for especially this reason, we are exploring means of intercepting tricyclic intermediates such as **6**. We also are involved in a detailed study of intramolecular azide–olefin cycloadditions and resulting triazoline photochemistry.

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Registry No. 1a, 73367-82-5; **1b**, 73367-83-6; **2**, 73367-84-7; **3**, 73367-85-8; **4**, 73367-86-9; **6**, 73367-87-0; **7**, 73367-47-2; **7** dimer, 73367-48-3.

(7) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965); R. Huisgen, L. Mobius, G. Mueller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965); R. Huisgen and G. Szeimies, *ibid.*, **98**, 1153 (1965); P. Scheiner, *J. Am. Chem. Soc.*, **88**, 4759 (1966).

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Chemistry of Naturally Occurring Polyamines. 1. Total Synthesis of Celacinnine, Celabenzine, and Maytenine

Summary: New methods for the selective functionalization of spermidine and other naturally occurring polyamines have been employed in highly convergent total syntheses of the title compounds.

Sir: Among nature's simplest macrocycles are the plant alkaloids derived from spermine (**1**) and spermidine (**2**),[1,2] two polyamines which are important constituents of every living cell.[3] In 1974 a new family of spermidine alkaloids typified by celacinnine (**3**) and celabenzine (**4**) was isolated from *Maytenus serrata* by Kupchan and co-workers.[4] These structures, which have never been synthesized, have in common a 13-membered lactam ring apparently originating in nature from the combination of spermidine with one β-phenylpropionate unit as depicted in Scheme I.

In this communication we report a biomimetic route to celacinnine and celabenzine directly from spermidine, which relies on a simple and effective new method for differentiating the basic nitrogens of **2**.

Retrosynthetic analysis suggested diamino lactam **5** as a preparatively useful intermediate for the entire family of alkaloids since selective monoacylation of **5** ought to be favored at the nonbenzylic secondary nitrogen. The planned precursor of **5**, triamino acid salt **6**,[5] is difficult to synthesize from free spermidine because the two primary amino groups in **2** have similar basicity[6] and reactivity.[7] This feature is characteristic of the general problem which for over a century has confronted synthetic biochemists working on metabolically important polyamines.[8] However, the 1,3-disposition of N^1 and N^2 in spermidine led us to believe that a number of strain-free, cyclic, six-center derivatives might form reversibly in preference to seven-membered structures and thus serve as compact, temporary blocking agents. For example, we discovered that urea **8** (Scheme II) arose in 95% yield from spermidine by exhaustive acylation ($ClCO_2CH_3$) and then hydrolysis [$Ba(OH)_2$]. As an illustration of its utility, straightforward chemistry on **8** (acrylonitrile, reduction, hydrolysis) resulted in the first rational synthesis of spermine (**1**) from spermidine (three steps, >50%). An even simpler derivative of **2** is hexahydropyrimidine **9** which was produced (87%) merely by mixing equivalent amounts of spermidine and formalin solution in water.

A well-defined order of amine reactivity exists in **9** which, as with many related substances we have prepared, can be exploited in a number of highly regioselective acylations and alkylations. For instance, treatment of **9** with 2 equiv of cinnamoyl chloride followed by deprotec-

(1) Hesse, M.; Schmid, H. "International Review of Science"; Hey, D. H., Wiesner, K., Eds.; 1976; pp 265–307, Series II, Vol. 9.
(2) Badawi, M. M.; Bernauer, K.; Van den Broek, P.; Groger, D.; Guggisberg, A.; Johne, S.; Kompis, I.; Schneider, F.; Veith, H.-J.; Hesse, M.; Schmid, H. *Pure Appl. Chem.* **1973**, *33*, 81.
(3) Bachrach, U. "Function of Naturally Occurring Polyamines"; Academic Press: New York, 1973.
(4) (a) Kupchan, S. M.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Cass, M. W.; Court, W. A.; Yatgai, M. *J. Chem. Soc., Chem. Commun.* **1974**, 329. (b) *J. Org. Chem.* **1977**, *42*, 3660.
(5) Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393.
(6) Palmer, B. N.; Powell, H. K. J. *J. Chem. Soc., Dalton Trans.* **1974**, 2089.
(7) See, for example, the following syntheses of N^1,N^3-dicinnamoylspermidine (maytenine): (a) Husson, H.-P.; Poupat, C.; Potier, P. *C. R. Hebd. Seances Acad. Sci.* **1973**, *276*, 1039; (b) Schlittler, E.; Spitaler, M.; Weber, N. *Helv. Chim. Acta* **1973**, *56*, 1097.
(8) For other examples of a "protected" spermidine, see: (a) Wachli-Schaer, E.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 928; (b) Humora, M.; Quick, J. *J. Org. Chem.* **1979**, *44*, 1166.

