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TOTAL SYNTHESIS OF THE CHIRAL LACTONE DERIVED FROM THERMOZYMOCIDIN (MYRIOCIN). RELATIVE CONFIGURATION OF THE NATURAL PRODUCT.

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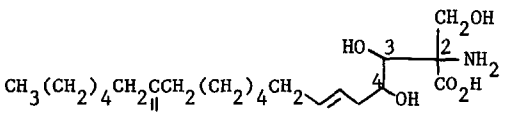
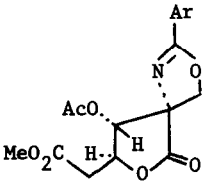
The antibiotic thermozymocidin (myriocin) was isolated in 1972 from a thermophilic fungus and assigned structure I, exclusive of its stereochemistry.[1] In 1973 Bagli et al.[2] published



I

a definitive article on the stereochemistry of this substance in which the relative configurational assignments were based on observations made inter al. with the chiral lactonic ester derived from the natural product. Our interest in the total synthesis of this antibiotic directed our attention to the preparation of the chiral lactonic ester and its subsequent conversion to the natural product. In the course of our investigation we have synthesized the pertinent isomeric systems and have established that the structure of the chiral lactonic ester derived from thermozymocidin does not conform to the functionally[3] all-trans configuration 5 proposed by Bagli et al. (loc. cit.). The natural product, in fact, possesses the relative configuration represented by the functionally[3] all-cis structure 12.

Condensation of 2-p-nitrophenyl-4-carbomethoxy-2-oxazoline[4] with p-nitrocinnamaldehyde (THF-DBN/25°) afforded the two diastereoisomeric aldols (1:1, 80%) separable by differential solubility in chloroform into the threo isomer mp 195-198°, Acetate 1a[5] mp 203-205° and the erythro isomer mp 160-161°, Acetate 1b[5] mp 150-151°. Ozonolysis [O_3/CH_3OH-CH_2Cl_2/-78°; $(CH_3)_2S$] of 1a followed by purification (silica gel/6% Acet-Chf./0°) and condensation of the unstable intermediate aldehyde (mp 126-128°; ir ($CHCl_3$) 5.7, 6.09, 6.22, 6.51, 7.42, 11.51, 11.70μ) with methyl acetate anion (CH_3COOCH_3/$(Me_3Si)_2NLi$-THF/-78°/20 min) proceeded almost exclusively via a trans-oriented pathway to give the Oxazoline lactone 2[5] (40%) mp 166-168°; ir ($CHCl_3$) 5.58, 5.72, 6.09, 6.2, 6.54, 7.46, 11.52, 11.71μ). The trans-orientation: C_3-OAc/C_4-$CH_2CO_2CH_3$ was ascertained by saponification of 2 (2 eq KOH-CH_3OH/25°) to the non-lactonizable hydroxy acid 2a which reverted to 2 on acetylation followed by methylation (CH_2N_2/THF-Et_2O). The cis-



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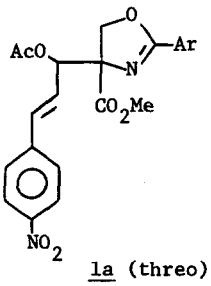
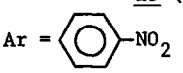
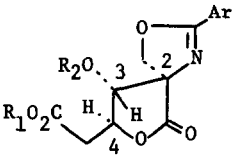
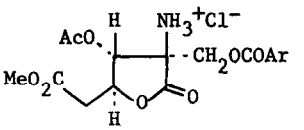


1a (threo)
1b (erythro)





2 R_1=CH_3; R_2=Ac
2a R_1=R_2=H



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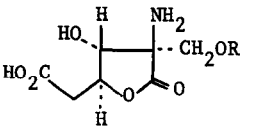
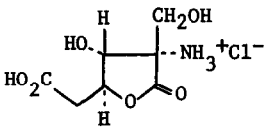


