Tetrahedron Letters Vol. 21, pp 3219 - 3222
0040-4039/80/0815-3219$02.00/0

THE SYNTHESIS OF THE (-)-ENANTIOMER OF (+)-ANHYDROMYRIOCIN (15), THE γ-LACTONE DERIVED FROM MYRIOCIN (THERMOZYMOCIDIN).

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The optical antipode of the lactone derived from myriocin or thermozymocidin has been synthesized from L-arabinose.

Myriocin and thermozymocidin were isolated from Myriococcum albomyces NRRL 3858[2] and Albomyces 20,349[3] respectively. They were quickly shown to have the same gross structure[4,5] and were always suspected of being identical. Conflicting reports concerning their relative configuration have appeared [4,6a] but the γ-lactone derived from natural thermozymocidin was definitely assigned the relative stereochemistry 13 by X-ray diffraction[6b]. The absolute configuration of neither myriocin nor thermozymocidin has ever been reported. We wish to describe a synthesis, from L-arabinose, of the optical antipode of anhydromyriocin, which proves its absolute configuration as 15 and therefore 16 for myriocin and at the same time confirms the identity of myriocin and thermozymocidin.

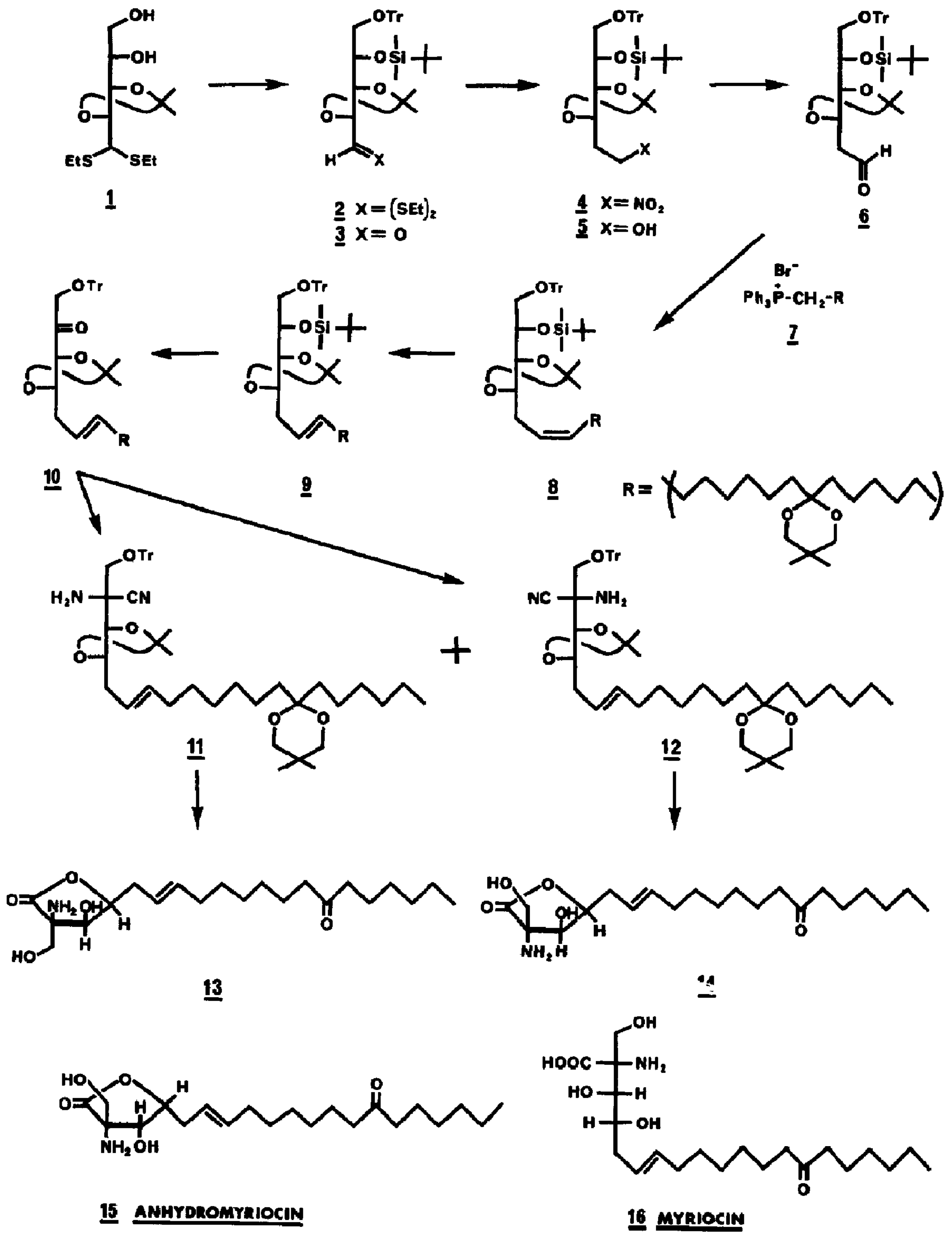
The L-arabinose derivative 1[7] was tritylated[8], and then silylated[9] to provide the t-butyldimethylsilyl ether 2, m.p. 91.5-92.5°C. Reaction with $HgCl_2/HgO$ in 95% aq. acetone gave aldehyde 3, which was transformed into the nitro compound 4 by the method described by Wollenberg and Miller[10]. Treatment with 1.2 equiv. EtONa in ethanol followed by ozonolysis of the nitronate salt at -70°C and immediate reductive work-up with $NaBH_4$ gave 5[11]. Oxidation of 5 with PCC[12] in CH_2Cl_2 gave the base sensitive aldehyde 6 in 66% yield, based on 2.

