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SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED 2,5-PIPERAZINEDIONES: REGIOSELECTIVE ALKYLATION OF PIPERAZINEDIONE DERIVATIVES

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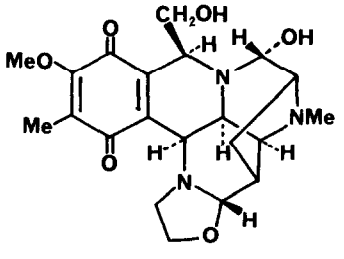
Abstract: A variety of unsymmetrically substituted 2,5-piperazinediones have been synthesized by regioselective alkylation of piperazinedione derivatives.

2,5-Piperazinediones are among the most ubiquitous peptides found in nature.[1] Symmetrically substituted piperazinediones can be synthesized by heating amino acids or their esters. The most typical synthetic pathway to unsymmetrically substituted piperazinediones is to cyclize the corresponding free dipeptide esters. During the course of our synthetic studies on naphthyridinomycin 1,[2] we considered the use of the piperazinediones 2 to construct the 3,8-diazabicyclo[3.2.1]octane skeleton 3 of the antibiotic. We now wish to report herein the facile procedure which gives a variety of unsymmetrically substituted piperazinediones by regioselective alkylation of the piperazinedione derivatives.



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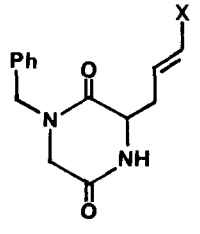

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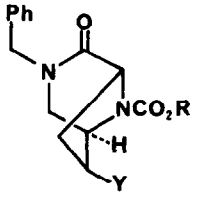
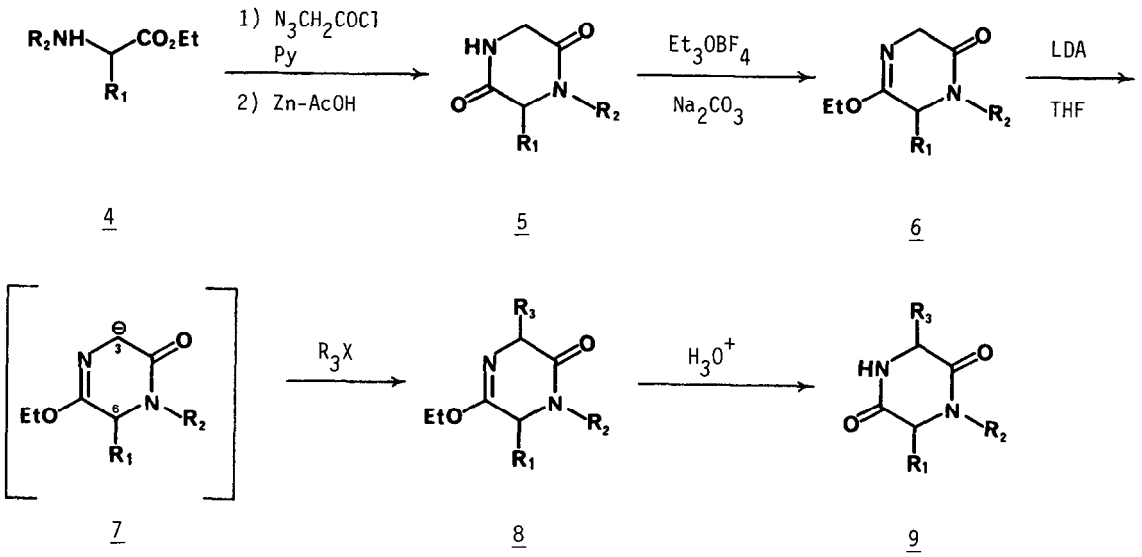