4 R= -C-Ar (O)
4a R=H, (HCl)



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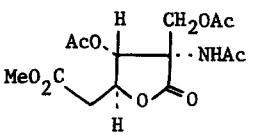

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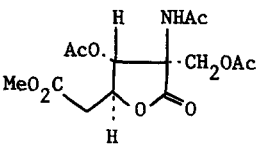

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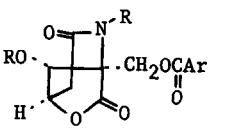
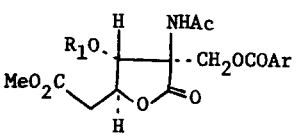
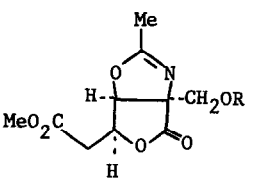


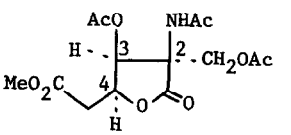
6 R=H
6a R=Ac



10 R_1=Ac
10a R_1=H



11 R= -C-Ar (O)
11a R=H



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orientation: C_2-NHAc/C_4-$CH_2CO_2CH_3$ was determined by two-stage hydrolysis 2 → 3 (2.5N HCl-CH_3OH/25°) followed by 3 → 4 + 4a (1:1) (2.5N HCl/90°); subsequent treatment of 4 with DCC in pyridine at 25° gave the Bicyclic lactam 6[5] (mp 220-223°, ir (Nujol) 2.79, 5.60, 5.75, 5.91μ). Acetylation of 4 alternatively produced the corresponding O,N-diacylated lactam 6a[5] (mp 182-184°; M^+ 420, 348, 291; ir ($CHCl_3$) 5.59, 5.70, 5.92, 6.59, 7.49μ; uv (CH_2Cl_2) 259nm (ε, 13,400). The functionally[3] all-trans stereochemistry of this series was thereby established. Esterification of 4a followed by acetylation[6] provided the corresponding Lactonic ester 5[5] (mp 136-138°; ir ($CHCl_3$) 2.91, 5.59, 5.69 (sh), 5.7, 5.94μ; M^+ 345; nmr ($CDCl_3$) δ2.05, 2.12 (9H, 2s, $-O-\overset{O}{\overset{\|}{C}}-CH_3$ + $NHCOCH_3$), 3.02 (2H, broad d, J=6.5 Hz, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.72 (3H, s, $COCH_3$), 4.23, 4.57 (2H, ABq, J=11 Hz, $-CH_2-O-$) 4.73 (1H, m, $-CH_2-\underset{H}{\overset{|}{C}}-O-$), 5.67 (1H, d, J=6.5 Hz, $AcO-\underset{H}{\overset{|}{C}}-$), 6.45 (1H, broad s, $NH-COCH_3$) which differed from the lactonic ester derived from thermozymocidin[2] in the nmr by the splitting pattern of the $-CH_2OAc$ group.

In a parallel reaction sequence the erythro isomer 1b was transformed to the Oxazoline lactone 7[5] (mp 197-200°; ir ($CHCl_3$) 5.58, 5.72, 6.09, 6.26, 6.56, 7.48, 11.05, 11.72μ) in which the stereochemistry at C_2/C_3 follows by difference with its isomer 2. Further, total hydrolysis of 7 (cf 2 → 3 → 4a) yielded 8 which on acetylation and methylation (CH_2N_2-THF-Et_2O) gave the same Lactonic ester 9[5] [mp 176-178°; ir ($CHCl_3$) 2.91, 5.59, 5.71, 5.91μ; ms M^+ 345, 314, 302, 285, 272; nmr ($CDCl_3$) 2.02, 2.08, 2.13 (9H, 3s, $O-\overset{O}{\overset{\|}{C}}-CH_3$ + $NHCOCH_3$), 2.90 (2H, d, J=6 Hz, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.70 (3H, s, $COOCH_3$), 4.50 (2H, s, $-CH_2-O-$), 4.95 (1H, q, $-CH_2-\underset{H}{\overset{|}{C}}-O-$), 5.23 (1H, d, J=6 Hz, $AcO-\underset{H}{\overset{|}{C}}-$), 6.51 (1H, broad s, $-NH-COCH_3$)] as that derived from 8 by initial esterification and subsequent acetylation.[6] This result established the trans-relationship of the C_4-$CH_2CO_2CH_3$ side-chain with respect to both the C_3-OH and the C_2-NH_2 functions since otherwise lactonization or lactamization would have occurred. The lactonic ester 9 differed from that derived from thermozymocidin[2] in chemical shifts of the acetoxy methylene and methinyl protons.

