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SYNTHESIS OF TRIOSTIN A

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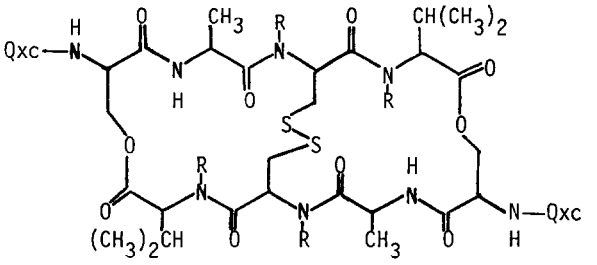
Triostin A (1) is the foremost member of the triostin family of the quinoxaline antibiotics.[1] The quinoxaline antibiotics are of current interest as a class of novel bifunctional intercalating agents in their mode of binding to DNA,[2] in which they function as potent inhibitors of RNA synthesis.[3] The antibiotics also possess antibacterial[4] and cytotoxic[5] activity. Recent NMR studies[6] have shown triostin A to exist in solution as two distinct cyclic depsipeptide conformers.

We recently reported[7] preparation of an analogue of 1, namely, des-N-tetramethyltriostin A (2). We herein report the total synthesis of the natural antibiotic, triostin A (1).



1 R=Me
2 R=H

Qxc = 2-Quinoxalinecarbonyl

The synthesis of triostin A (Scheme I), while similar to the procedure developed in preparation of the des-N-methyl analogue 2, required significant modifications, as described below, due to the incorporation of N-methylamino acids in triostin A. Tridepsipeptide 3 was prepared in 72% yield by condensation of Z-D-Ser-Ala-OTce[7] with Boc-MeVal-OH[8] using N,N'-

dicyclohexylcarbodiimide in pyridine. Deprotection of 3 with trifluoroacetic acid (TFA), followed by coupling with Boc-MeCys(Bam)-OH[9] (mixed anhydride[10] prepared from isobutylchloroformate) gave tetrapeptide 4 in 65% yield. The thiol function of the N-methyl-L-cysteine residue in 4 was protected with the benzamidomethyl (Bam) group, which protective group was developed[9] during this study for use with N-methylcysteine in peptide synthesis.

Removal of the β,β,β-trichloroethyl (Tce) ester[11] function in tetrapeptide 4 with zinc in acetic acid gave a mixture of 4 and 5, from which 5 was isolated in 65% yield by column chromatography on silica gel. The incomplete removal of the Tce ester group, as noted by the recovery of 4 in the above reaction, appears to be a problem in deblocking peptides prepared in this study that contain N-methylamino acids. Thus, incomplete removal of the Tce group was a more serious problem[12] with octadepsipeptide 8 (R=Tce), prepared by fragment coupling of 5 and 6, and rendered impractical the synthesis of triostin A via 8.

A modified approach that proved to be successful involved fragment coupling of the mixed anhydride of 5 and the free tetradepsipeptide 7 to furnish, in 76% yield, linear octadepsipeptide 9 (R=H) already having the carboxyl end deprotected. Tetradepsipeptide 7 was prepared (93%) from 5 by removal of the N-t-butyloxycarbonyl group with TFA. It should be noted that several of the intermediates prepared in this study were obtained, due to the presence of N-methylamino acid residues, as oils and were purified by column chromatography on silica gel.

Deprotection (TFA, room temperature) of the amino terminus of 9, followed by neutralization and cyclization [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, N-hydroxysuccinimide,[13] 0.39 mmol in 155 ml THF, 96 hr] furnished cyclic depsipeptide 10 in 22% yield following purification on a silica gel column. Treatment of 9 with iodine in methanol[14] gave a quantitative yield of disulfide 11. Triostin A was prepared in 30% yield from 11 by a sequence[7] involving removal of the benzyloxycarbonyl group (HBr in acetic acid), neutralization, acylation with 2-quinoxalinecarbonyl chloride, and purification by column chromatography on silica gel. The synthetic antibiotic (mp 239-43°dec, $[\alpha]_D^{25}$-154, c=1.0, $CHCl_3$) was identical with natural triostin A (lit[1] mp 245-48°dec, $[\alpha]_D^{23.5}$-157±2, c=0.97, $CHCl_3$[1]) in three tlc systems and by superimposable IR and NMR spectra.

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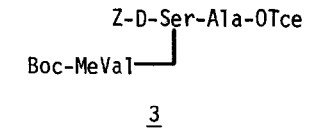
Scheme I



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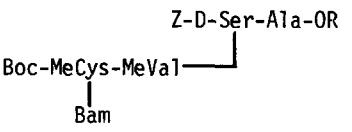
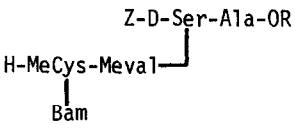


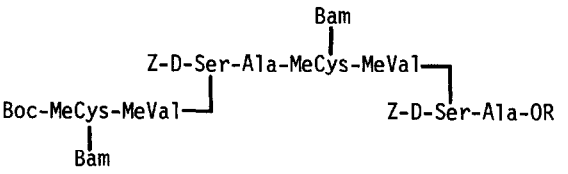
4 R=Tce

5 R=H



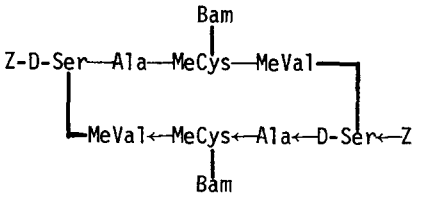
6 R=Tce

7 R=H (as trifluoroacetate salt)



8 R=Tce

9 R=H



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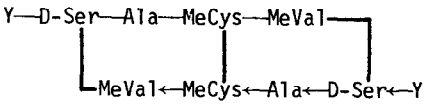

11 Y=Benzyloxycarbonyl (Z)

1 Y=2-Quinoxalinecarbonyl (Qxc)

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