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A CONVERGENT SCHEME FOR THE SYNTHESIS OF SPIROKETALS AND THE SYNTHESIS OF (±)-CHALCOGRAN

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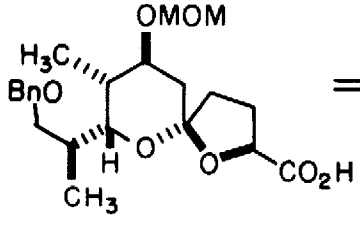
Summary: The hetero-Diels-Alder condensation between furanoid and pyranoid exocyclic vinyl ethers establishes the spiroketal system and subsequent oxidative ring contraction leads to 1.6-dioxaspiroalkane carboxylic acids. The latter are useful subunits for polyether antibiotic synthesis.

As part of a program directed toward the total synthesis of a variety of polyether antibiotics and their analogs, it was necessary to develop a strategy for the synthesis of a spiroketal subunit. With a subunit such as the spiroketal 1 available, application of the enolate Claisen rearrangement[2] technology, already proven effective for the total synthesis[3] of lasalocid A, would provide access to other polyether systems, such as monesin (2)[4]. While for the ultimate natural product synthesis itself the chirality of the spiroketal 1 is a critical point, the initial explorations for suitable bond forming reactions were undertaken with racemic model compounds. The result of this effort has been the development of an efficient, convergent scheme for the synthesis of such spiroketal systems from materials that can potentially be prepared from carbohydrate precursors and then satisfy the chirality criterion of a total synthesis.



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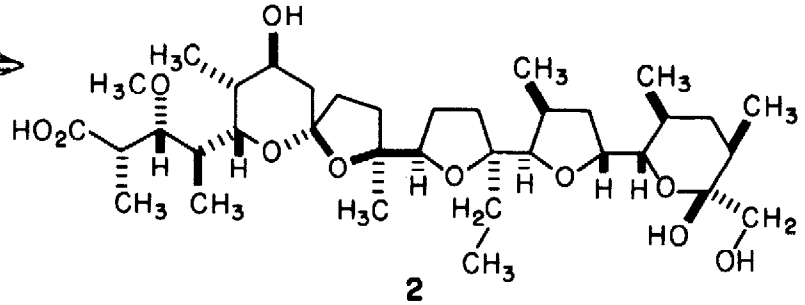

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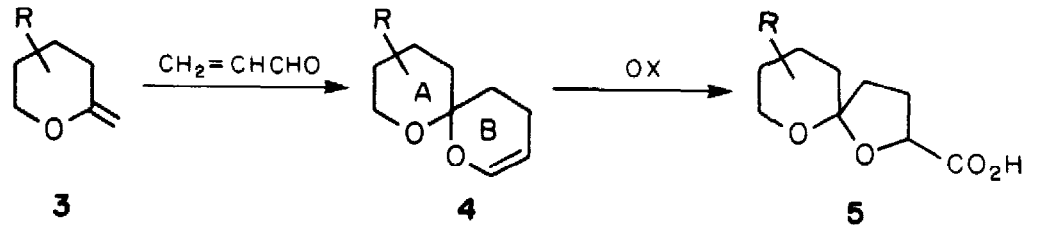
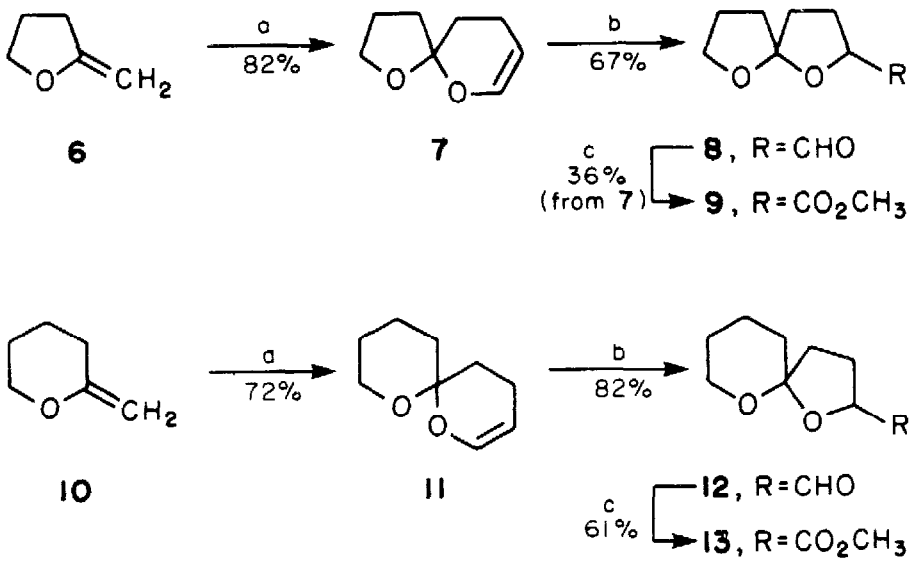
The generality of this approach to the construction of this crucial structural feature of many polyether antibiotics warrants this preliminary report.

