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PREPARATION OF 2,9-DIOXABICYCLO[3.3.1]NONANES. A MODEL FOR TIRANDAMYCIN

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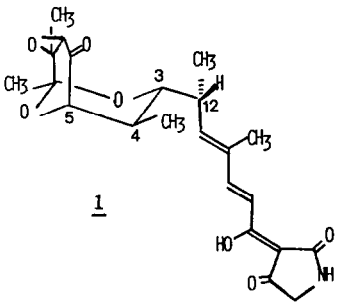
Summary: An efficient synthesis of a 2,9-dioxabicyclo[3.3.1]nonane system, similar to that of tirandamycin, is accomplished from 2,3-dimethylfuran.

Tirandamycin[1,2] (1) is a member of the 3-acyl tetramic acid family of antibiotics which includes streptolydigin[1,3], nocamycin[4], antibiotics Bu-2313 A and B[5], ikarugamycin[6], and others.[7-9] It displays antibiotic activity[10], as well as inhibitory activity against DNA-directed RNA polymerase.[11] These activities contrast sharply with those of simple 3-acyl tetramic acids and it has been proposed that the altered activity results from the presence of the 2,9-dioxabicyclo[3.3.1]nonane moiety found in these systems.[1]



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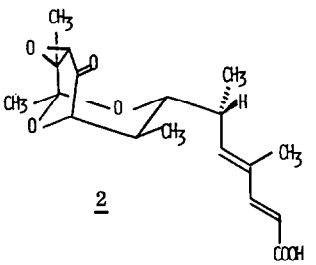

2

Ireland and co-workers have reported a synthesis of tirandamycinic acid (2), a degradation product of 1[2], in which the bicyclic ring system was prepared from D-glucose in a multistep scheme.[12] Recently, a second approach to the bicyclic system of tirandamycin has been reported by Ziegler and Thottathil which involves a furan precursor.[13] This latter report has prompted us to report our preliminary results on a similar system. We have found that the 2,9-dioxabicyclo [3.3.1]non-7-ene-6-one system 3 can be efficiently prepared from 2,3-dimethylfuran (4)(see Scheme).

Lithiation of 2,3-dimethylfuran (4; ^{n}BuLi, TMEDA, ether, R.T.) followed by condensation with THP ether-aldehyde 5[15,16] gave furan-alcohol 6[17], as a mixture of diastereomers, in 65% yield after flash chromatography. The ratio of diastereomers was approximately 27:16:15:42 based upon HPLC analysis. The diastereomers, although unstable to chromatography, could be purified by HPLC. Rather than separate the diastereomers (6) at this point however, it was advantageous to employ the mixture without purification.

Oxidation of 6 can be accomplished by a variety of reagents (PCC, 0°, 15'[18]; $^1O_2$, CH_3OH -20°[19]; m-CPBA, CH_2Cl_2, 0°, 30'[20]; Br_2, CH_3OH, -20°, with or without added base, 15'[21]). Following oxidation treatment of the reaction mixture with 0.1N HCl in THF at R.T. gave bicyclic enone 3[22] as a single isomer in 25% yield. Since 6 employed in the oxidation was a mixture of four diastereomers, oxidation-THP hydrolysis was expected to produce two intermediates 7 and 7'. Acid treatment of 7 would give bicyclic enone 3; similar treatment of 7' would result in the formation of 8. However, 8 was not detected. This result was not unexpected since 8 would carry three axial substituents on the six-membered ring - an unfavorable situation! It had been assumed that these conformational factors would preclude formation of 8 from 7'. In fact, a compound tentatively assigned the structure 10 (isolated as the acetate[23]) could be obtained from the reaction mixture which had yielded 3. This product (10) did not give 3 upon resubjection to acid treatment, thus suggesting that it was the isomer (7') incapable of undergoing bicycle formation.

The low yield of 3 produced from the mixture of diastereomers (25%) was discouraging until it was determined that only the two highest Rf diastereomers of 6 - comprising ~43% of the mixture - could be converted into 3. The other two isomers gave 10 upon oxidation. Therefore, the overall yield of bicycle 3 from the furan bearing the correct stereochemistry at C-1' and C-3' in 6 was >60%.

