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SYNTHESIS OF CHIRAL SUBUNITS FOR MACROLIDE SYNTHESIS: AN EFFICIENT METHOD FOR CONVERTING SPIROKETALS INTO OPEN-CHAIN DERIVATIVES

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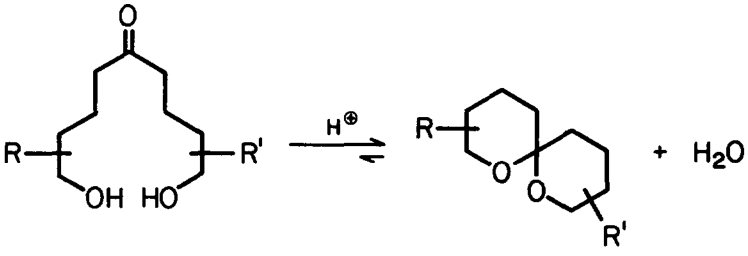
Summary: *An efficient method for the conversion of the spiroketals 9, 11 and 15 into open-chain derivatives by thioketal exchange is reported.*

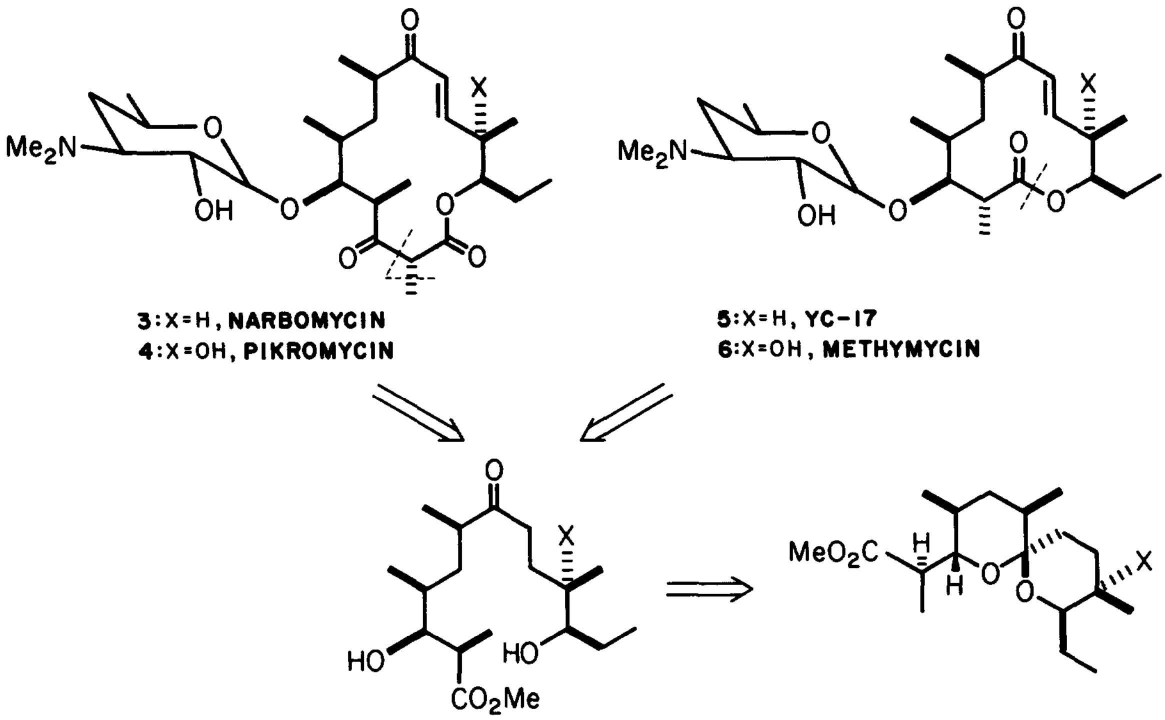
The preparation of spiroketals 2 by acid catalyzed cyclization of ketodiols 1 has proved to be a versatile and efficient synthetic method,[2] especially for the total synthesis of polyether ionophore antibiotics. Since the equilibrium lies far to the right, the reverse transformation (2 → 1) is not simply realized.



1 2

An approach,[3] also under investigation independently by P. Deslongchamps,[4] to the macrolide antibiotics narbomycin (3),[5] pikromycin (4),[6] YC-17 (5),[7] and methymycin (6)[8] via a common spiroketal intermediate 8, available through hetero-Diels-Alder condensation between an exocyclic enol ether and an α,β-unsaturated carbonyl compound,[9] requires an efficient method for the conversion of the spiroketals 8 into open-chain ketodiols 7 or their equivalent. Herein are reported model studies in which this very useful transformation is efficiently realized.

