STERICALLY GUIDED REARRANGEMENT OF 3,3-DISUBSTITUTED \(\beta\)-LACTONES. A RAPID CONSTRUCTION OF CYCLOHEPTANO TRANS-FUSED BUTYROLACTONES

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Abstract: 4-Cyclohexyl 3,3-disubstituted oxetan-2-ones rearrange under Lewis acid catalysis to afford trans-fused cycloheptano butyrolactones.

A host of natural products, most notably the guaianolide and pseudo-guaianolides, contain a butyrolactone which is trans-fused to a cycloheptane ring, and a number of ingenious techniques have been reported for their synthesis. The primary difficulties in guaianolide synthesis reside in the construction of the seven-membered ring, complete with stereochemically defined substituents, and fixation of the trans lactone ring in a highly stereoselective manner. An attractive approach to the synthesis of these molecules would involve the functionalization of a cyclohexane ring, where stereochemical control is considerably more facile, followed by expansion to the cycloheptyl homolog with simultaneous formation of the required trans-lactone. Marshall’s elegant cyclopropylcarbinol solvolysis scheme exemplifies this strategy. We now wish to report a short, conceptually unique synthetic method which accomplishes the construction of cycloheptano trans-fused butyrolactones in three steps from six-membered carbocyclic precursors.

We have recently reported a number of useful lactone syntheses based on the rearrangement of alkyl- or cycloalkyl \(\beta\)-lactones. As illustrated below, cyclohexyl \(\beta\)-lactones 2 (derived in two steps from the aldehyde 1) are transformed into spiro butyrolactones 3 when the ring is situated trans to a 3-substituent, since rotation of the cyclohexyl-lactone bond is relatively...
unhindered. In an attempt to sterically bias the rearrangement toward carbon migration, we prepared a series of 3,3-disubstituted β-lactones, hoping that the cis 3-substituent would provide a sufficient impediment to cyclohexyl-lactone bond rotation that a cyclohexyl ring methylene would be situated anticoplanar to the lactone ring oxygen. The cycloaddition of dichloroketene provided a rapid, albeit low-yield, route to the prototypical dichloro compound, while condensation with acetic acid derivatives as the dianions followed by dehydration was employed to acquire dialkyl-substituted lactones. The sequence is depicted below. Thus, cyclohexanecarboxaldehyde (1) was

\[
\begin{align*}
\text{a (R-Cl)} & \quad \text{or} \\
\text{b (R=alkyl)} & \\
\text{c or d} & \\
\end{align*}
\]

\[
\begin{align*}
\text{(1)} & \quad \text{(4, R=Cl)} \\
\text{+} & \\
\text{(5)} & \\
\text{(6)} & \\
\end{align*}
\]

\[a=\text{ZnCl}_2\;\text{CCOCl} \; b=R_2\text{CLICO}_2\text{Li} \; \text{then} \; \text{PhSO}_2\text{Cl} \; c=\text{MgBr}_2 \; d=\text{TiCl}_4\]

The sequence is depicted below. Thus, cyclohexanecarboxaldehyde (1) was treated with dichloroketene to afford 3,3-dichloro-4-cyclohexyloxetan-2-one (4, R=Cl) in 25% yield. Exposure of this lactone to magnesium bromide etherate in dichloromethane solvent effected a complete reaction in 4 hours to

