Highly stereoselective synthesis of spiro-α-methylene-γ-butyrolactones: the role of α-hydroxy substitution

Mangesh S. Sawant, Rita Katoch, Girish K. Trivedi* and Umesh R. Desai
Department of Chemistry, Indian Institute of Technology, Powai, Mumbai-400 076, India

An α-alkoxy substituent provides acceleration and greater diastereoselectivity in organometallic additions to chiral ketones. We find that α-hydroxy substitution also plays a similar role. Whereas the addition of a Reformatsky reagent to unsubstituted steroidal ketones does not yield the desired products, α-hydroxy substitution provides the α-methylene-γ-butyrolactone steroid in good yields and very high diastereoselectivity. The α-methylene-γ-butyrolactone moiety has been synthesized at several positions on the steroid nucleus. The stereochemistry can be explained through a chelated transition state, while the enhancement in the rate may be due to both the electron-withdrawing nature of the Reformatsky reagent and the neighbouring group effect.

Introduction

The addition of organometallic reagents to chiral ketones is a useful reaction in modern synthetic organic chemistry. α-Substituted ketones serve as a particularly interesting class of reactants due to their electronic properties. Relative to an α-alkyl or an unsubstituted variant, an α-alkoxy substituent provides both higher rates of reaction and greater diastereoselectivity in the addition of organometallics to cyclic and acyclic ketones. Eliel and co-workers suggest that the addition of an achiral organometallic reagent to chiral α-alkoxy ketones proceeds through a chelate intermediate that lowers the transition state energy and restricts bond rotation. Das and Thornton, however, implicate the substituent field (or inductive) effects for the large rate enhancements in aldol additions to α-alkoxy ketones. It is difficult to assess the contribution of inductive effects in a chelated transition state because of the inherent nature of the substituents involved. We reasoned that (i) an, as-yet untested, α-hydroxy group will also accelerate the reaction, and (ii) the appropriate disposition of hydroxy and keto groups in a rather inflexible steroidal backbone would allow either chelated or unchelated transition states for addressing the concerns of reactivity and stereochemistry. The results highlight the significance of both chelation and electron-withdrawal of the α-hydroxy group in directing the stereochemical outcome and rate acceleration in the Reformatsky reaction with chiral ketones. It is important to note that the α-hydroxy substituent is reported to regulate allylation and crotlylation of α-hydroxy ketones through a chelated transition state.

The α-methylene-γ-butyrolactone moiety is known to be responsible for various biological activities such as antitumour, phytotoxic and antibacterial. We chose to employ the Reformatsky reaction (see Scheme 1) on α-hydroxy substituted steroidal ketones in the synthesis of spiro-α-methylene-γ-butyrolactones.

Results and discussion

Table 1 reports the results of the Reformatsky reaction on selected keto steroids. On reaction with Reformatsky reagent, ketone 1 results in a poor yield of a diastereomeric mixture; whereas 3, bearing an α-hydroxy substituent, provides a single diastereomer in better yield. A more striking effect of the α-hydroxy group is observed with 5 and 7 (Table 1). To extend the generality of the hydroxy group effect on stereoselectivity, several α-hydroxy ketones at different positions on the steroid backbone were synthesized and subjected to the Reformatsky conditions. The α-hydroxy ketones 9, 11 and 13 all gave single diastereomers in good isolated yields, irrespective of the position of substitution.

The enhanced reactivity and stereoselectivity observed for the ketones 3, 7, 9 and 11 is explicable if one assumes the reaction to proceed via a bicyclic transition state, involving a chelate intermediate. In this intermediate, zinc is coordinated with both the hydroxy and carbonyl oxygens to form a five membered ring that can exist in either the envelope or the twist conformations. Both these conformations will necessarily have the hydroxy oxygen oriented below the plane defined by the other atoms, while zinc will be oriented either above the plane in a twist conformation or will be co-planar in the envelope conformation (Fig. 1). The delivery of the reagent in the cyclic transition state can take place either from the Re- or the Si-face of the carbonyl group (Figs. 1(a) and 1(b), respect-

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Abstract:
An α-alkoxy substituent provides acceleration and greater diastereoselectivity in organometallic additions to chiral ketones. We find that α-hydroxy substitution also plays a similar role. Whereas the addition of a Reformatsky reagent to unsubstituted steroidal ketones does not yield the desired products, α-hydroxy substitution provides a modified γ-butyrolactone steroid in good yields and very high diastereoselectivity. The α-methylene-γ-butyrolactone moiety has been synthesized at several positions on the steroid nucleus. The stereochemistry can be explained through a chelated transition state, while the enhancement in the rate may be due to both the electron-withdrawing nature of the Reformatsky reagent and the neighbouring group effect.