3

Scheme I



4 5 6

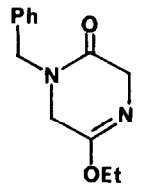
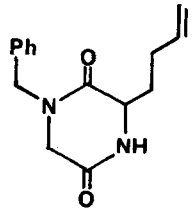
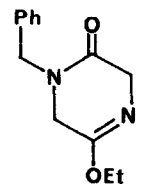
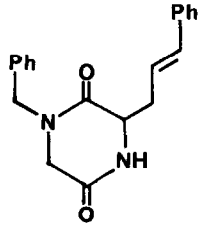
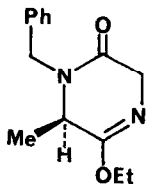
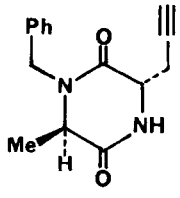
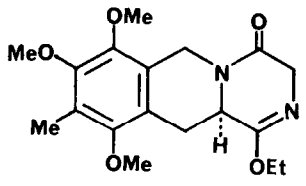
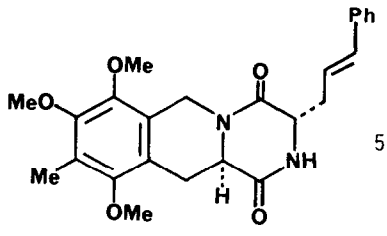
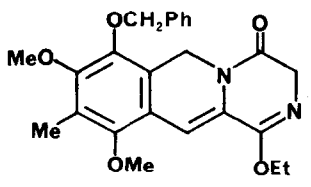
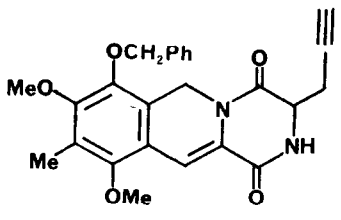
7 8 9

As shown in Scheme I, the piperazinedione 5 can be readily prepared from the amino acid ester 4 in two steps ((1) N_3CH_2COCl, pyridine, CH_2Cl_2; (2) Zn, AcOH, MeOH-CH_2Cl_2 (1:9)). Meerwein's reagent preferentially attacked the unsubstituted lactam of 5 to give the imino ester 6 in 70-80% yield. Treatment of the imino ester 6 with 1.3 equivalent of lithium diisopropylamide (LDA) at -78° generated exclusively the carbanion 7, which gave the alkylated compound 8 upon addition of an alkylating agent. No trace of C-6 alkylation product was found in the reaction mixture. Subsequent acid hydrolysis of the imino ester 8 furnished the desired piperazinedione 9.

A general experimental procedure is as follows: To a solution of the imino ester 6 (2.0 mmole) in anhydrous THF (6 ml) was added, with stirring at -78°, 1.3 eq (2.6 mmole) of LDA in THF (2 ml). After 5 min, 1.3 eq (2.6 mmole) of the alkylating agent (R_3X) was added and the solution was allowed to warm to 0°. After stirring for 20 min at 0°, 3N HCl (1 ml) was added. Upon completion of the hydrolysis of 8 (ca. 10 min), the solution was basified with saturated Na_2CO_3 (2 ml) and stirred for an additional 30 min. The mixture was extracted with ether and the ether extracts dried ($MgSO_4$), evaporated, and chromatographed on silica gel (MPLC) to give the piperazinedione 9.

Some representative examples are presented in Table I. Highly stereospecific alkylation was achieved on the monosubstituted substrates, giving predominantly trans products (entry 3 and 4).[3,4] Our method is particularly suited for synthesis of a variety of side chain analogues from the parent piperazinedione. Application of this reaction to construction of the 3,8-diazabicyclo[3.2.1]octane system 3 will be described in due course.

Table I - Regioselective Alkylation of 2,5-Piperazinedione Derivatives

Entry	Starting Material[5,6]	Alkylating Agent	Product[6]	Yield[7]
1		4-Bromo-1-butene		87%
2		Cinnamyl chloride		71%
3		Propargyl bromide		91%
4		Cinnamyl chloride		55%
5		Propargyl bromide		67%

Acknowledgment: This work was supported by Grant CA-28119, awarded by the National Institutes of Health, and by Research Corporation.

References and Notes

1. For a review of naturally occurring 2,5-piperazinediones, see: P. G. Sammes, Prog. Chem. Org. Nat. Prod., 32, 51 (1975).

2. J. Sygusch, F. Brisse, S. Hanessian, and D. Kluepfel, Tetrahedron Lett., 4021 (1974), correct structural drawing is shown in errata, Tetrahedron Lett., No. 3 (1975).

3. High stereospecficity was observed on the alkylation of the similar systems: U. Schollkopf, W. Harwig, and U. Groth, Angew. Chem. Int. Ed., 18, 863 (1979).

4. While high stereospecificity was achieved using such reactive alkylating agents as methyl iodide, benzyl bromide, allyl bromide, less reactive alkyl halides, n-butyl bromide for example, gave poor results presumably due to the scrambling of the carbanions.

5. Prepared in the following manner: A mixture of the piperazinedione 5 (2 mmole), Et_3OBF_4 (6 mmole), and anhydrous Na_2CO_3 (10 mmole) in CH_2Cl_2 (20 ml) was stirred for 1 hr at ambient temperature. The mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried (Na_2SO_4), evaporated, and chromatographed on silica gel (MPLC) to give the imino ester 6.

6. Satisfactory spectroscopic data were obtained for these substances.

7. No attempts were made to optimize yields.

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