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SYNTHETIC STUDIES ON POLYETHER ANTIBIOTICS. III.[1] A STEREOCONTROLLED SYNTHESIS OF ISOLASALOCID KETONE FROM ACYCLIC PRECURSORS.

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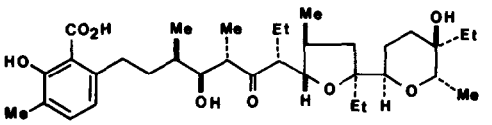
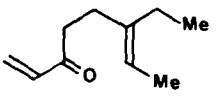
We recently reported the first total synthesis of lasalocid A (1).[2] One of the key intermediates in this synthesis is the isolasalocid ketone 11, which was synthesized by a 19-step procedure in about 3.5% overall yield from a readily available starting material. In this communication, we would like to report a new, short, efficient, and highly stereospecific synthesis of the isolasalocid ketone 11 using *only* acyclic precursors.



1 : lasalocid A

Application of the synthetic method developed recently in our laboratory[1] to the readily available unsaturated ketone 2[3,4] gave the tetrahydrofuran 3[3,5] (65% yield) along with a small amount of its stereoisomer 4[3] (6% yield). The tetrahydrofuran 3 was easily separated from 4 by medium pressure column chromatography (silica gel; EtOAc-hexane=1-5). Optical resolution of 3 was achieved through its hemiphthalate using strychnine as the resolving reagent.[6] After the secondary alcoholic group was protected as its benzyl ether ($C_6H_5CH_2Br$/KH/THF/RT), the levorotatory tetrahydrofuran 3 ($[\alpha]_D^{22}$ -18.2° (*c* 0.90, $CHCl_3$)) was ozonized to give the aldehyde 5[3,7] in 79% yield. Grignard reaction of 5 with 2-methyl-3-butenylmagnesium bromide 6, prepared from (+)-1-bromo-2-methyl-3-butene[8] in THF, yielded the alcohol 7[3]. Jones oxidation of 7, followed by treatment with ethylmagnesium bromide in ether, gave exclusively the alcohol 8[3,9] in 45% overall yield from 5. The stereochemistry of 7 and 8 was assigned based on the cyclic model of Cram's rule.[10] Ozonolysis of 8, followed by dimethyl sulfide workup, afforded the lactol 9[3,11] (mp 47-49°C) in 78% yield. Treatment of 9 with the magnesium enolate[12] prepared from 4-bromo-3-hexanone gave a mixture of aldols,



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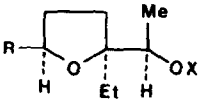
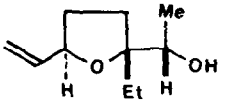


3 : R=CH=CH$_2$, X=H

5 : R=CHO, X=CH$_2$C$_6$H$_5$



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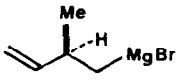

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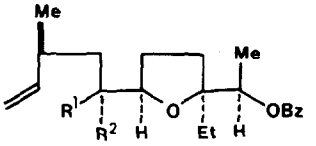
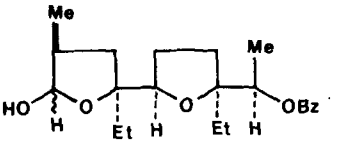


7 : R^1=H, R^2=OH

8 : R^1=OH, R^2=Et



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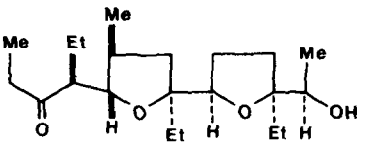

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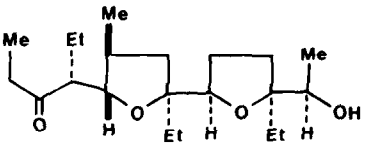
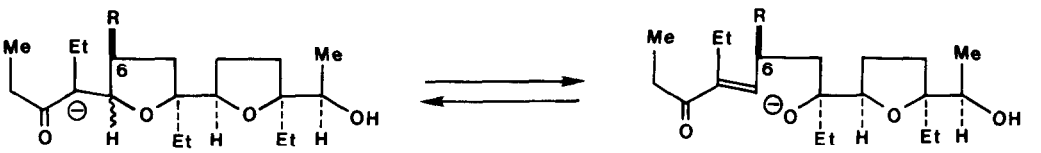


11

which was treated with *p*-TSA in boiling benzene and then deprotected (H_2/Pd-C/CH_3OH) to yield a mixture of the epi-isolasalocid ketone 10[2,3] (3 parts) and the isolasalocid ketone 11[2,3] (2 parts) in 60% overall yield. Sodium hydroxide treatment of 10 yielded an equilibrium mixture (1:1) of 10 and 11.[2] The synthetic isolasalocid ketone 11 was identical in all respects with the authentic substance[2] (NMR, IR, MS, α_D, and tlc).

The base catalyzed equilibration described above seems to involve ring opening and closing of the tetrahydrofuran moiety (i.e., A ⇄ B), since sodium hydroxide treatment of the norketone[1,3] (i.e., R = H in A) resulted in a mixture of four isomeric ketones. However, because epimerization at the C-6 position was not observed in 10, 11, nor their C-6 epimers[1,3] under these conditions, optically active Grignard reagent 6 was necessary for this synthesis.