Schematically, the approach investigated entailed the hetero-Diels-Alder reaction between an appropriate vinyl ether 3 and acrolein.



It was envisaged to follow this condensation which rapidly establishes the spiroketal functionality 4, with an oxidative step that would contract the initially formed six-membered B ring to the desired tetrahydrofuran carboxylic acid 5. To explore the feasibility of this approach both the furanoid and pyranoid vinyl ethers 6 and 10[5] were employed (Chart I.)

CHART I: Synthesis of Spiroketals 9 and 13[a] [6]

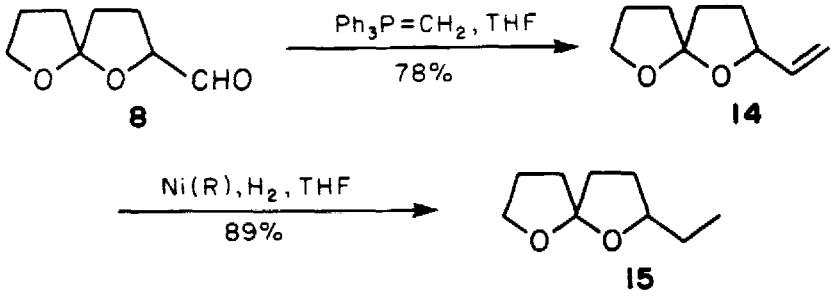


[a] a, CH_2=CHCH=O(1 equiv), RT, 4-6 days; b, MCPBA, CH_3OH, -5°→RT; c, $AgNO_3$, KOH, C_2H_5OH-H_2O; CH_3I, HMPA, C_2H_5OH.

Substituted 2-alkoyx-3, 4-dihydro-2H-pyrans are generally prepared by either thermally promoted[7] (120-240°) condensation between a large excess of the appropriate vinyl ether and an α,β-unsaturated ketone or aldehyde or, more recently, from the same reactants at or near room temperature by the use of Lewis acid catalysis[8]. Clearly for the purposes at hand a large excess of a valuable vinyl ether was unacceptable, and high temperatures or Lewis acids very rapidly led to rearrangement of the exocyclic double bond of the model vinyl ethers 6 and 10 to the more stable, less reactive endocyclic position. Very good yields of the desired condensation products were, however, readily available when stiochiometric amounts of the reactants were allowed to stand at room temperature in the presence of 0.5-1.0 mol % of hydroquinone for 4-6 days. In this fashion both spiroketals 7 and 11 were prepared in large scale.

Several attempts to effect the oxidative ring contraction step with m-chloroperbenzoic acid in either buffered or unbuffered methylene chloride led to a plethora of products and only minor (>10%) of the desired aldehydes 8 and 12. Interestingly, in the more polar, protic solvent methanol, the oxidation proceeded smoothly and gave the aldehydes 8 and 12 together with minor amounts of the methyl esters 9 and 13 from over-oxidation. Silver promoted oxidation of the crude aldehyde products and then esterification afforded useful quantities of the desired esters 9 and 13. The observed yields (CHART I) belie the cleanliness of these reactions, as the products in this model series are volatile and difficult to isolate quantitatively from the reaction solvent mixtures used. With the more highly substituted series necessary for polyether antibiotic synthesis, these manipulative problems will not be encountered. As well in this model series with no dramatic steric bias, both diastereomers of the aldehydes 8 and 12 (and hence, the esters 9 and 13) were formed in approximately equal amounts. Such will not necessarily be the case in the total synthesis scheme.

In order to demonstrate the value of this hetero-Diels-Alder/oxidative ring contraction sequence for the synthesis of natural products, the aldehyde 8 was converted into racemic chalcogran (15), the principal aggregation pheromone of the beetle "Kupferstecher"-pityogenes chalcographus (L.), a pest of Norway spruce. The natural pheromone, isolated by W. Francke and coworkers[9], was shown to be a 1:1 mixture of diastereomers and the absolute configuration at C-2 was not determined. Two alternate syntheses of an optically active mixture of diastereomers of this pheromone have recently appeared.[10]



Work is presently underway to prepare an appropriate vinyl ether analogous to the pyran 10 from carbohydrates so that this chiral material may be used in the above sequence for the preparation of the monensin subunit 1.

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References and Notes

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