Reaction of cyclooctanone with n-hexylmagnesium bromide and dehydration of the resulting tertiary alcohol with iodine in refluxing xylene[13] gave 1-hexylcyclooctene. Ozonolysis in ethanol at -70°C, followed by reductive work-up with $NaBH_4$ gave 1,8-tetradecanediol, m.p. 47.5-48.5°C. Selective oxidation of the secondary alcohol with Br_2/HMPT[14] gave 1-hydroxy-8-tetradecanone, m.p. 52-53°C (72%), which was ketalized with 2,2-dimethyl-1,3-propanediol in refluxing benzene (TsOH). The primary alcohol function was then converted to the corresponding bromide (NBS-Ph_3P/DMF[15], 87%) which was treated with 1.5 equiv. Ph_3P in a boiling mixture of acetonitrile and trimethyl orthoformate (4:1) for 14 hours to give the phosphonium salt 7 as a glass.

A solution of 1.3 equiv. 7 in dry THF under argon was treated with 1.1 equiv. n-BuLi in hexane at 25°C for 10 min., then cooled to -70°C. A THF solution of the freshly prepared aldehyde 6 was added dropwise. After stirring at −70°C for 5 min., 1 ml t-BuOH in THF was added and the mixture was allowed to warm up to 20°C. The olefin 8 (>90% cis^{20,21}), obtained in 86% yield, was converted to its trans isomer 9 in 90% yield by epoxidation with m-chloroperbenzoic acid in cyclohexane followed by successive treatment with Ph_2PLi/THF and MeI^{17}. Desilylation ($N\overset{+}{B}u_4\overset{-}{F}$)^{9} and oxidation with DMSO-Ac_2O^{18} gave ketone 10. Reaction of 10 with 1.5 equiv. NaCN and 1.5 equiv. NH_4Cl in MeOH saturated with NH_3 for 8 days at 20-25°C gave cyanoamines 11 and 12 in a 4:5 ratio (75% total yield) which were separated by flash chromatography^{16}. The more polar cyanoamine 11 was heated in MeOH/H_2O (97/3) saturated with HCl gas fo 3 hours at 45°C. Neutralization with aq. K_2CO_3 and extraction with $CHCl_3$ gave, after chromatography, lactone 13, m.p. 79.5-80.0°C, $[\alpha]_D^{23}$ −24° (c 3.0, MeOH) and −38° (c 0.55, 0.037 N HC in MeOH). Its 200 MHz pmr, ir and mass spectra were superimposable with that of the lactone derived from natural myriocin, m.p. 76-77°C, $[\alpha]_D^{24}$ +33.4° (c 0.718, MeOH)^{5}. The rotation reported for anhydrothermozymocidin hydrochloride was $[\alpha]_D^{25}$ +33° (c 1.0, MeOH)^{5b}. The less polar cyanoamine 12 was likewise transformed into the lactone 14, m.p. 76-76.5°C, $[\alpha]_D^{23}$ −54° (c 2.7, MeOH). Its spectra, while confirming the structure, showed significant differences with that of 13.

This synthesis therefore confirms 15 as the structure of anhydromyriocin and anhydrotherm zymocidin.

Acknowledgements. We are grateful to the Natural Sciences and Engineering Research Counci of Canada for financial support. We also thank Mr. A. Ugolini, Dr. W. Dawson, Dr. J. Everett and Ms. L. Ayotte for C^{13} and 200 MHz n.m.r. spectra; and Dr. O.A. Mamer, Dr. V. Taguchi, and Ms. J. Montgomery for the mass spectra. The gift of an authentic sample of myriocin from Dr. J. Bagli, Ayerst Laboratories, Montreal, Canada, is gratefully acknowledged.


1
2 X=(SEt)$_2$
3 X=O
4 X=NO$_2$
5 X=OH
6
7
Br^-
$Ph_3\overset{+}{P}$-CH_2-R
8
9
10
R=
11
12
13
14
15 ANHYDROMYRIOCIN
16 MYRIOCIN
OTr
OH
EtS
SEt
HOOC
NH_2
H_2N
CN
NC

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19. N.m.r. and I.r. data, rotation and elemental analysis were obtained for all pertinent intermediates.
20. As established by C^{13} n.m.r. experiments on closely related model compounds, to be published.
21. C^{13} spectrum of 13 showed no detectable amount of cis olefin (<5%).

(Received in USA 6 May 1980)