THE SYNTHESIS OF VOLATILE STREPTOMYCES LACTONES

Zhang, Kan-Yin, Anthony J. Borgerding and Robert M. Carlson* Department of Chemistry, University of Minnesota, Duluth, MN 55812

Summary: A synthetic pathway to the volatile <u>streptomyces</u> lactones has been developed using as a key step sequential addition / alkylation to anions generated from 2,2-dimethyl-5-methylene-1,3-dioxane.

A synthetic pathway to α, γ -substituted butenolides can be conceptualized through a sequential addition / alkylation of an acrylic acid dianion synthon (Scheme 1). We wish to report the use of anions derived from 2,2-dimethyl-5-methylene-1,3-dioxane¹ as the synthetic equivalent of the corresponding methacrylaldehyde dianion (I).

SCHEME 1



ALKYLATION (RX)



Volatile streptomyces lactones (II) R₂ = H; R₃ = CH₃ ; R =n-C₃H₇ = n-C₅H₁₁ = isopentyl

= isobutyl



The technique (Scheme 2) has been used to synthesize several of the reported volatile streptomyces lactones $(II)^2$.



REACTION CONDITIONS:

- A. BF3.ether / excess 2,2-dimethoxypropane / 5 minutes; the starting diol prepared from the commercially available dichloride (Aldrich Chemical Company) by the method of Ducharme, et al.³. Alternatively, the diol can be formed in 50% yield by extended treatment with KOH/H₂O (10.0g dichloride, 11.2g KOH, 250 cc H₂O, 40 hrs reflux, 5x ether extraction; Li, Jing lin, these laboratories.
- B. g-Butyl lithium in hexane (1.3 M, 8.6 mmol), THF (50cc), / -78° C / N₂ / 15 minutes.
- C. CH3CHO (8.6 mmol, neat solution).
- D. g-Butyl lithium (11.7 mmol in hexane) / 15 minutes / -78° C.
- E. R-Br (11.7 mmol, 2 hours) / -78° C.
- F. H₂O, extract with ether ($5 \times 15 \text{ cc}$).
- G. 85% H3PO4 / room temperature / 10 minutes ; add H20 / ether extraction (5 x 15 cc).
- H. Freshly prepared Ag(NH3)⁺ (23.5 mmol AgNO3 in 10 cc H₂O + 5N NaOH until basic, then conc. NH4OH until the solid is dissolved.)/aldehyde (1.0g) in THF(15cc)/ 2 hour reflux; 6N HNO3 until acidic; ether extraction (515cc).
- I. Mixture of lactone and uncyclized acid in ether stirred overnight with 2-3 drops concentrated H2SO4 and 4A molecular sieves ; NaHCO3 added until neutral ; filtered ; evaporated.

Discussion:

Butenolides have attracted a considerable amount of synthetic activity due to their presence in a broad spectrum of natural products⁴. However, methodology for the preparation of α,γ -disubstituted butenolides is limited and the synthesis of streptomyces lactones has remained elusive. The current methodology takes advantage of the fact that allylic carbanions possessing a destabilizing group generally undergo alkylation at the γ -position (i.e. the site of highest electron density) while carbonyl compounds generally react through a proposed cyclic transition state to give the $\alpha\text{-}addition\ \text{product}^5$. For example, in an initial study of the addition of H2O and CH3I to the monoanion (I), only α -addition products (>95%) are formed while the reaction with propionaldehyde provides γ -addition as the only observable product (>95%). This is in contrast to Kozikowski's original paper¹ where unimpressive regioselectivity in reactions with aldehydes or alkylating agents was observed. Having available this background information it was therefore possible to propose the synthesis of the streptomyces lactones using the "disconnection" approach⁶ leading to a methacrylic acid dianion (Scheme 3). The synthetic equivalent of this synthon would be the dianion from the unsaturated 1,3-dioxane. In this specific case the "dianion" can not be formed directly and must be generated sequentially.

SCHEME 3



In the synthesis sequence to the streptomyces lactones the initial anion formation and acetaldehyde addition occurs as expected at the α -position. The second anion generation (without isolation of the intermediate) occurs away from the alkoxide and the subsequent alkylation proceeds to give γ -substitution. However, little stereospecificity is observed in diastereomer formation (step E, approx. 1:1 by GC-MS). The unique sequence of reactions that proceed in near quantitative yields (\geq 90% B through G) provides the masked aldehyde that can be oxidized and cyclized to the desired lactones (yields +10%/GC-MS for reactions H and I where R=n-C3, n-C5, i-C4 and i-C5, were 90%, 60%, 50% and 50% respectively.

Acknowledgement

A summer undergraduate research fellowship was provided to one of us (AJB) through the University of Minnesota Undergraduate Research Opportunities Program (UROP). Other support for this effort was provided by the Petroleum Research Foundation.

References

- 1. A.P. Kozikowski and K. Isobe, Tetrahedron Lett., 10, 83 (1979).
- 2. N.N. Gerber, Tetrahedron Lett., 10, 771 (1973).
- 3. Y. Ducharme, S. Latour and J.D. West, Organomet., 3, 208 (1984).
- Y.S. Rao, <u>Chem. Rev.</u>, 76, 625 (1976); R.C. Larock, B. Riefling and C.A. Fellows, <u>J. Org. Chem.</u>, 43, 131 (1978); A.A. Avetisyan and M.T. Dagyan, <u>Russ. Chem. Rev.</u>, 46, 643 (1977).
- D. Seebach and K.H. Geiss in D. Seyferth, ed. "New Applications of Organometallic Reagents in Organic Synthesis" Elsevier Publishing Company. Amsterdam, Chapter 1, p. 21.
- S. Warren "Organic Synthesis: The Disconnection Approach", J. Wiley and Sons, New York, 1982.

(Received in USA 13 January 1988)

5706