Synthesis of bicyclic tetrahydrofurans from linear precursors using manganese(III) acetate†

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We have recently developed methodology based on oxidative radical reactions for the synthesis of [3.3.0]-bicyclic lactones containing both cyclopentanes and \( \gamma \)-lactams along with application of this methodology to the synthesis of natural products and complex molecular architectures. Herein we report an extension of this methodology to the synthesis of oxygen heterocycles including bicyclic bis-lactones.

The tetrahydrofuran (THF) moiety is present in a vast array of biologically active natural products including: the polyketides, the acetogenins, halogenated natural products from Laurencia species, and numerous terpenes.\(^1,2\) As a result the development of new methodology for the synthesis of THFs, and related 5-membered oxygen heterocycles, is an on-going and important aspect of modern synthetic organic chemistry.\(^3\) Recently we have developed methodology based on oxidative radical reactions\(^4\) for the synthesis of [3.3.0]-bicyclic lactones containing both cyclopentanes\(^5\) and \( \gamma \)-lactams\(^6\) along with application of this methodology to the synthesis of natural products\(^6,7\) and complex molecular architectures.\(^8,9\) Herein we report an extension of this methodology to the synthesis of 5-membered oxygen heterocycles containing bicyclic bis-lactones with up to four stereocentres. In accord with our previous work,\(^5,6\) we proposed that exposure of substrates such as \( 1 \) to a transition metal oxidant could generate the corresponding malonyl radical \( 2 \), which would undergo 5-\( \text{exo-trig} \) cyclisation presumably via the pre-transition state assembly \( 3 \) in accord with the Beckwith–Houk model of 5-\( \text{exo-trig} \) radical cyclisation, to give the adduct radical \( 4 \) (Fig. 1).\(^10,11\) Oxidation of the so formed adduct radical with concomitant C–O bond formation would deliver the dioxocarbenium ion \( 5 \) which gives the desired [3.3.0]-bicyclic \( \gamma \)-lactone \( 6 \) on hydrolysis. As in our study of the cyclisation of radicals derived from amidomalonates,\(^6\) we were aware that malonyl radicals such as \( 2 \) are captodative in nature\(^12\) and, as such might be prone oxidation to the corresponding oxocarbenium ions prior to cyclisation.

The initial substrates we selected for study were the terminal and phenyl-substituted olefins \( 7a \) and \( 7c \) as we had demonstrated that the corresponding substrates, in the all carbon series, could be successfully converted into [3.3.0]-bicyclic \( \gamma \)-lactones under oxidative conditions.\(^5,9\) These substrates, and all of the substrates in the paper were prepared by O–H insertion into the corresponding diazo-malonates according to the procedure described by Hatakeyama and co-workers (see ESI†).\(^13\)

Exposure of the dimethyl malonate \( 7a \) to two equivalents of the one electron oxidant manganese(III) acetate\(^14,15\) in the presence of one equivalent of copper(ii) triflate in acetonitrile at 40 °C, according to our previous work, gave the corresponding [3.3.0]-bicyclic \( \gamma \)-lactone \( 8a \) in 81% yield (Table 1, entry 1).\(^\dagger\) The corresponding di-\( \text{tert-butyl} \) malonate \( 7b \) cyclised with...
similar efficiency (Table 1, entry 2). Using the phenyl-substituted alkenes 7c and 7d gave the corresponding [3.3.0]-bicyclic lactones 8e and 8d in good yield and with high diastereoselectivity at the lactone bearing stereocentre (major diastereomer shown, Table 1, entries 3 and 4). In keeping with previously reported results in the all carbon series,5 cyclisation of ethyl-substituted alkene 7e gave the product 8e in reduced yield and with lower diastereoselectivity and hence we focussed our attention on substrates bearing a terminal alkene or styrene. Given the successful cyclisation of substrates 7, we turned our attention to substrates carrying a substituent at the allylic position (Table 2). With relatively small substituents (9, R3 = Me, CH2CO2Bu), the corresponding lactones 10 were formed with moderate diastereoselectivity (Table 2, entries 1, 2, 4 and 5). In the cyclisation of 5-hexenyl radicals, allylic substituents frequently impart higher levels of diastereoselectivity than exhibited above. This is a result of the allylic substituents having a preference for the pseudo-equatorial position in the chair-like transition state so as to minimise both allylic strain and 1,3-diaxial interactions. The modest selectivity exhibited in the cyclisation of substrates 9a,b,d and e is in keeping with the chair-like pre-transition state assembly where R3 occupies a pseudo-equatorial position (Fig. 2, TSmaj). However the preference for R3 to occupy a pseudo-equatorial position is determined by allylic strain;12 if R3 occupies a pseudo-axial position it would suffer only very minimal 1,3-diaxial interactions with one of the lone pairs of the oxygen atom of the forming THF (TSmin). With much larger substituents (9c and f), the corresponding lactones 10c,f were formed with high levels of diastereoselectivity (Table 2, entries 3 and 6). In all cases, the [3.3.0]-bicyclic γ-lactones were formed in synthetically useful yields.