<table>
<thead>
<tr>
<th>R</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>5:6 ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>MgBr\textsubscript{2}</td>
<td>46</td>
<td>&gt;99:1</td>
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<tr>
<td>Me</td>
<td>MgBr\textsubscript{2}</td>
<td>72</td>
<td>69:31</td>
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<tr>
<td></td>
<td>TiCl\textsubscript{4}</td>
<td>75</td>
<td>90:10</td>
</tr>
<tr>
<td>Et</td>
<td>MgBr\textsubscript{2}</td>
<td>31</td>
<td>75:25</td>
</tr>
<tr>
<td></td>
<td>TiCl\textsubscript{4}</td>
<td>62</td>
<td>80:20</td>
</tr>
<tr>
<td>Pr</td>
<td>MgBr\textsubscript{2}</td>
<td>64</td>
<td>&gt;1:99</td>
</tr>
<tr>
<td></td>
<td>TiCl\textsubscript{4}</td>
<td>84</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>-(CH\textsubscript{2})\textsubscript{5}</td>
<td>MgBr\textsubscript{2}</td>
<td>72</td>
<td>64:36</td>
</tr>
<tr>
<td></td>
<td>TiCl\textsubscript{4}</td>
<td>89</td>
<td>80:20</td>
</tr>
</tbody>
</table>

*determined by both proton NMR and gas chromatography*
afford the dichloro trans-fused cycloheptano butyrolactone 5 (R=Cl) in 46% yield as a low-melting (42-42.5 °C), crystalline solid. Reductive dechlorination of this product was easily accomplished via treatment with zinc dust and TMEDA in ethyl acetate/acetic acid, providing the unsubstituted lactone 5 (R=H), which was spectroscopically consistent with reported data.

In order to unambiguously implicate the chlorine atoms in the steric guidance of the reaction, dichloro β-lactone 4 (R=Cl) was dechlorinated as above, and 4-cyclohexyloxetan-2-one (4, R=H) was isolated in 77% yield. Treatment with magnesium bromide–dichloromethane resulted in the production of the spiro butyrolactone 6 (R=H), whose physical data were consistent with literature values.

Encouraged by the dichloro test case, we then examined several gem-dialkyl β-lactones 4 (R=alkyl) (prepared from the appropriate acid and 1 via our reported method as outlined above), and discovered that, with one exception, the rearrangement to predominantly fused products is indeed general. The dipropyl case was anomalous in that not only did the reaction require 12 days to reach completion, but the spiro lactone was produced almost exclusively. The overall yields for these conversions were considerably higher than for the dichloro case, since the low-yield cycloaddition step was replaced by a dianion condensation/dehydration sequence; the β-lactones were typically obtained in 75% yield for the two steps.

Employing titanium tetrachloride as catalyst provided even more gratifying results. Not only was the reaction time reduced to five minutes, but the yields and ratio of fused to spiro lactones were increased substantially. Most intriguing of all was the observation that the dipropyl β-lactone was converted exclusively to the fused lactone, as originally anticipated. Thus, when titanium tetrachloride was employed, increasing the steric bulk of the substituents resulted in a higher fused:spiro ratio in accordance with expectation. The origin of the unique dipropyl dependence of reaction course on the catalyst is under active investigation. The yield data are collected in the Table.

Thus, we have determined that β-lactone rearrangements are amenable to steric guidance, when titanium tetrachloride is used as the catalyst, such that trans-fused cycloheptano butyrolactones are available in three rapid steps from cyclohexanone. We are examining extensions of this methodology to more complex substrates. Since many methods are available for the homologation of ketones to aldehydes, this sequence should be capable of effecting a ring expansion/trans-lactone annulation on a variety of cyclohexanone-containing molecules.
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References


7. Yields are unoptimized.


9. \(\text{IR (film)} 2932, 2860, 1778, 1384, 1229, 1183, 1004 \text{ cm}^{-1}; \text{NMR (CDCl}_3\text{)}: \)

10. \(\text{IR (film)} 2936, 2862, 1771, 1293, 1272, 1222, 1152, 1049, 959 \text{ cm}^{-1}; \text{NMR (CDCl}_3\text{)}: \)

11. \(\text{IR (film)} 2936, 2862, 1771, 1293, 1272, 1222, 1152, 1049, 959 \text{ cm}^{-1}; \text{NMR (CDCl}_3\text{)}: \)


13. For an excellent review, see Martin, S.F. Synthesis 1979, 633.

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