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SYNTHESIS OF 3,5-DISUBSTITUTED BUTENOLIDES.
A SHORT PREPARATION OF
VOLATILE STREPTOMYCES LACTONES

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Abstract: α-Chloro carboxylic acid dianions condense with propanal to form β-lactones which, upon treatment with magnesium bromide, form 3,5-disubstituted butenolides.

For some time, we have been involved in an investigation of β-lactone rearrangements and reactions for the synthesis of a wide range of useful functionalities, including butyrolactones, 3 butenolides, 4 β,γ-unsaturated carboxylic acids, 5 and other moieties. Some time ago, the structures of a series of volatile 3,5-disubstituted butenolides isolated from Streptomyces cultures were reported, 6 and in 1988 Carlson et al. published a nine-step synthesis of these molecules. 7 This sequence utilized anions derived from 2,2-dimethyl-5-methylene-1,3-dioxane as synthons for methacrylaldehyde dianion. Hoping to develop a somewhat more streamlined approach, we attempted to apply a newly-discovered reaction in our laboratories to these molecules. We wish now to report a four-step preparation of
SCHEME

TABLE

Yield Data for All Compounds

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<th>3</th>
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<td>56%</td>
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<td>74%</td>
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<td>72%</td>
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<tr>
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<td>46%</td>
<td>60%</td>
<td>72%</td>
<td>82%</td>
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</table>

3,5-disubstituted butenolides of the *Streptomyces* variety that utilizes as its key transformation our newly-developed expansion-elimination reaction of α-chloro β-lactones.

The overall sequence is diagrammed in the Scheme, and yield data are collected in the Table. α-Chloro carboxylic acids 2 are obtainable via a number of published methods, including the direct chlorination of carboxylic acids, but we
found the most satisfactory route to entail the reaction of iodo alkanes 1 with the
dianion of chloroacetic acid. This obviated the tendency for dichlorination inherent
in other methods and necessitated only distillation to achieve sufficient purity to
carry on in the sequence. The dianions of 2 were generated via reaction with two
equivalents of LDA, whereupon condensation with propanal at -80 °C afforded the
corresponding β-hydroxy acids 3. Condensation at this very low temperature,
followed by a rapid quench with dilute acid, was mandatory to avoid significant
competition from a Darzens-type reaction to provide the epoxy acid as the
predominant product. Dehydration with benzenesulfonyl chloride in pyridine
solution for 15 hours at 0 °C provided the β-lactones 4 which, upon treatment with
freshly-generated anhydrous magnesium bromide etherate in dichloromethane
solvent, rearranged and eliminated HCl to generate the target butenolides 5. Since
α-bromo carboxylic acids are generally more readily available than their chloro
analogs, we examined 2-bromohexanoic acid (available commercially) in the above
sequence. Unfortunately, the aldol condensation with propanal was unsuccessful
despite repeated attempts under various conditions, probably via a combination of
Darzens reactions and α-elimination of bromide from the dianion.

The preparation of 5-methyl-3-propyl-2(5H)-furanone (5a) is illustrative of the
method and representative of the purity of material produced by this technique.
Freshly-prepared magnesium bromide diethyl etherate\textsuperscript{4a} (1.63 g, 6.35 mmol) was
magnetically stirred with dichloromethane (50 mL) under a nitrogen atmosphere,
whereupon β-lactone 4a (224 mg, 1.27 mmol) was added in one portion. The
mixture was stirred at ambient temperature for 24 hours, at which time water (100 mL) was added and the product was isolated via ether extraction as a pale yellow oil (131 mg, 74% yield) displaying the following analytical data: TLC (CH₂Cl₂) Rₖ = 0.51. IR (neat) 3028, 2981, 1750, 1651 cm⁻¹ (lit. 6 5.8 μ). ¹H-NMR (CDCl₃) δ 6.89 (narrow m, 1H), 4.82 (m, 1H), 2.28 (br m, 2H), 1.38 (d (J=7 Hz), 3H), 1.12 (br m, 2H), 0.96 (t, 3H) ppm (lit. 6 6.8 (narrow m, 1H), 4.9 (br m, 1H), 2.2 (br m, 2H), 1.4 (d (J=7), 3H), 1.06 (narrow m, 3H) ppm. ¹³C-NMR (CDCl₃) δ 172.5, 146.8, 136.0, 82.1, 26.5, 18.6, 11.8, 9.0 ppm.

In summary, we have developed a short and operationally-facile route to Streptomyces-type lactones that should be applicable to the synthesis of virtually any 3,5-disubstituted butenolides.

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References

1. Camille and Henry Dreyfus Scholar (1993-1995), to whom all correspondence should be addressed.


3,5-DISUBSTITUTED BUTENOLIDES


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