The results presented in this report show that an appropriately substituted furan can effectively serve as the precursor to the enedione moiety found in tirandamycin. Secondly, they confirm that the stereochemistry at C-3' in 6 controls the ease of formation of the bicyclic enone system (7 ⟶ 3, but 7' ⇸ 8). A successful synthesis of tirandamycin via analogous methodology will require utilization of aldehyde 11, instead of 5, in which the C-2, C-3, C-4 stereochemistry of 11 will lead to the appropriate stereochemistry at C-3, C-4, C-5, and C-12 in 1. Studies related to the synthesis of optically active 11 and its utilization in the synthesis of tirandamycin will be reported in due course.

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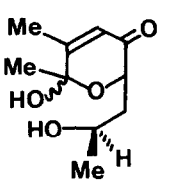
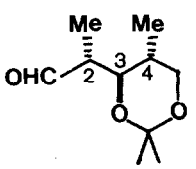
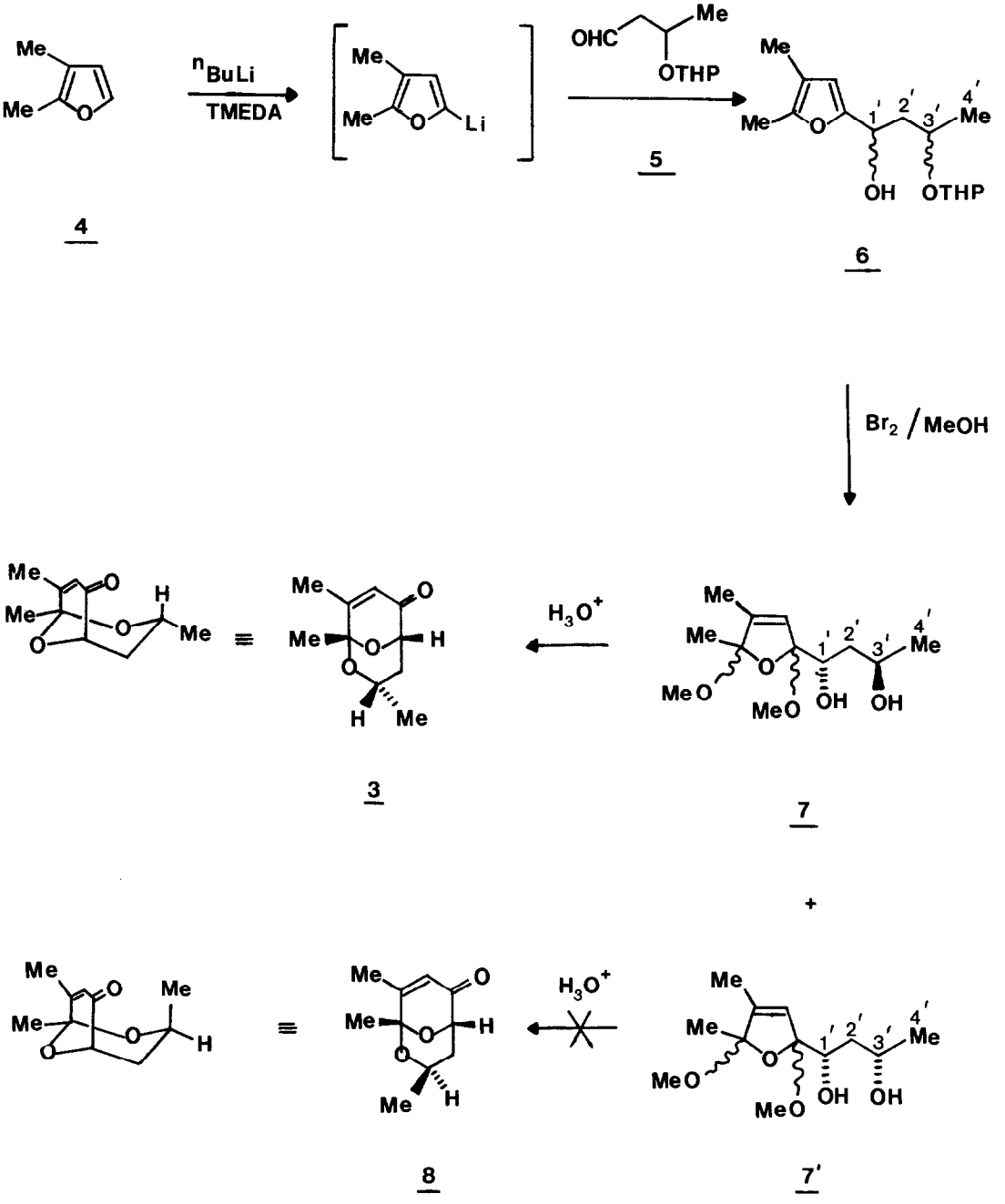


