
Downloaded from: http://e-space.mmu.ac.uk/623050/

Version: Accepted Version

Publisher: Wiley

DOI: https://doi.org/10.1002/cctc.201900658

Please cite the published version

https://e-space.mmu.ac.uk
Alcohol Dehydrogenase Triggered Oxa-Michael Reaction for the Asymmetric Synthesis of Disubstituted Tetrahydropyrans and Tetrahydrofurans

Harry Eastman,[a] James Ryan,*[a] Beatriz Maciá,[b] Vittorio Caprio[b] and Elaine O’Reilly*[a,c]

Abstract: An alcohol dehydrogenase-mediated asymmetric reduction and subsequent intramolecular oxa-Michael reaction has been developed for the preparation of tetrahydropyrans (or oxanes) and tetrahydrofurans, in excellent conversion, yield and high enantiomeric and diastereomeric excess. To highlight the utility of the methodology, we report the synthesis of an analogue of the fungal antioxidant brocaketone A. Also described is the preparation of the (−)-(R,R)-enantiomer of the natural product, (+)-(S,S)-(cis-6-methyltetrahydropyran-2-yl)acetic acid.

The intramolecular oxa-Michael reaction (IMOMR) is a direct and rapid approach for carbon-oxygen bond formation, which allows the construction of synthetically useful cyclic oxygen-containing heterocycles.[1] In particular, the IMOMR is exploited as a key step in cascade strategies for the preparation of chiral tetrahydropyrans (THPs) and tetrahydrofurans (THFs), which are prevalent in natural products (Figure 1).[1d,2] The syntheses of these motifs often commence from the chiral pool, to provide the desired enantiomer of the nucleophilic alcohol, prior to the IMOMR. This chiral centre has also been installed via asymmetric catalysis but the scope of this chemistry is limited.[3c,1p,2d]

Figure 1. A selection of tetrahydropyran and tetrahydrofuran-containing natural products.

A useful approach for the synthesis of THPs/THFs is represented in Scheme 1 and involves the chemo- and stereo-selective reduction of ketoenone 1, followed by a spontaneous IMOMR to afford oxa-Michael product 3. However, this strategy has a number of challenges (highlighted in blue), which would be difficult to overcome when using traditional reduction chemistry.

The growing toolbox of biocatalysts, which can mediate synthetically challenging reactions and complement traditional chemical synthesis, has inspired the concept of biocatalytic retrosynthesis.[3] Incorporating enzymes into retrosynthetic design strategies enables completely new disconnections, which would not be feasible using more traditional synthetic approaches. We have previously reported a transaminase-triggered intramolecular aza-Michael reaction (IMAMR) for the synthesis of chiral 2,6-disubstituted piperidines,[4] and envisaged that an analogous approach could be used for the chemo-enzymatic synthesis of THPs/THFs, by employing an alcohol dehydrogenase (ADH). These enzymes have been heavily exploited for the selective reduction of prochiral ketones to afford the corresponding chiral alcohol. This methodology has been used both in vitro and in vivo, often in combination with a suitable co-factor recycling system.[5] ADHs are also used for the selective oxidation of primary or secondary alcohols, with the latter typically resulting in a kinetic resolution.[6]

Herein, we report an expansion of our aza-Michael methodology to include the biocatalytic ADH reduction/IMOMR cascade on a panel of prochiral ketoenone substrates. An (R)-selective ADH from Lactobacillus kefiri (LK) DSM 20587 has been selected to showcase this methodology, due to its broad substrate specificity and high enantioselectivity in the synthesis of chiral alcohols, including dicarbonyl substrates.[7]