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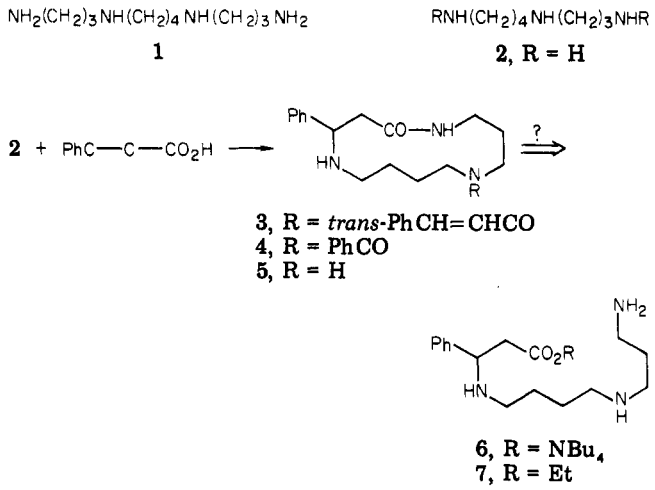
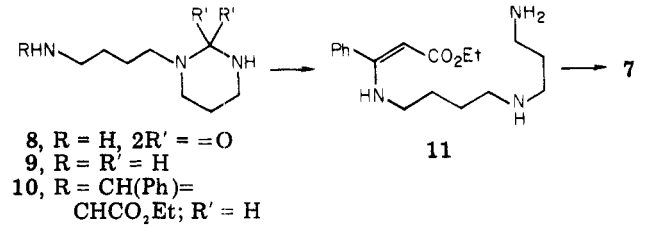
Scheme I



Scheme II



tion using the Knoevenagel reaction (ethyl hydrogen malonate, piperidine, EtOH, 70 °C, 18 h) furnished maytenine (**2**, R = PhCH=CHCO) in 85% yield.[7] When reacted with ethyl phenylpropiolate (EtOH, reflux, 40 min), **9** led to enamino ester **10**. Deblocking as before produced **11** which was reduced ($NaBH_3CN$) to afford **7** (43% from **9**).[9] Hydrolysis of **7** (Bu_4NOH) afforded the pyridine-soluble tetrabutylammonium triaminocarboxylate **6**.

Anhydrous solutions of **6** failed to cyclize with *B*-chlorocatecholborane,[5] but in the presence of catecholborane itself (pyridine, 80 °C), **6** reproducibly afforded a single lactam, **5**, in 61–66% yield. The structure of **5** was fully supported by spectral data and ultimately confirmed by its transformation to **3** (40%) and **4** (40%) upon treatment with PhCH=CHCOCl and PhCOCl, respectively.[10]

(9) An independent synthesis of **7** confirmed its structure: condensation of putrescine with ethyl benzoylacetate (TsOH, EtOH) generated an enamino ester which underwent 1,4-addition with acrylonitrile and then two reduction steps ($NaBH_3CN$, $NaBH_4$–$CoCl_2$) to furnish **7** (49% overall yield).

(10) The recently reported "Zip" reaction of *N*-(γ-aminopropyl) lactams virtually ensures that any smaller cyclic species would have undergone ring expansion to form **5**; cf.: Kramer, U.; Guggisberg, A.; Hesse, M.; Schmid, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 200 and references cited therein.

Synthetic celacinnine [mp 166–169 °C (C_6H_6)] and celabenzine [mp 150–155 °C (EtOAc)][11,12] were spectroscopically indistinguishable from the naturally occurring alkaloids. Moreover, authentic (–)-celacinnine[13] exhibited silica gel TLC behavior in three solvent systems identical with a sample of racemic **3**.[14]

The mechanism of ring closure leading to **5** is interesting and may involve intramolecular disproportionation of a first-formed boronate complex with evolution of H_2. The conjugate active ester–nucleophile pair thus generated must suffer spontaneous cyclization to **5**. Other experiments suggest that this modification of our original procedure[5] is a generally viable method for making amides and lactams.[15]

All of the methodology described herein for tandem nitrogen protection in spermidine may be applied equally well to spermine, where two 1,3-diamine moieties exist and bis-cyclic derivatives arise. Other examples of new, multiple protecting functions and their application to the total synthesis of clinically significant polyamines and polyamine conjugates are presently under investigation.

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Registry No. **1**, 71-44-3; **2** (R = H), 124-20-9; **2** (R = PhCH=CHCO), 41590-65-2; **3**, 73465-24-4; **4**, 73465-25-5; **5**, 73397-35-0; **6**, 73397-37-2; **7**, 73397-38-3; **8**, 73397-39-4; **9**, 73453-98-2; **10**, 73397-40-7; **11**, 73397-41-8; ethyl phenylpropiolate, 2216-94-6; cinnamoyl chloride, 17082-09-6; benzoyl chloride, 98-88-4.

(11) Celabenzine is difficult to purify and demonstrates unusual melting behavior. Moreover, the natural material, which is presumably chiral like its congeners, has $[\alpha]^{25}_D$ 0° ($CHCl_3$). Its ORD spectrum has not been recorded. The melting point that we report which most closely corresponds to the literature values [mp 156–158 °C;[4] 163–167 °C[12]] was determined in an open capillary with rapid heating. A more standard measurement shows a double melting point: 147–148 °C (softens, then solidifies), 190–194 °C (melts). In a nonevacuated, sealed capillary celabenzine melts only at 190–193 °C.

(12) Wagner, H.; Burghart, J.; Hull, W. E. *Tetrahedron Lett.* **1978**, 3893.

(13) A specimen of authentic celacinnine was obtained from the sample collection of the late Professor S. M. Kupchan at the University of Virginia. We are grateful to Dr. J. C. Schmidt for his kind assistance.

(14) R_f 0.12 (two elutions with EtOAc); R_f 0.34 (9:1 EtOAc–CH_3OH); R_f 0.44 (acetone).

(15) Unpublished results of Dr. V. S. Parmar in these laboratories.

(16) Fellow of the A. P. Sloan Foundation, 1978–1980, and recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1978–1983.

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