10



11

Scheme


Me
Me
4
nBuLi
TMEDA
Me
Me
O
Li
OHC
Me
OTHP
5
Me
Me
O
1'
2'
3'
4'
Me
OH
OTHP
6
Br2 / MeOH
Me
Me
O
H
Me
O
3
H3O+
Me
Me
O
1'
2'
3'
4'
Me
MeO
MeO
OH
OH
7
+
Me
Me
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Me
H
O
8
H3O+
Me
Me
O
1'
2'
3'
4'
Me
MeO
MeO
OH
OH
7'

References and Notes

≠ National Science Foundation Undergraduate Summer Research Participant, 1981.

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17. Furan-alcohol 6 (mixture of diastereomers): IR (neat): 3400, 3010 cm^{-1}. NMR ($CDCl_3$): δ 6.0 (s, 1H), 4.4-5.0 (m, 2H), 3.4-4.2 (m, 3H), 2.5-3.1 (m, 2H), 2.1-2.2 (series of singlets, 3H), 1.9 (series of singlets, 3H), 1.5-1.7 (m, 6H), 1.2 (series of doublets, 3H). Four diastereomers of 6 were detectable by tlc. First isomer (highest Rf): NMR ($CDCl_3$): δ 6.02 (s, 1H), 4.96 (s, 1H), 2.18 (s, 3H), 1.93 (s, 3H), 1.20 (d, J=7 Hz, 3H). Second isomer: NMR ($CDCl_3$): δ 6.02 (s, 1H), 5.00 (s, 1H), 2.20 (s, 3H), 1.96 (s, 3H), 1.23 (d, J=6 Hz, 3H). Third isomer: NMR ($CDCl_3$): δ 5.98 (s, 1H), 4.80 (s, 1H), 2.22 (s, 3H), 1.92 (s, 3H), 1.27 (d, J=6 Hz, 3H). Fourth isomer (lowest Rf): NMR ($CDCl_3$): δ 5.90 (s, 1H), 4.65 (s, 1H), 2.14 (s, 3H), 1.84 (s, 3H), 1.08 (d, J=7 Hz, 3H).
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22. Bicyclic enone 3: IR (CCl_4): 2950, 1690 cm^{-1}. NMR ($CDCl_3$): δ 6.15 (broad s,1H), 4.31 (dd, J=2, 7 Hz, 1H), 3.90 (m, 1H), 1.97 (d, J=1 Hz, 3H), 1.88 (m, 1H), 1.60 (m, 1H), 1.54 (s, 3H), 1.20 (d, J=6 Hz). Decoupling experiments confirmed the structure of the bicyclic enone as 3 and not the epimer 8. ^{13}C NMR ($CDCl_3$): δ 197.3, 156.9, 126.9, 96.0, 75.0, 64.2, 34.1, 24.8, 21.9, 19.5.
23. 10: 3500, 1685 cm^{-1}. Acetate of 10 (mixture of isomers): IR (CCl_4): 1740, 1680 cm^{-1}. Partial NMR ($CDCl_3$): δ 6.14 (broad s,1H); 2.05 (s, 3H); 2.00 (broad s, 3H); 1.76 (s, 3H).

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