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Scheme 1: Synthesis of spiro-α-methylene-γ-butyrolactones using the Reformatsky reaction

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Fig. 1: Transition states for Re- and Si-face attack of the Reformatsky reagent on chiral α-hydroxy steroidal ketones. The geometry of the carbonyl group leads to the co-planarity of Zn, carbonyl and Cu atoms in the transition state. An envelope conformation is most likely with the α-hydroxy group forming the flap of the envelope. Attack of the developing carbanion of the Reformatsky reagent from the Si-face is disfavoured due to repulsion with the lone-pair. See text for additional details.
Table 1  Synthesis of spiro-α-methylene-γ-butyrolactones by Reformatsky reaction of keto steroids with ethyl 2-(bromomethyl)acrylate and zinc in THF

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Major product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Ketone 1" /> R&lt;sub&gt;1&lt;/sub&gt; = R&lt;sub&gt;2&lt;/sub&gt; = H</td>
<td><img src="image2.png" alt="Major product 1" /></td>
<td>39 (70:30)</td>
</tr>
<tr>
<td><img src="image3.png" alt="Ketone 3" /> R&lt;sub&gt;1&lt;/sub&gt; = H; R&lt;sub&gt;2&lt;/sub&gt; = OH</td>
<td><img src="image4.png" alt="Major product 3" /></td>
<td>nil</td>
</tr>
<tr>
<td><img src="image5.png" alt="Ketone 5" /> R&lt;sub&gt;1&lt;/sub&gt; = R&lt;sub&gt;2&lt;/sub&gt; = H</td>
<td><img src="image6.png" alt="Major product 5" /></td>
<td>62 (100:0)</td>
</tr>
<tr>
<td><img src="image7.png" alt="Ketone 9" /></td>
<td><img src="image8.png" alt="Major product 9" /></td>
<td>76 (100:0)</td>
</tr>
<tr>
<td><img src="image9.png" alt="Ketone 11" /></td>
<td><img src="image10.png" alt="Major product 11" /></td>
<td>73 (100:0)</td>
</tr>
<tr>
<td><img src="image11.png" alt="Ketone 13" /></td>
<td><img src="image12.png" alt="Major product 13" /></td>
<td>79 (100:0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Molar ratio of reagents used was as follows: ketone : zinc : ethyl 2-(bromomethyl)acrylate = 1.0 : 1.2 : 1.2. Isolated yield. The ratio of major to minor diastereomers is shown in parentheses.

However, due to the presence of the steroidal backbone the resulting bicyclic transition state has limited conformational flexibility. The transition state resulting from an attack from the same side as that of the hydroxy substituent (syn-attack) will be disfavoured due to electrostatic repulsion between the pseudo-carbanionic centre on the reagent moiety and the lone pairs on the α-hydroxy substituent. Such repulsions are reduced in the anti-attack. Formation of a chelate with such constrained conformational space leads to rate enhancement. Whether increased reactivity can be achieved via the substituent field effect, and without a chelated transition state, was examined with 5α-hydroxy-6-keto steroid 13. The axial disposition of the 5α-hydroxy group clearly disfavours the formation of a chelate intermediate and affords an assessment of inductive effects. The Reformatsky reaction of 13 is accelerated<sup>13</sup> and is highly stereoselective. The stereochemical outcome may be rationalised by invoking complexation of the reagent with the 5α-hydroxy group leading to a syn-attack. The β-face of the carbonyl group becomes inaccessible to the reagent moiety due to steric crowding with the dominant 19-CH<sub>3</sub> group. The substantial increase in reactivity, in the absence of a chelation model, can only come about due to the inductive effect exerted by the zinc coordinated α-hydroxy group.

In conclusion, the introduction of an α-hydroxy substituent leads to higher reactivity and stereoselectivity in the organometallic addition to a carbonyl functionality. Whereas chelation is primarily responsible for directing the stereochemical out-
come; both chelation and the substituent field effects lead to rate accelerations. Detailed electron density calculations may be able to elucidate the dominant rate enhancement mechanism.

