Tetrahedron Letters,Vol.22,No.49,pp 4883-4886,1981 0040-4039/81/494883-04$02.0
Printed in Great Britain

A FACILE CONSTRUCTION OF THE 2,9-DIOXABICYCLO-[3.3.1]-NON-7-EN-6-ONE RING SYSTEM: A MODEL FOR TIRANDAMYCIN.

Frederick E. Ziegler and John K. Thottathil

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511

Summary: The bicyclic oxygenated ring system present in tirandamycin is readily constructed from a furan precursor.

Tirandamycin 1a has been shown to have antibacterial activity, inhibitory activity toward RNA polymerase, and to interfere with oxidative phosphorylation.[1] Oxidative degradation of tirandamycin provides tirandamycic acid 1b, which has recently been synthesized by Ireland from D-glucose.[2,3] Our interest in this problem lay in the development of a method for the facile construction of the 2,9-dioxabicyclo[3.3.1]-non-7-en-6-one ring system inherent in this antibiotic.[4]

It is well recognized that furans undergo oxidative bis-2,5-alkoxylation.[5] When this process is applied to 1-(α-hydroxy)alkylfurans, acid hydrolysis provides the 6-hydroxy-2H-pyran-3(6H)-one ring (e.g., 3a).[6,7] Achmatowicz has noted that closure of 3 to 4 is incomplete (26%), even under anhydrous conditions, yielding principally hemiacetal 3b.[6] We reasoned that closure of the 6-membered ring should be more facile than the 5-membered ring and that a 5-alkyl substituent on the furan would help stabilize the carbonium ion necessary for ring closure.

Vilsmeier-Haack formylation (DMF-$POCl_3$, 0°C, 0.5 h → 40°C, 1h) of 2,3-dimethylfuran[8] afforded the known[9] 4,5-dimethylfurfural in 93% yield. Condensation of the aldehyde with the lithium enolate of ethyl propionate (LDA, -78°C, THF, 97%) afforded β-hydroxyesters 5a (erythro)[10,11] and 6a (threo) as a nearly equal mixture of diastereomers. This *intentionally* prepared mixture was readily separated (Waters Prep-500, SiO_2, 30% EtAc-Hexane) and the esters were readily reduced ($LiAlH_4$, ether, 25°C) to their respective diols. Oxidation of erythro diol 5b (Br_2, MeOH, K_2CO_3, -78°C, 10 min) gave rise to crude dihydrofuran as a complex mixture of diastereomers. Hydrolysis of 7 in 0.7N HCl (aq. THF,

25°C, 3 h) afforded the bicyclic enone 9 [IR(CCl_4) 1686 and 1630 cm^{-1}; MS(70 eV) M^+182; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.72 (3H, d, J = 7.0 Hz), 1.53 (3H, s), 1.95 (3H, d, J = 1.5 Hz), 2.42 (1H, m), 3.44 (1H, t, J = 12.0 Hz), 3.78 (1H, dd, J = 12.0 and 5.5 Hz), 4.09 (1H, d, J = 5.9 Hz), and 6.17 (1 H, bd.s); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 194.5, 154.8, 127.4, 95.0, 78.7, 64.5, 30.5, 24.0, 19.0, and 11.4] in 90% yield from 5b *in aqueous medium*. The intermediate pyranone 8 was observed as a mixture of hemiketal diastereomers when dihydrofuran 7 was hydrolyzed in weakly acidic solution (1.3 x 10^{-3}N HCl, aq. THF, 45 min, 25°C, 83%). The IR spectrum revealed hydroxyl absorption at 3400 cm^{-1} in addition to the enone function (1680 cm^{-1}) while the ^1H NMR spectrum displayed a pair of methyl doublets (δ 0.76 and 1.13, J = 7.0 Hz), two pairs of methyl singlets (δ 1.80 and 2.03; δ 1.53 and 1.56) and two vinylic protons (δ 5.36 and 5.86). Exposure of 8 to 0.7N HCl (aq. THF) provided the bicyclic ketone 9.

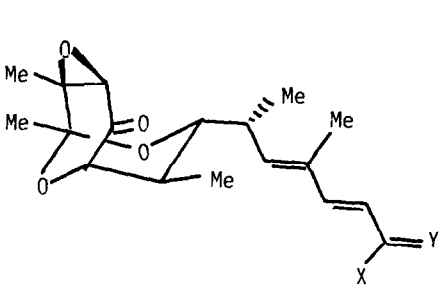
A similar set of experiments performed on the threo diol 6b gave rise to the bicyclic enone 10 [mp 47-48°C; IR (CCl_4) 1688 and 1632 cm^{-1}; MS (70 eV), M^+182; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.41 (3H, d, J = 7.0 Hz), 1.53 (3H, s), 1.64 (1H, m), 1.95 (3H, d, J = 1.5 Hz), 3.56 (1H, bd.d, J = 12.1 Hz), 3.99 (1H, s), 4.02 (1H, dd, J = 12.1 Hz and 3.7 Hz), and 6.18 (1H, bd.s); ^{13}C NMR ($CDCl_3$) 197.2, 155.1, 126.6, 95.7, 79.7, 64.0, 30.4, 24.4, 19.1, and 16.6.]

