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α-OXYGENATION OF A TRANS-3,4-DISUBSTITUTED γ-LACTONE. A COMPARATIVE STUDY

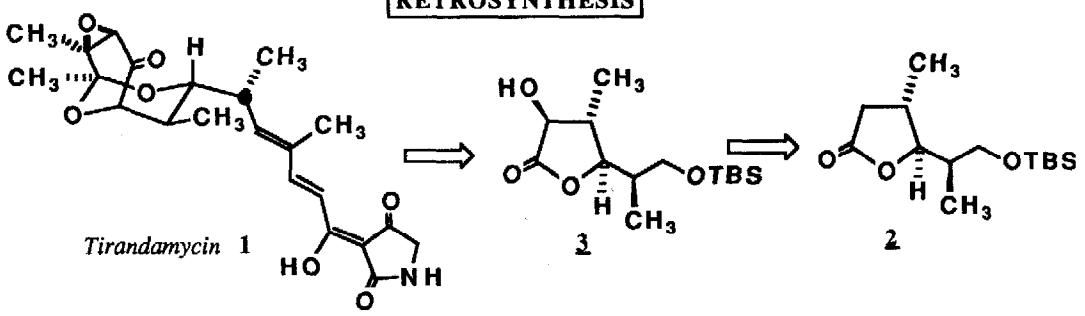
Michael J. Taschner* and Anand S. Aminbhavi

Department of Chemistry, The University of Akron,
Akron, Ohio 44325

Abstract: The available methods for the α-oxygenation of a carbonyl derivative are examined for a *trans*-3,4-disubstituted γ-lactone and analyzed with respect to chemical yield and diastereomeric control.

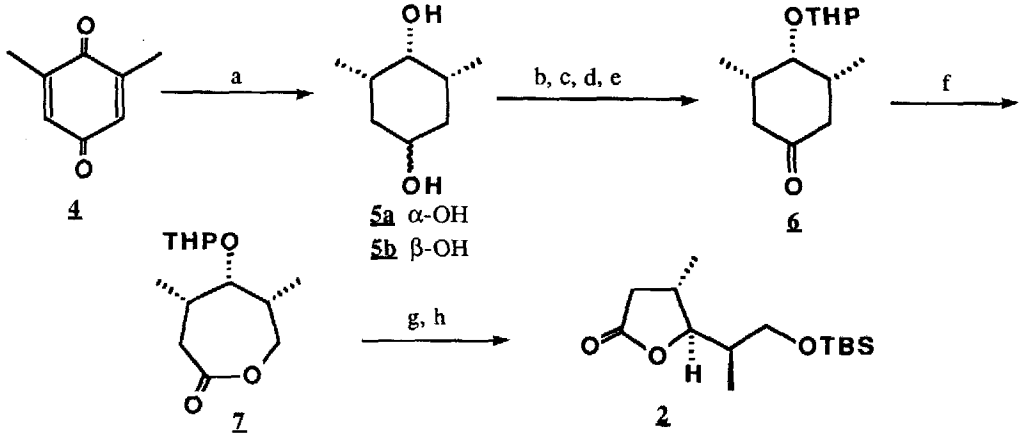
In connection with a program aimed at the total syntheses of the 3-acyltetramic acid (e.g., Tirandamycin **1**[2,3]), an α-oxygenation of a 3,4-disubstituted γ-lactone which produced an all *trans*-arrangement of the three substituents on the lactone ring was required. The lactone of interest is shown below in the analysis of the tirandamycin problem. The control of the stereochemical outcome, with all the substituents *trans*, in the α-oxygenation of some related lactones has been disclosed by Stork[4] and Hannesian.[5] Their solution to the problem relied on the use of the tris(thiophenyl)methyl or the tris(methylthio)methyl substituents as a bulky methyl surrogates to control the relative stereochemistry of the newly introduced oxygen. The latent methyl group had to be unveiled in a subsequent desulfurization process. In our studies, we had examined a wide range of oxygen electrophiles under a variety of conditions for the α-oxygenation of lactone **2** in the hopes a simple and direct solution to the problem of controlling the relative stereochemistry could be uncovered. We wish to report in this communication the results of this study.