**Experimental**

Steroid starting materials of high purity were obtained from Aldrich Chemicals. Ketone 1 was prepared from 17ß-hydroxy-5α-androstan-3-one (5α-androstan-17β-ol-3-one) by following standard acetylation conditions. Ketone 3 was obtained by treating 17ß-hydroxy-5α-androstan-3-one with bromine in glacial acetic acid followed by hydrolysis of the α-bromo-ketone. For the preparation of 7 and 11 from (+)-dehydroisoandrosterone (DHA) (5) see ref. 10(c). Compound 9 was obtained from 17ß-hydroxy-5α-androstan-3-one following the method of Bridgeman et al. IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. Finnigan Mat 1020 automated GC-MS and Kratos Ms 80RF A spectrometers were used to record the mass spectra. Elemental analyses were performed on a CEST MOD.110 analyser. NMR spectra were recorded on Varian VXR 300S and Bruker AMX 500 spectrometers.

**General procedure used for Reformatsky reaction**

To a solution of ketone (1 mmol) in anhydrous THF (8 ml) under argon, freshly activated zinc dust (1.2 mmol) was added and the mixture was stirred at 37°C for 15 min. Ethyl 2-(bromomethyl)acrylate (1.2 mmol) in anhydrous THF (4 ml) was then added and the reaction mixture was monitored intermittently by silica gel thin layer chromatography (TLC). After stirring at 37°C for 15 h the reaction mixture was brought to room temperature, 10% (w/v) HCl (2 ml) was added and the mixture left stirring at room temperature for 0.5 h. The solution was then filtered and extracted with ethyl acetate. The organic extract was washed with water followed by brine and dried over anhydrous Na₂SO₄. Ethyl acetate was evaporated in vacuo and the crude material was subjected to 1H NMR spectral analysis to deduce the formation of multiple products. Unique sets of spiro-α-methylene-γ-butyrolactone signals were pooled to calculate the isolated yields.

**Spiro-o-methylene-γ-butyrolactone 8**

Mp 254–256°C (Found: C: 74.02; H: 8.77. C₂₅H₂₉O₄ requires C, 74.14; H, 8.67%). νₑᵣₑₘ (KBr)/cm⁻¹ 3550 (OH), 1750 (O–C), 1665 (C–O), acetate), 1662 (C–C); δₒ₃₀₀ MHz, CDCl₃) 0.80 (3H, s, 18-Me), 2.03 (3H, s, 21-Me), 2.52 (1H, dd, J 2.9, 17.0, 3′-pro-S-H), 3.21 (1H, td, J 2.6, 17.0, 3′-pro-R-H), 3.63–3.54 (1H, m, 28-H), 4.60 (1H, dd, J 7.8, 9.2, 17α-H), 5.60 (1H, t, J 2.5, 6′-E-H), 6.21 (1H, t, J 3.0, 6′-Z-H); m/z (EI) 416 (M⁺, 6%), 398 (6), 356 (60), 341 (28), 323 (15), 148 (100).

**Spiro-o-methylene-γ-butyrolactone 9**

Mp 254–256°C (Found: C: 74.02; H: 8.77. C₂₅H₂₉O₄ requires C, 74.14; H, 8.67%). νₑᵣₑₘ (KBr)/cm⁻¹ 3550 (OH), 1750 (O–C), 1665 (C–O), acetate), 1662 (C–C); δₒ₃₀₀ MHz, CDCl₃) 0.80 (3H, s, 18-Me), 1.94 (1H, dd, J 4.9, 12.4, 1β-H), 2.03 (3H, s, 21-Me), 2.52 (1H, dd, J 2.9, 17.0, 3′-pro-S-H), 3.21 (1H, td, J 2.6, 17.0, 3′-pro-R-H), 3.63–3.54 (1H, m, 28-H), 4.60 (1H, dd, J 7.8, 9.2, 17α-H), 5.60 (1H, t, J 2.5, 6′-E-H), 6.21 (1H, t, J 3.0, 6′-Z-H); m/z (EI) 416 (M⁺, 6%), 398 (6), 356 (60), 341 (28), 323 (15), 148 (100).

**References**