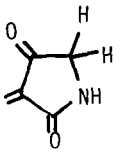
The mass spectra of bicyclic ketones 9 and 10 were virtually identical. The ^{13}C-NMR spectra of the two diastereomers differed significantly in the position of the secondary methyl group which suffered an upfield shift (Δ ppm = +5.2) in isomer 10.

The exclusive formation of a single diastereomeric bicyclic enone from the erythro and threo diols requires the absence of pyrylium salt formation in the closure of the second ring.

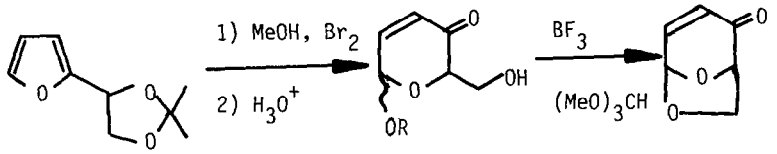
The application of this high yield, facile process to the synthesis of tirandamycic acid and tirandamycin is under investigation.

ACKNOWLEDGMENTS: This program was supported by the Institute for Allergic and Infectious Diseases (AI-15617), NIH. The 270-MHz NMR spectrometer is supported by grant CHE-7916210 from the Chemistry Division of the NSF.

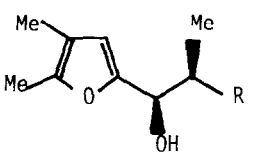


1a, X=OH, Y= 

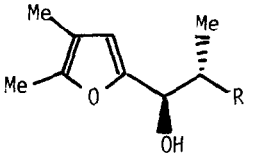
b, X=OH, Y=O



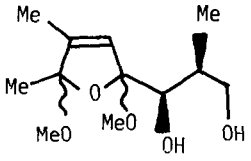
2 3a, R=H b, R=OMe 4



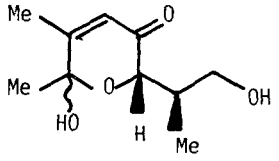
5a, R=CO_2Et
b, R=CH_2OH



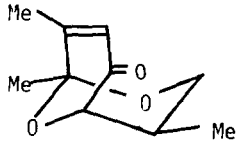
6a, R=CO_2Et
b, R=CH_2OH



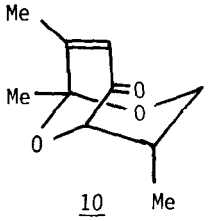
7



8



9



10

REFERENCES:

1. C. E. Meyers, J. Antibiot., 24, 558 (1971); F. Reusser, Infect. Immun., 2, 77, 82 (1970). Structure: F. A. Mackellar, M. F. Grostic, E. C. Olson, R. J. Wnuk, A. R. Branfman, K. L. Rinehart, Jr., J. Am. Chem. Soc., 93, 4943 (1971); D. J. Duchamp, A. R. Branfman, A. C. Button, K. L. Rinehart, Jr., J. Am. Chem. Soc., 95, 4077 (1973).
2. R. E. Ireland, P. G. M. Wuts, and B. Ernst, J. Am. Chem. Soc., 103, 3205 (1981).
3. For earlier studies, see: V. J. Lee, A. R. Branfman, T. R. Herrin, and K. L. Rinehart, Jr., J. Am. Chem. Soc., 100, 4225 (1978); D. Cartwright, V. J. Lee, and K. L. Rinehart, Jr., ibid, 100, 4237 (1978).
4. The Ireland synthesis has demonstrated that the correct stereochemistry of the epoxide can be prepared by alkaline epoxidation of the corresponding enone.[2]
5. Niels Elming, "Dialkoxydihydrofurans and Diacyloxydihydrofurans as Synthetic Intermediates," in Advances in Organic Chemistry, R. A. Raphael, ed., Vol II, p 67, Interscience, 1960, New York.
6. O. Achmatowicz, Jr., P. Buckowski, B. Szechner, Z. Zwierzchowska, and A. Zamojski, Tetrahedron, 27, 1973 (1971).
7. Y. Lefebvre, Tetrahedron Lett., 133 (1972); P. D. Weeks, D. E. Kuhla, R. P. Allingham, H. A. Watson, and B. Wlodecki, Carbohyd. Res., 56, 195 (1977); G. Piancatelli, A. Screttri, and M. A'Auria, Tetrahedron Lett., 2199 (1977); P. D. Weeks, T. M. Brennan, D. P. Brannegan, D. E. Kuhla, M. L. Elliot, H. A. Watson, B. Wlodecki, and R. Breitenbach, J. Org. Chem., 45, 1109 (1980).
8. K. C. Rice and J. R. Dyer, J. Heterocyclic Chem., 12, 1325 (1975).
9. R. Reichstein and Gruessner, Helv. Chim. Acta., 16, 28 (1933).
10. The nomenclature convention is that employed by Heathcock. C. H. Heathcock, C. T. White, J. J. Morrison, and D. VanDerveer, J. Org. Chem., 46, 1296 (1981).
11. Stereochemical assignments were made by ^{1}H NMR. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem. Soc., 95, 3310 (1973).

(Received in USA 10 August 1981)