A B

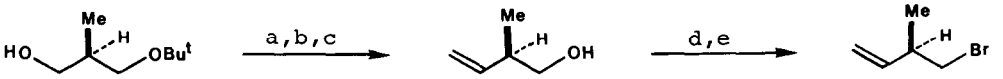
Thus, the isolasalocid ketone 11 was synthesized by an 11-step procedure in about 10% overall yield (after 2 cycles of epimerization of 10; the conditions have not been optimized) from acyclic, conformationally mobile precursors with a high degree of stereospecificity. The ketone 11 has, in turn, been converted to lasalocid A (1) by a 4-step procedure in about 45% overall yield in our laboratory.[2]

Acknowledgment Financial support from National Institutes of Health, National Science Foundation, and Hoffmann-La Roche Company is gratefully acknowledged.

References and Footnotes

1. For Part II of this series, see the preceding paper.
2. T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, J. Am. Chem. Soc., in press.
3. Satisfactory spectroscopic and analytical data were obtained for this substance
4. This substance was synthesized by adapting Johnson's method (W. S. Johnson, L. Wertheman, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, J. Am. Chem. Soc., 92, 741 (1970)): oil; NMR ($CDCl_3$, δ) 0.99 (3H, t, J=7 Hz), 1.58 (3H, d, J=7 Hz), 5.17 (1H, q, J=7 Hz), 5.70-6.55 (3H, m).

5. Oil; NMR ($CDCl_3$, δ) 0.94 (3H, t, J=7 Hz), 1.13 (3H, d, J=7 Hz), 3.79 (1H, q, J=7 Hz), 4.35 (1H, q, J=7 Hz), 5.00-5.30 (2H, m), 5.65-6.06 (1H, m).
6. Optical resolution of 3 involved the following five steps: 1. hemiphthalate formation (phthalic anhydride/Py/reflux), 2. strychnine salt formation of the hemiphthalate, 3. recrystallization of the salt (2 times from MeOH-Et_2O; mp 202-203°C; $[\alpha]_D^{22}$ -41.8° (*c* 0.50, MeOH)), 4. regeneration of the hemiphthalate (3N HCl/Et_2O; mp 111-112°C; $[\alpha]_D^{22}$ -99.4° (*c* 0.50, MeOH)), 5. regeneration of 3 (1N NaOH/reflux; $[\alpha]_D^{22}$ -18.2° (*c* 0.90, $CHCl_3$)).
7. Oil; NMR ($CDCl_3$, δ) 0.93 (3H, t, J=7 Hz), 1.17 (3H, d, J=7 Hz), 3.57 (1H, q, J=7 Hz), 4.22 (1H, m), 4.53 (2H, dd, J=15, 12 Hz), 7.27 (5H, s), 9.57 (1H, d, J=2 Hz); IR ($CHCl_3$) 1725 cm^{-1}; $[\alpha]_D^{22}$ +3.36 (*c* 1.22, $CHCl_3$).
8. This substance was synthesized as shown below. We are indebted to Dr. Noal Cohen, Hoffmann-La Roche Company, for a sample of (S)-(+)-3-hydroxy-2-methylpropionic acid, the starting material for i (N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, J. Org. Chem., 41, 3505 (1976)).



i ii Bp 117-119°C iii Bp 110-112°C

α_D^{22} +28.5° (*c* 1.76, $CHCl_3$) α_D^{22} +9.22° (*c* 2.95, $CHCl_3$)

Reagents: a. pyridinium chlorochromate/CH_2Cl_2/RT, b. $(C_6H_5)_3P{=}CH_2/Et_2O$/RT, c. TFA/0°C, d. MsCl/Et_3N/CH_2Cl_2/0°C, e. LiBr/DMF/100°C.

9. Oil; NMR ($CDCl_3$, δ) 0.85 (3H, t, J=7 Hz), 0.90 (3H, t, J=7 Hz), 0.99 (3H, d, J=7 Hz), 1.12 (3H, d, J=7 Hz), 3.53 (1H, q, J=7 Hz), 3.85 (1H, t, J=7 Hz), 4.51 (2H, dd, J=15, 12 Hz), 4.76-5.05 (2H, m), 5.61-6.05 (1H, m), 7.28 (5H, s); $[\alpha]_D^{22}$ -25.1° (*c* 2.29, $CHCl_3$).
10. For example, J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", American Chemical Society, Washington, D.C., 1976, p 84 ff.
11. Mp 47-49°C; NMR ($CDCl_3$, δ) 0.8-1.01 (3X3H), 1.18 (3H, d, J=7 Hz), 3.53 (1H, q, J=7 Hz), 3.90 (1H, dd, J=11, 5 Hz), 4.53 (2H, dd, J=18, 12 Hz), 5.05 (1H, dd, J=11, 4 Hz), 7.26 (5H, s); $[\alpha]_D^{22}$ -66.3° (*c* 1.50, $CHCl_3$).
12. J. Colonge and J. Grenet, Bull. Soc. Chim. Fr., 1304 (1954).
13. This substance was synthesized by the same method as the one described in this communication; T. Nakata and Y. Kishi, unpublished results.