Ketoenone substrates 1a-c and 1e-i (Table 1) were prepared via oxidative cleavage of 1-methylcyclopentene or 6-methyl-5-hepten-2-one, followed by reaction with a suitable phosphorus ylid. Ketoenone 1d was prepared via an
alternative strategy, starting from carboxylic acid 5 (Scheme 3). The biocatalytic reduction of dimethyl ketoone 1a was initially examined, using LK-ADH in combination with a glucose dehydrogenase (GDH)/NADPH recycling system (Scheme 2).[7a] The un hindered methyl ketone and methyl enone make the regioselective reduction of 1a particularly challenging. We recently reported an analogous transaminase-triggered IMOMR on this substrate, where despite a lack of regioselectivity, the reversibility of the biotransformation allows isolation of the desired product via a dynamic ‘shuttling’ mechanism.[9] However, it is not possible to exploit the same reversibility during the ADH reaction, and therefore regioselective reduction of the ketone over the enone is essential. After one hour, 1a was quantitatively converted to undesired diol 4a, using LK-ADH. Close monitoring of the biotransformation over time revealed that the desired IMOM precursor 2a, along with a small quantity of THP 3a, is formed within approximately 8 minutes, in 82% conversion. This mixture can be fully converted to the desired cyclic product 3a by stirring in ethereal hydrogen chloride solution, to provide cis-3a, in 75% yield, as a 12:1 ratio of cis/trans isomers.[10] Further incubation of the biotransformation led to a second undesired ADH-mediated reduction taking place, affording diol 4a. This impressive selectivity means that the biotransformation can be controlled and the target precursor for the IMOM reaction prepared selectively.

Substrates 1b-c were then used to further probe the scope of the methodology. As the enone substituent on these two substrates is relatively large compared to the methyl group in 1a, over reduction of the IMOM precursor to the corresponding diol was not expected to be an issue with this particular ADH, due to its preference for carbonyls with small substituents. Ketoones 1b-c were converted to a mixture of 2b-c (major) and 3b-c (minor) after 20 minutes, in >99% conversion. Treatment with ethereal HCl catalysed the IMOMR and afforded 3b-c in 98% yield and high cis/trans ratio16 (Table 1, entries 2 and 3). It was envisaged that selective reduction of the methyl ketone in 1c, followed by IMOMR and hydrolysis would afford (−)-(R,R)-(cis-6-methyltetrahydropyran-2-yl)acetic acid; the enantiomer of the natural product present in the glandular secretions of the civet cat,[12] whose synthesis has received considerable attention.[13] There have been a number of chemical routes reported for the preparation of 3e, including those exploiting an IMOMR,[13c,13d] but many preparations rely on complex multistep synthesis and harsh reaction conditions. Reaction of 1e with LK-ADH afforded 2e after 1 hour in >99% ee,10] with no cyclised product observed. Subsequent treatment of 2e with sodium hydride led to efficient IMOMR, initially affording a 1:1 mixture of cis/trans isomers,[10] which epimerised in solution over 48 hours to give a dr of 91:9. Purification on silica gel provided solely cis-3e (dr >99:1) in 48% yield (Table 1, entry 5), which was hydrolysed in aqueous LiOH, affording the target (−)-(R,R)-(cis-6-methyltetrahydropyran-2-yl)acetic acid (compound 1-3 in supporting information).

The corresponding tetrahydrofurran derivatives were also accessible using this approach. Substrates 1g-i were transformed in high conversion (87->99%) to THPs 3g-i in good yields (54-99%, Table 1, entries 7-9), but as expected[2] epimerisation of these compounds was not achievable in either the acidic or basic conditions employed for the THPs 1a-e. Unlike the analogous THP derivative 1a that was synthesised using this approach, attempts to control the reduction and isolate the mono-reduced IMOM precursor 2f were unsuccessful and only the corresponding diol and starting material were observed after the biotransformation with LK-ADH.