We next moved to investigate cyclisation reactions of homoallyl-substituted substrates 11 (Table 3). Cyclisation of such substrates would give access to THFs carrying 2/5-substituents – positions that are frequently substituted in THF-containing natural products.1,2 Cyclisation of the substrates 11a–d (Table 3, entries 1–4) gave the product bicyclic lactones 12a–d in good yields with pleasing levels of diastereoselectivity.8 With the phenyl-substituted alkenes 11e–h the corresponding products 12e–h were formed as a mixture of three diastereomers.§ For all the products 12, the relative configuration of the major

![Fig. 2 Plausible pre-transition state assemblies for formation of major and minor diastereomers relating to Table 2.](image-url)
Scheme 1 Synthetic manipulations of lactone 8b.

Table 4 Cyclisations to form bicyclic bis-lactones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>H</td>
<td>77</td>
<td>—</td>
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<tr>
<td>2</td>
<td>b</td>
<td>iPr</td>
<td>H</td>
<td>73</td>
<td>24:1</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>H</td>
<td>Ph</td>
<td>62</td>
<td>9.6:1</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>iPr</td>
<td>Ph</td>
<td>77</td>
<td>9.6:1</td>
</tr>
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<sup>a</sup> Combined isolated yield of mixture of diastereomers >90% pure.
<sup>b</sup> Ratio is given as major diastereomer : sum of minor diastereomers.

diastereomer of the products was in keeping with the Beckwith–Houk model<sup>10,11</sup> for 5-hexenyl radical cyclisation. The levels of stereocontrol are in keeping with related cyclisations and examples from our group.<sup>5</sup>

Having investigated the cyclisation of ether substrates we briefly turned to investigate cyclisation of ester substrates (Table 4). Gratifyingly, under our previously optimised conditions efficient cyclisation occurred to give the bicyclic bis-lactones 14 with good levels of diastereocontrol, although it was not always possible to isolate the products in pure form.

Many of the small densely functionalised products formed in the above cyclisation reactions contain differentiated oxygen functional groups which can be independently manipulated (Scheme 1). For example, on treatment of the [3.3.0]-bicyclic γ-lactone 8b with the phenyl selenide anion the carboxylic acid 15 is formed in 54% yield. Reduction of the carboxylic acid 15 in the presence of the ester could be readily achieved by initial conversion into the corresponding acid chloride followed by treatment with lithium tri-tert-butoxylaluminum hydride<sup>18</sup> giving the alcohol 16. Oxidative elimination from 16 then provided the exo-methylene THF 17 bearing full substitution at C-2.

Table 4 Cyclisations to form bicyclic bis-lactones

In summary, we have reported a mild and operationally simple synthesis of bicyclic THFs and bicyclic bis-lactones in synthetically useful yields and with good levels of diastereocontrol. Application of this methodology to the synthesis of natural products and related targets is on-going.

Conclusions

Acknowledgements

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Notes and references