Tetrahedron Letters,Vol.27,No.24,pp 2727-2730,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# STEREOCHEMICAL STUDIES OF LASALOCID ALDOL EPIMERS. ASSIGNMENTS AND INTERCONVERSIONS.

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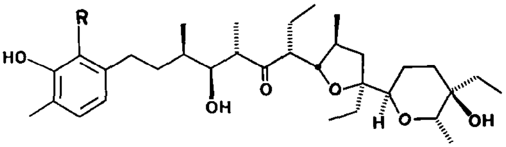
Abstract: The stereochemistries of the epimeric aldols of lasalocid have been determined by chemical correlation and new methods for establishing relative stereochemistry in this series have been discovered.

The major problem with the aldol fragment-coupling approach[1] to polyether antibiotic synthesis is stereocontrol at the newly formed chiral centers. As part of a study directed toward finding new solutions to this problem, we needed to verify the stereochemical assignments for the aldol epimers (2, 3 and 4)[2] of lasalocid (1). We report here that the assignments made by Ireland[3] using NMR are correct and that a number of transformations of lasalocid-like intermediates are highly stereocontrolled.



1 Lasalocid (R = COOH)

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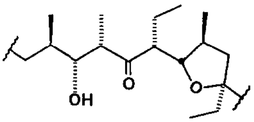

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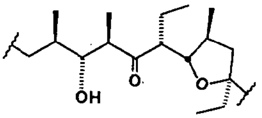

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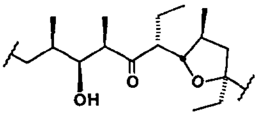

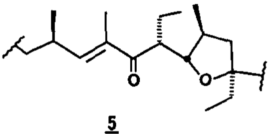

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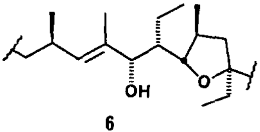

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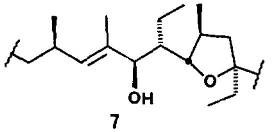

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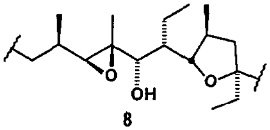
To determine the identity of the epimers, Bn lasalocid (1, R = $CO_2Bn$) was first dehydrated to enone 5 (pTsOH, $PhCH_3$, $65^\circ$, 15h; 82% yield) and reduced to allylic alcohol 6 ($NaBH_4$, MeOH, $-5^\circ$; 71% yield, >10:1 6:7). The epimeric allylic alcohol 7 could be produced with accompanying reduction of the benzylic ester using DIBAL ($CH_2Cl_2$, $-78^\circ$; 63% yield, 6:1 7:6). The E-stereochemistry of 5 was verified by hydroboration (1. $BH_3$, THF; 2. NaOOH) of a mixture of 6 and 7 (R = $CH_2OH$) which yielded products which were identical to those formed by DIBAL reduction of lasalocid and isomer 3. These transformations thus allowed identification of 3 as the doubly epimeric anti-aldol isomer of lasalocid shown above.



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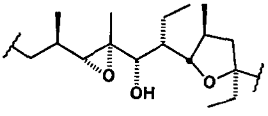

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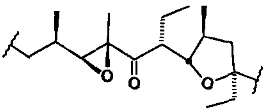

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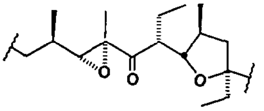

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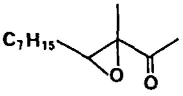
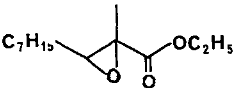
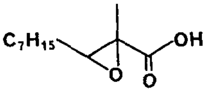
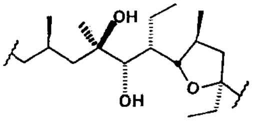
For assignment of the syn-aldols 2 and 4, allylic alcohol 6 was epoxidized with $VO(acac)_2$/tBuOOH (giving 10:1 8:9) and with MCPBA (giving 7:3 8:9) to yield pure epoxides 8 and 9 after silica gel chromatography.[4] Jones oxidation gave the corresponding epoxyketones 10 and 11. To verify the epoxide stereochemistry shown, 10 and 11 were separately reduced with lithium in ammonia/Et$_2$O (5 min, -78$^0$; isoprene and aq. NH$_4$Cl quench) to yield lithium lasalocid (85%) and lithium 3 (63%) respectively. No other isomers could be detected. Stereocontrol in these reductions occurs during protonation of the intermediate enolates and seems to be a property of the lasalocid-like systems since analogous reduction of the simpler epoxycarbonyl systems below gave essentially no stereocontrol.[5]







With the epoxide stereochemistries of 8 and 9 determined, pure 8 was reduced with DIBAL (8 equiv., CH$_2$Cl$_2$, 25$^0$, 12hr.) and epoxide reduction products 12 (48% yield) and 13 (19% yield)[6] were isolated. The remainder of the reduction product had the epoxide intact. Diols 12 and 13 were readily distinguished by treatment with Pb(OAc)$_4$ which cleaved 12 but not 13. Inversion of stereochemistry followed from the nonidentity of 13 with the hydroboration products of 6 and from its identity with the DIBAL reduction product of isomer 4.



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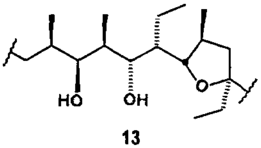

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The original diastereomer assignments for 2-4 are thus confirmed by chemical correlation based on compound identities and the syn nature of the hydroboration reaction. Novel stereoselection in the reduction of lasalocid-like epoxyketones was also observed and could serve as a useful synthetic approach to the aldol substructure of ionophores.

## Notes and References:

1. (a) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer and Y. Kishi, J. Am. Chem. Soc., 100, 2933 (1978); (b) T. Fukuyama, K. Akasaka, D.S. Karanewsky, C.-L.J. Wang, G. Schmid and Y. Kishi, J. Am. Chem. Soc., 101, 263 (1979); (c) W.C. Still, J. McDonald and D.B. Collum, J. Am. Chem. Soc., 102, 2120 (1980); (d) R.E. Ireland, R.C. Anderson, R. Badoud, B.J. Fitzsimmons, G.J. McGarvey, S. Thaisrivongs and C.S. Wilcox, J. Am. Chem. Soc., 105, 1988 (1983).

2. Lasalocid epimers were stereorandomly prepared from the known[1d] thermal retroaldol products of benzyl lasalocid (Rf (25% EtOAC/pentane) 0.45) using LDA and $Ti(iPrO)_3Cl$ to yield 2 (20% yield, $R_f$ = 0.39), 3 (12% yield, $R_f$ = 0.32) and 4 (11% yield, $R_f$ = 0.26).

3) We wish to thank Professor Ireland for spectra of aldols 2-4 and information on his stereochemical assignments.

4) Cf. B.E. Rossiter, T.R. Verhoeven and K.B. Sharpless, Tetrahedron Lett., 4733 (1979).

5) Using our standard $Li/NH_3$ reduction with an isoprene and ammonium chloride quench: the epoxyketone gave a 1.7:1 diastereomeric mixture (83% yield), the epoxyester gave a 1.7:1 diastereomeric mixture (67% yield) and the epoxyacid gave a 1.4:1 diastereomeric mixture (85% yield).

6) Cf. H.C. Brown and N.M. Yoon, J. Am. Chem. Soc., 90, 2686 (1968); R.O. Hutchins, I.M. Taffer and W. Burgoyne, J. Org. Chem., 46, 5214 (1981).

(Received in USA 14 January 1986)