The essential identity of the splitting pattern of the acetoxy methylene group of 9 in the nmr with that of the natural lactonic ester suggested the same C_2/C_3 but different C_3/C_4 configurations in the two substances. Consequently the C_3-OH of isomer 5 was inverted. To this end acetylation[6] of 3 yielded 10[5] (mp 95-97°) converted (CH_3OH-HCl) to 10a[5] (mp 161-163°). Treatment of 10a with trifluoromethanesulfonic anhydride in pyridine at 0° proceeded with accompanying inversion at C_3 and formation of the oxazoline 11[5] (mp 183-185°; ir ($CHCl_3$) 5.59, 5.75, 6.02μ; M^+ 392). Removal of the p-nitrobenzoyl group (CH_3OH-KOAc) followed by hydrolysis (2.5N HCl/CH_3OH-THF/25°) completed the N → O acetyl transfer yielding the corresponding O-acetyl amine hydrochloride. Acetylation of the latter yielded the functionally[3] all-cis Lactonic ester 12[5] (mp 142-144°); ir ($CHCl_3$) 2.91, 5.59, 5.71, 5.92μ; ms M^+ 345, 302, 272; nmr ($CDCl_3$) 2.03, 2.04 (6H, 2s, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 2.14 (3H, s, $NH-COCH_3$), 2.87 (2H, d, J=7 Hz, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.72 (3H, s, $COOCH_3$), 4.49 (2H, s, $-CH_2-OAc$), 5.25 (1H, d of t, J=5.5 Hz, 7.0 Hz, $-CH_2-\underset{H}{\overset{|}{C}}-O-$), 5.73 (1H, d, J=5.5 Hz, $AcO-\underset{H}{\overset{|}{C}}-$), 6.02 (1H, broad s, $NHCOCH_3$) identical spectroscopically with the chiral lactonic ester derived from thermozymocidin.[2,7]

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References

1. (a) F. Aragozzini, P. L. Manachini, R. Craveri, B. Rindone and C. Scholastico, Tetrahedron, 28, 5493 (1972); (b) D. Kluepfel, J. F. Bagli, H. Baker, M. Charest, A. Kudelski, S. N. Sehgal and C. Vezina, J. Antibiotics, 25, 109 (1972).

2. J. F. Bagli, D. Kluepfel and M. St. Jacques, J. Org. Chem., 38, 1253 (1973).

3. The term "functionally" refers to functions: C_2-NH_2, C_3-OH, and C_4-$CH_2CO_2CH_3$ which are transformationally involved in the configurational determinations.

4. S. Ginsburg and I. B. Wilson, J. Am. Chem. Soc., 86, 4716 (1964).

5. Satisfactory elemental analyses and acceptable nmr spectra were obtained for all pertinent compounds.

6. Acetylations were effected with acetic anhydride in pyridine (1:3/25°) and esterification with methanol saturated with hydrogen chloride at 0-25°.

7. The same stereochemistry has recently been derived from X-ray determination on thermozymocidin. (Private communication from Dr. C. Scholastico of the Inst. Chim. Org. Centro Naz. Chim. Sost. Org. Nat. CNR, Milano. We thank Dr. Scholastico for informing us of this finding prior to its publication.)