RETROSYNTHESIS



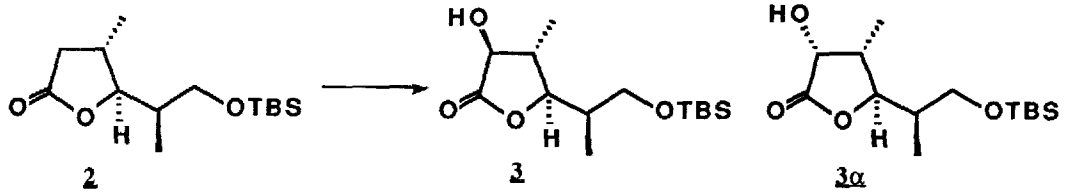
The synthesis of **2** begins with the catalytic hydrogenation[6] of 2,6-dimethylbenzoquinone[7] which affords a mixture of diols **5a** and **5b** in a 2:1 ratio, respectively. These could be readily separated by flash chromatography[8] (R_f = 0.25 and 0.16; 1:1 EtOAc/hexanes, respectively) and processed individually through the following sequence of reactions. However, upon obtaining the same ketone **6**, it was more convenient to process the mixture of diols. The diols could be selectively monobenzoylated at C4 with benzoyl chloride in pyridine to afford the corresponding benzoates. Tetrahydropyranylation of the remaining alcohol with DHP/PPTS[9] produced the differentially protected diols. The benzoates were hydrolyzed and the resulting mixture of alcohols oxidized with Jones' reagent[10] to provide ketone **6** (mp 61-62 °C) in 72% overall yield from quinone **4**. The ketone **6** was subjected to Baeyer-

Villiger oxidation by treatment with MCPBA/$KHCO_3$(solid) in CH_2Cl_2[11] to produce lactone **7** (mp 86.5-88 °C). All attempts to directly oxygenate either the lithium or potassium enolate derived from lactone **7** with a variety of electrophilic oxygen sources (MoOPH,[12] O_2,[13] Davis's phenylsulfonyl oxaziridine,[14] and TMSCl/MCPBA[15]) proved unsuccessful. With the inability to effectively oxygenate the α-position of the ε–lactone **7**,[16] it was reasoned more success might be attained in oxygenating a five-membered ring lactone. We therefore opted for lactone **2** as the oxygenation substrate. This was available in 90% overall yield from lactone **7** by an efficient deprotection-contraction and protection sequence. Treatment of lactone **7** with PPTS in CH_3OH[9] at 50 °C effects not only removal of the THP protecting group but also contraction of the seven-membered ring lactone to the five-membered ring lactone. Protection of the primary alcohol as the *t*-butyl dimethylsilyl(TBS) ether[17] provided the desired γ-lactone **2**.



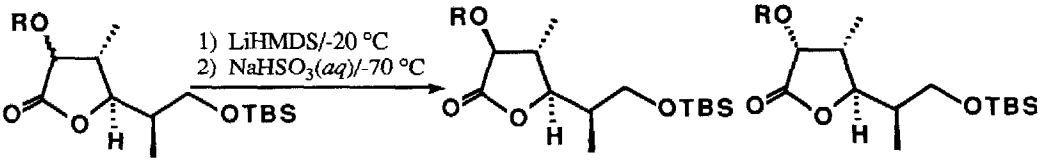
a) H_2 (60 psi)/Rh/Al_2O_3; b) BzCl/Pyr.; c) DHP/PPTS/CH_2Cl_2; d) KOH/H_2O/MeOH;
e) H_2CrO_4/acetone; f) *m*-CPBA/$KHCO_3$/CH_2Cl_2; g) PPTS/MeOH/50 °C; h) *t*-$BuMe_2SiCl$/imidazole

The results of the studies on the oxygenation of lactone **2** to produce mixtures of the desired β-hydroxy lactone **3** and the undesired α-hydroxy lactone **3α** are summarized in the following table.