Table 1. Conversion of 1a-i to 3a-i using LK-ADH and subsequent acid/base-catalysed IMOMR.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>n Conv. (%)</th>
<th>Yield (%)</th>
<th>d.r. (cis/trans) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>1</td>
<td>82</td>
<td>75(8)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Bu</td>
<td>1</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Ph</td>
<td>1</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>CH2Ar</td>
<td>1</td>
<td>91</td>
<td>80(8)</td>
</tr>
<tr>
<td>5</td>
<td>1e&lt;sup&gt;h&lt;/sup&gt;</td>
<td>EIO</td>
<td>1</td>
<td>&gt;99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>Me</td>
<td>0</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>1g&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Bu</td>
<td>0</td>
<td>87</td>
<td>77(7)</td>
</tr>
<tr>
<td>8&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1h</td>
<td>Ph</td>
<td>0</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>1i&lt;sup&gt;k&lt;/sup&gt;</td>
<td>EIO</td>
<td>0</td>
<td>&gt;99</td>
<td>54(1)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: (i) LK-ADH (100 µL resuspended whole cells from 100 mg/mL wet cell resuspension), GDH (6U), substrate (50 mM), glucose (250 mM), NADP<sup>+</sup> (0.01 mM), Tris.HCl buffer (100 mM, pH 7.5, 1 mL), 30 °C, 200 rpm, 8 min for 1a, 60 min for 1b-i; (ii) HCl;EtO<sub>2</sub> (2 M, r.t., 1 h). [b] Conv. determined by NMR after cyclisation. [c] Combined isolated yield of both diastereoisomers. [d] cis/trans ratio determined by NMR spectroscopy (after purification for 2a, 2d, 2e, 2g, 2i). [e] Isolated yield after column chromatography. [f] oxa-Michael reaction carried out with NaH, r.t. 48 h. [g] Only the corresponding diol 4f and starting material 1f were recovered. [h] 10% MeOH added as co-solvent during biotransformation. [i] oxa-Michael reaction carried out with BuOK, r.t., 1 h.

Having successfully demonstrated the feasibility and scope of the biocatalytic reduction/oxa-Michael reaction, the optimised conditions were applied in the chemoenzymatic asymmetric total synthesis of brocaketone A analogue 3d. This natural product was recently isolated from *Penicillium brocaketone MA-192.[11]* Precursor ketocone 1d...
was synthesised in 35% yield over three steps, starting from commercially available acid 5 (Scheme 3). An LK-ADH-catalysed reduction followed by cyclisation afforded the brocaketone A derivative 3d (80% yield, 11:1 dr). Asymmetric reduction of the carbonyl in 3d would provide a formal synthesis of the biologically active natural product, cladosporin.[12]

Scheme 3. Chemo-enzymatic asymmetric total synthesis of brocaketone A analogue. a) N,O-Dimethylhydroxyamine hydrochloride, 1,1’-carbonyldimidazole, CH₂Cl₂, r.t., 24 h. b) CH₂=CMe₂Br, THF, 0 °C – r.t., 2 h. c) Hoveyda-Grubbs II, hept-6-en-2-one, CH₂Cl₂, 24 h. d) i) LK-ADH, GDH, glucose, Tris.HCl, 30 °C, 200 rpm., 1 h ii) HCl.Et₂O (2 M), r.t., 1 h.

In conclusion, we have developed a biocatalytic route for the asymmetric synthesis of tetrahydrofuran/pyran cyclic ethers, starting from easily accessible ketoenones. The strategy relies on an ADH-mediated asymmetric reduction of the ketoenone, followed by an intramolecular oxo-Michael reaction. This novel approach has enabled the asymmetric synthesis of the enantiomer of the natural product (+)-(S,S)-(cis-6-methyltriahydroxyprop-2-yl)lacetic acid as well as a derivative of recently reported brocaketone A, and represents an alternative chemoenzymatic approach for the stereoselective synthesis of cyclic ethers.

Acknowledgements

Research leading to these results has received funding from the EPSRC. The UK Catalysis Hub is kindly thanked for resources and support provided via our membership of the UK Catalysis Hub Consortium and funded by EPSRC (grants EP/K014706/2, EP/K014668/1, EP/K014854/1, EP/K014714/1 and EP/M013219/1). We are grateful to Prof. Wolfgang Kroutil from the University of Graz for supplying the ADH used in this study.

Keywords: asymmetric reduction • alcohol dehydrogenase • biocatalysis • ketoenone • oxo-Michael reaction

An alcohol dehydrogenase-triggered asymmetric reduction and subsequent intramolecular oxa-Michael reaction has been developed for the preparation of tetrahydropyrans (or oxanes) and tetrahydrofurans, in excellent conversion, yield and high enantiomeric and diastereomeric excess.

Harry Eastman, James Ryan,*, Beatriz Maciá, Vittorio Caprio and Elaine O’Reilly*