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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.[1c,1g, 2d]

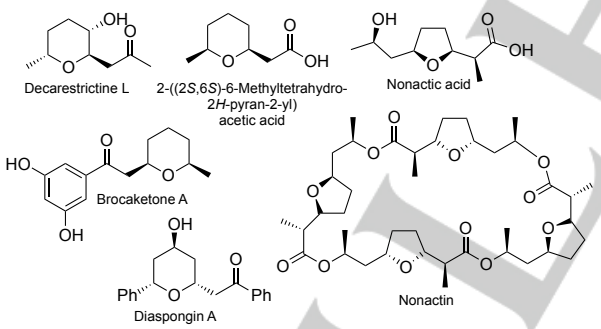

Figure 1. A selection of tetrahydropyran and tetrahydrofuran-containing natural products.

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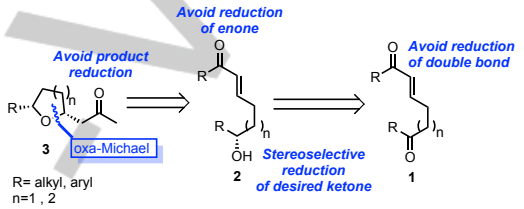
A useful approach for the synthesis of THPs/THFs is represented in Scheme 1 and involves the chemo- and stereo-selective reduction of ketoenone **1**, followed by a spontaneous IMOMR to afford oxa-Michael product **3**. However, this strategy has a number of challenges (highlighted in blue), which would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



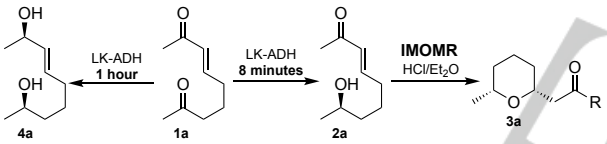
Scheme 1. A retrosynthetic approach for the synthesis of THP/THF derivatives starting from ketoenone **1**.

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 keto-enone substrates. An (*R*)-selective ADH from *Lactobacillus kefir* (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 ketoenone **1a** was initially examined, using LK-ADH in combination with a glucose dehydrogenase (GDH)/NADPH recycling system (Scheme 2).[7a] The unhindered methyl ketone and methyl enone make the regioselective reduction of **1a** particularly challenging. We recently reported an analogous transaminase-triggered IMAMR 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.[4] 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.[1h] 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.

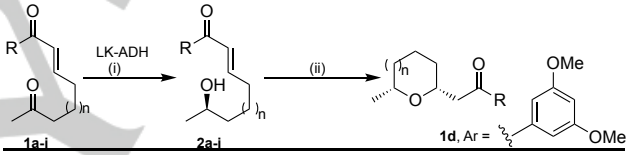


Scheme 2. Conversion of **1a** to **2a** after 8 minutes incubation with LK-ADH**,** followed by IMOMR to give THP **3a**. 1-hour incubation with LK-ADH afforded diol **4a**.

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. Ketoenones **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* ratio[1h] (Table 1, entries 2 and 3). It was envisaged that selective reduction of the methyl ketone in **1e**, 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,[8] whose synthesis has received considerable attention.[9] There have been a number of chemical routes reported for the preparation of **3e**, including those exploiting an IMOMR,[9c,d] but many preparations rely on complex multi-step 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,[1h] 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 I-3 in supporting information).

The corresponding tetrahydrofuran derivatives were also accessible using this approach. Substrates **1g-i** were transformed in high conversion (87->99%) to THFs **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.

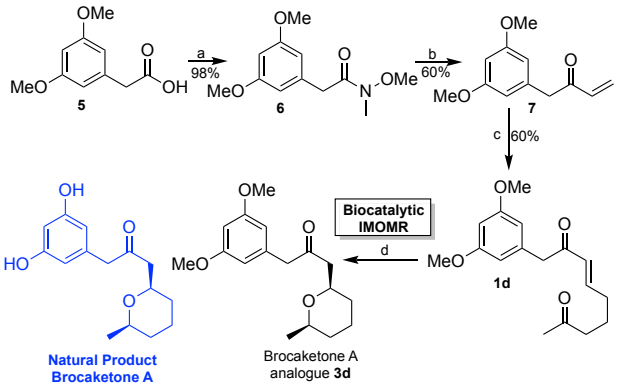


Entry	Substrate	R	n	Conv. (%)[b]	Yield (%)[c]	*d.r.* (*cis*:*trans*)[d]
1	**1a**	Me	1	82	75[e]	12:1
2	**1b**	^{t}Bu	1	>99	>99	8:1
3	**1c**	Ph	1	>99	>99	10:1
4	**1d**	CH_2Ar	1	91	80[e]	11:1
5	**1e**[f]	EtO	1	>99	48[e]	>99:1
6	**1f**	Me	0	na[g]	na	na
7	**1g**	^{t}Bu	0	87	77[e]	1:1
8[h]	**1h**	Ph	0	>99	>99	1:1
9	**1i**[i]	EtO	0	>99	54[e]	1:1

[a] Reaction conditions: (i) LK-ADH (100 µL resuspended whole cells from a 100mg/mL wet cell resuspension), GDH (6U), substrate (50 mM), glucose (250 mM), $NADP^+$ (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.Et_2O (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 ^{t}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 chemo-enzymatic asymmetric total synthesis of brocaketone A analogue **3d**. This natural product was recently isolated from *Penicillium brocae* MA-192.[11] Precursor ketoenone **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*-Dimethylhydroxylamine hydrochloride, 1,1′-carbonyldiimidazole, CH_2Cl_2, r.t., 24 h. b) CH_2=CH_2MgBr, THF, 0 °C – r.t., 2 h. c) Hoveyda-Grubbs II, hept-6-en-2-one, CH_2Cl_2, 24 h. d) i) LK-ADH, GDH, glucose, Tris.HCl, 30 °C, 200 rpm., 1 h ii) HCl.Et_2O (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 oxa-Michael reaction. This novel approach has enabled the asymmetric synthesis of the enantiomer of the natural product (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic 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

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

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[10] This reaction, as well as the biotransformation of the widely accepted substrate acetophenone, was initially used to determine the selectivity of the enzyme. In both cases, LK-ADH exclusively afforded the (*R*)-alcohol (see SI for details). Optical rotation values for compounds 3b-d and I-3 were then measured and compared to those reported in the literature. Other assignments were then based on this trend.

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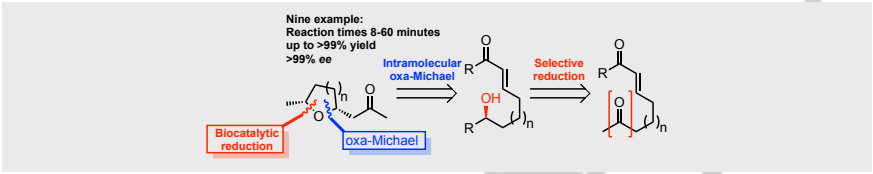

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An alcohol dehydrogenase-triggered asymmetric reduction and subsequent intramolecular oxa-Michael reaction has been developed for the preparation of tetrahydropyrans (or oxanes) and tetrahydrofurans, in excellent conversion, yield and high enantiomeric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