The spiroketal derived from erythronolide A has been opened as the oxime derivative.[10] This is naturally an attractive method, since in only one step an equivalent to the open-chain keto-diol is obtained. Application of this method under modified conditions to the spiroketals 9[11] and 11[11] afforded the oxime-



3:X=H, **NARBOMYCIN**
4:X=OH, **PIKROMYCIN**

5:X=H, **YC-17**
6:X=OH, **METHYMYCIN**

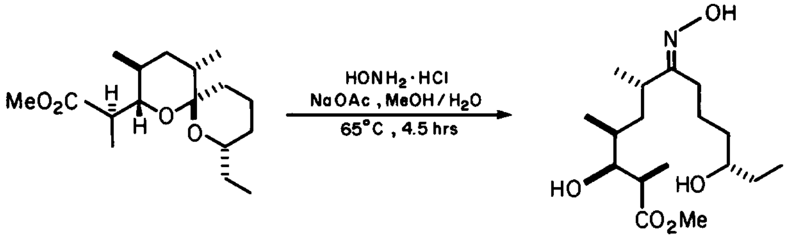
7: X=H or OH

8: X=H or OH

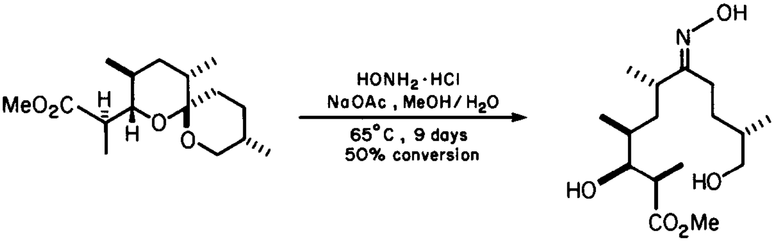
diols[12] 10 and 12, respectively, in good yields (75-85%). Note the large rate difference between spiroketals 9 and 11 for this reaction. This rate difference is due to destabilizing interactions[13] present in spiroketal 9 but absent in spiroketal 11. This result indicates the difficulty to be expected in opening the spiroketals 8, which, like spiroketal 11, possess no such steric interactions that would labilize the spiroketal system. In spite of the encouraging results with this oxime methodology, no further optimization was attempted due to the success of the following thioketal exchange.

Initial studies on thioketal exchange were focused on spiroketal 9 because its lability should provide a more favorable equilibrium. Treatment of this system with boron trifluoride etherate in 1,2-ethanedithiol at -40°C afforded the corresponding open-chain thioketal-diol in 90% yield.[14] Substitution of 1,3-propanedithiol provided the analogous dithiane derivative; however, the equilibrium was not as favorable and only a 70% conversion was observed.

Application of the 1,2-ethanedithiol procedure to the model epimeric spiroketals 11 and 15[11] afforded the open-chain thioketal-diol derivatives 13 and 16 in 90% yields without any apparent epimerization of the methyl group. The preservation of the stereochemistry of this methyl group is important for the synthesis of the natural products. Transformation into the open-chain ketones 14 and 17 in yields of 86% and 82%, respectively, verifies the viability of this



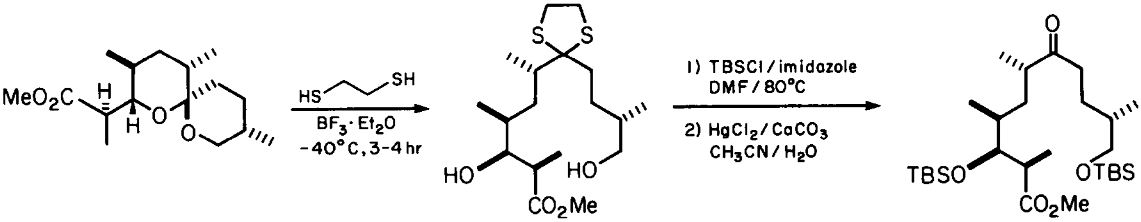
9 10



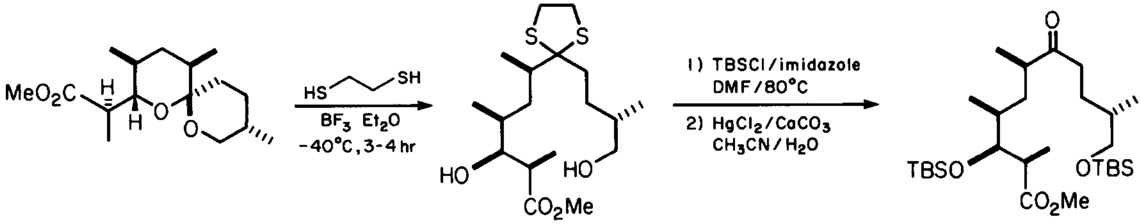
11 12

approach.

Application of this methodology to the spiroketals 8 and conversion into the natural macrolides is currently under investigation in these laboratories.[16]



11 13 14



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11. The preparation of these spiroketals through hetero-Diels-Alder condensation[9] and other spectral and physical data that confirm the indicated stereochemistry will be reported in a future full paper.
12. The oximes were obtained as a mixture of syn and anti isomers.
13. In the conformation of spiroketal 9 which enjoys stabilization by the anomeric effect[2f] there is a destabilizing 1,3-diaxial interaction between the ethyl group and the pyran oxygen. To alleviate this steric effect requires the molecule to adopt a conformation in which an electronically favorable anomeric effect has been lost.
14. Higher reaction temperatures afforded products in which an internal oxidation-reduction has occured as observed by C. Djerassi[15] with sapogenins.
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16. All new compounds displayed satisfactory spectral and analytical data.

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