Base (Equiv)	Electrophile (Equiv)	Temp/Time	% Yield	Ratio β:α
LDA (2.0)	Phenylsulfonyl oxaziridine (1.5)	-70 °C/1.5 h	35	1:1
LiHMDS (2.5)	Phenylsulfonyl oxaziridine (2.5)	-70 °C/1.5 h	63	1:1
KHMDS (1.5)	Phenylsulfonyl oxaziridine (1.5)	-70 °C/1.5 h	41	1:1
LDA (1.2)	TMSCl/*m*-CPBA (2.0)	25 °C/6.0 h	47	2:1
LDA (2.0)	MoOPH (2.0)	-20 °C/0.5 h	70	2:1
LiHMDS (2.2)	MoOPH (2.2)	-20 °C/0.5 h	82	4:1
LiHMDS (2.5)	MoOPH (2.5)	-20 °C/0.5 h	78	6:1
LiHMDS (3.0)	MoOPH (1.5)	-20 °C/0.5 h	80	8:1
LiHMDS (4.0)	MoOPH (1.5)	-20 °C/0.5 h	80	8:1
KHMDS (3.0)	MoOPH (1.5)	-20 °C/0.5 h	70	3:1

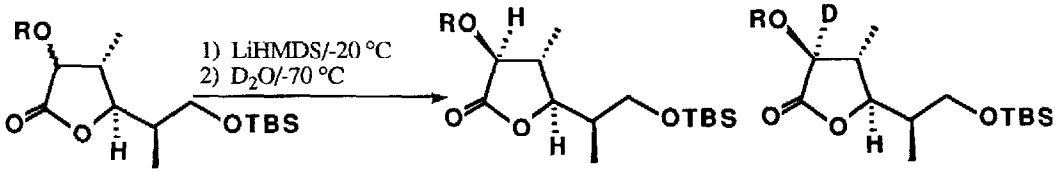
The results indicated that the optimal base was lithium hexamethyldisilazide with the MoOPH reagent of Vedejs as the oxygen electrophile of choice. An interesting trend was evident in the table; as the amount of the base employed increased, the ratio of β:α-isomers also increased. It reached a maximum of 8:1 in favor of the desired β-isomer when 3.0 equivalents of LiHMDS were employed. This suggested the possibility of a potential equilibration process taking place. To test this hypothesis, a 1:1 mixture of the two isomers **3α** and **3** was resubjected to the enolization conditions. Treatment of the 1:1 mixture with LiHMDS at -20 °C resulted in the formation of an 8:1 mixture, again, in favor of the desired β-isomer. In an effort to increase the amount of the required isomer, it was felt that bulking up the hydroxyl might lead to an improved ratio. In this context, the hydroxyl group was protected as the triethylsilyl ether prior to submission to the enolization conditions. When subjected to the reaction with LiHMDS, a 1:1 mixture of triethylsilyl derivatives **8** delivered *exclusively* the β-isomer.



R = H; **3**:**3α**; 1:1
R = Et_3Si-; **8β**:**8α**; 1:1

R = H; **3**:**3α**; 8:1
R = Et_3Si-; **8β** ONLY

To further investigate this apparent equilibration process, an experiment was conducted with the aim of removing any free amine from the equilibrium. Toward this end, an 8:1 mixture of **8β**:**8α** was again submitted to the LiHMDS enolization conditions. Only this time, prior to quenching the reaction, an equivalent amount of *n*-BuLi was added to remove the free amine. This experiment resulted in the formation of **8β** in a yield which corresponded to the 1 part of the α-isomer in the original mixture. The remainder of the product, corresponding to the amount of the β–isomer, was apparently the product which was the result of the addition of *n*-BuLi to the lactone. It appeared that only the α-isomer was undergoing enolization and subsequent epimerization to produce the β-isomer. Additional evidence for this phenomenon was seen in the result of a D_2O quench of the LiHMDS reaction. If an 8:1 mixture of **8β**:**8α** was reacted with LiHMDS at -20 °C and then quenched with D_2O at -70 °C, deuterium was incorporated only to the extent corresponding to the original amount of α-isomer.



R = Et_3Si-; **8β**:**8α**; 8:1

8β; H:D; 8:1

A simple and efficient solution for the control of the all *trans* relative stereochemistry in the α-oxygenation of a 3,4-disubstituted γ–lactone has been developed, as well as an approach for the synthesis of a C5-C10 subunit of the 3-acyltetramic acid antibiotics. The application of this oxygenation technique to other substituted γ-lactones in an effort to determine its generality and further elaboration of the C5-C10 tetramic acid subunit are under current investigation and will be the subjects of a future communications.[18]

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