Stereoselective routes to aryl substituted $\gamma$-butyrolactones and their application towards the synthesis of highly oxidised furanocembranoids†

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Titanium chelate addition of aryl nucleophiles to cyclopropyl aldehyde 6 followed by a tin-catalyzed one-pot retro-aldol, acetalisation and lactonisation sequence afforded cis and trans $\gamma$-aryllactone acetals. A $\gamma$-furyllactone derived by this approach was further transformed in two steps to model compounds for the oxidised northeastern sectors of selected Pseudopterogorgia diterpenoids.

Highly substituted $\gamma$-butyrolactone motifs are profusely present in many synthetic intermediates and biologically active structures.1 In general, their enantiomeric purity and absolute configuration play a significant role on their purported pharmacological properties.2 Thus, much effort has been invested in their asymmetric synthesis.3 Among the derivatives thus far reported, less attention has been devoted to the stereoselective synthesis of trans and especially, cis $\gamma$-aryl- or heteroarylbutyrolactones.4 Such lactone-based synthons may serve as intermediates for the synthesis of highly oxidised furanocembranoids (e.g. 1–3) and lignan natural products (e.g. 4) (Fig. 1).

We previously reported that Hosomi–Sakurai allylation of furan ester 5 derived cyclopropyl aldehyde 6 affords trans lactones 7 with high diastereoselectivity following the Felkin–Ahn paradigm as the operating addition pathway.6 A useful alternative would appear to be the addition of nucleophiles through a substrate-controlled Cram chelate addition pathway that should lead to the corresponding cis-lactones. In this study, we wish to disclose the addition of aryl- and heteroaryltitanium nucleophiles to 6 leading to either cis- or trans-lactones 9, which appear to be useful building blocks towards the synthesis of 1–4 (Scheme 1).

We initiated our experiments by screening furyl nucleophiles taking into consideration the sensitive nature of the methyl oxalate moiety in 6 under basic nucleophilic conditions. Initial attempts to add several different 2-furyl metal reagents (ArCeCl2, ArCuCl, ArZnCl) alone or in combination with BF3·OEt2 to aldehyde 6 were unsuccessful (Scheme 2). Either decomposition or no reaction of the starting material was observed. Organotitanium reagents display high chemo- and diastereoselectivity towards aldehydes in comparison to other carbonyl functionalities and are considered as “well-behaved reagents” because of their ability to mitigate chemical reactivity and basicity.7 Nevertheless, reaction of the 2-furyltitanium reagent 8a with 6 was also unsuccessful, however, when BF3·OEt2 was additionally employed, the desired furyl transfer was finally achieved to give rise to 10a.
While 10a can be isolated, due to its sensitive nature we opted to directly convert it to the corresponding lactone 9a through a retro-aldol and lactonisation sequence upon saponifying the oxalylic ester, making use of the 1,2-donor–acceptor relationship in the cyclopropane ring (Scheme 2). Previously, we reported Ba(OH)\(_2\)·8H\(_2\)O and Otera stannoxanes as effective reagents to carry out this transformation for allylated derivatives of 6. Treatment of 10a with Ba(OH)\(_2\)·8H\(_2\)O however, failed to give the expected furyllactone carbaldehyde. Gratifyingly, stannoxane 11a furnished the desired lactone acetal 9a, albeit in only 23% overall yield based on 6. Screening of other stannoxane derivatives revealed 11c to be more effective, improving the overall yield of the two-step sequence from 6 to 9a to 40% (Table 1, entry 1–3).

Subsequently, a representative number of other aryltitanium reagents, being readily prepared by dehydrolithiation or dehalolithiation of aryl derivatives followed by titanation with ClTi(OPr\(_i\))\(_3\), were tested for the synthesis of lactones 9 (Scheme 2).\(^6\) Besides 2-thienyl (entry 4) and phenyl (entry 5), alkoxy substituted aryl groups (entries 6–9) being especially relevant towards naturally occurring compounds such as 4 could be successfully introduced. However, aryltitanium nucleophiles bearing substitutions at the ortho-position, e.g. those derived from 2-bromoanisole and 2-bromotoluene, were not amenable with this reaction sequence, which is most likely due to steric hindrance.

The stereochemistry of 9a–g was confirmed through 2D-NOESY correlation experiments and X-ray analysis of 9c (see supporting information). Thus, it was revealed that the diastereoselectivity of this reaction sequence was greatly influenced by the type of aryl nucleophile being used. While the 2-furyltitanium 8a gave rise predominantly to the trans-lactone 9a (86 : 14), the aryl substituted lactones 9c–9g were obtained with moderate to excellent cis-selectivity (3 : 1 to >99 : 1), demonstrating for the first time that addition of nucleophiles to 6 can ultimately lead to cis-lactone of type 9 as the major products.

The cis-selectivity observed in the formation of 9c–9g with aryltitanium/BF\(_3\)·OEt\(_2\) reagents, contrasting the high trans-selectivity achieved in the corresponding transformations with allylsilanes/BF\(_3\)·OEt\(_2\), and the excellent oxygen-chelating capabilities of titanium reagents make us propose a cyclic Cram chelate-type featuring a rather unusual 8-membered titanium complex (Scheme 3, pathway I).\(^{11}\) The aryl nucleophile is delivered externally from the sterically less hindered face of the carbonyl group, giving rise to 10c–g as the major diastereomer. In contrast, the syn-selectivity observed with furan titanate 8a results through the formation of an incipient bond between the furyl nucleophile and the electrophilic aldehyde carbon while...
<table>
<thead>
<tr>
<th>Entry</th>
<th>Organotitanium nucleophile</th>
<th>Aldehyde</th>
<th>Lactone*</th>
<th>Yieldb</th>
<th>cis : trans ratio*e</th>
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<tr>
<td>1</td>
<td>8a</td>
<td>6</td>
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</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>6</td>
<td>9b</td>
<td>29°</td>
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<tr>
<td>3</td>
<td>8c</td>
<td>6</td>
<td>9c</td>
<td>40</td>
<td>54 : 46</td>
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<tr>
<td>4</td>
<td>8d</td>
<td>6</td>
<td>9d</td>
<td>38</td>
<td>82 : 18</td>
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<tr>
<td>5</td>
<td>8e</td>
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<td>9e</td>
<td>45</td>
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<tr>
<td>6</td>
<td>8f</td>
<td>ent-6</td>
<td>9f</td>
<td>33</td>
<td>76 : 24</td>
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<tr>
<td>7</td>
<td>8g</td>
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<td>9g</td>
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<td>92 : 8</td>
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<tr>
<td>10</td>
<td>8h</td>
<td>6</td>
<td>9h</td>
<td>29°</td>
<td>6 : 94</td>
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</table>

* Major diastereomer shown. b Unless otherwise stated, 11c was used as catalyst. Overall yield in two steps. c 11a was used. d 11b was used. e Based on relative integrals in the 'H NMR spectrum. f Lactonisation was carried out with Ba(OH)\(_2\)·8\(\text{H}_2\text{O}\).
The oxygen atom in the furan ring is coordinated with titanium, favoring the formation syn addition product 10a (Scheme 3, pathway II).

The poor diastereoselectivity achieved with the thienyl nucleophile 8b could be explained by the weaker coordination ability of sulfur to titanium, thus resulting in no preference either for pathway I or II. The lower diastereoselectivity for oxygenated aryltitanium reagents leading to 9d–9g compared to 9a might reflect different degrees of internal delivery of the nucleophile via coordination of titanium to the oxygen substituents in the aryl rings. In agreement with this proposal is the highly selective addition of allyltitanium 8h to 6 (Table 1, entry 10), leading to 13 by directed delivery of the allyl nucleophile via a Zimmerman–Traxler-like transition state (Scheme 3, pathway III).

Lactone 9a seemed to be a suitable precursor to study the synthesis of the northeastern segments of diterpenoids 1 and 2 (Scheme 4). Initial attempts to perform oxidative transformations on the furan ring using a number of methods known for that moiety, i.e. singlet oxygen oxidation, mCPBA or Jones oxidation12 to furnish a γ-hydroxybutenolide were unsuccessful. Using bromine11 in methanol, however, afforded the 2,5-dimethoxy-2,5-dihydrofuran 14 in 75% yield, albeit as a mixture of three diastereomers in a 1:1:2 ratio, from which 14c could be separated by chromatography. From the mixture of 14a and 14b the former was obtained in pure form by crystallisation and its structure could be assigned unambiguously by X-ray structural analysis. The major diastereomer 14c was heated with Bredereck’s reagent14 to install the α-dimethylaminomethylene handle, furnishing 15 in good yield (81%). The model precursor product thus obtained satisfies the 1S,2S,3S (and 6S) configurations required in furanocembranoids 1 and 2.

In conclusion, we have developed a new diastereoselective approach towards γ-aryl lactones utilising aryltitanium reagents in combination with the readily available cyclopropanecarbaldehyde 6. This methodology extends the previously reported functionalisation of 6 with allylsilanes in substrate scope, but also offers for the first time a reversal of stereochemistry. Thus, cis-disubstituted γ-aryl-β-methyl acetal lactones with good diastereoselectivity in enantiomerically pure form can be obtained, which compares well with previously reported methods.1,4

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References


