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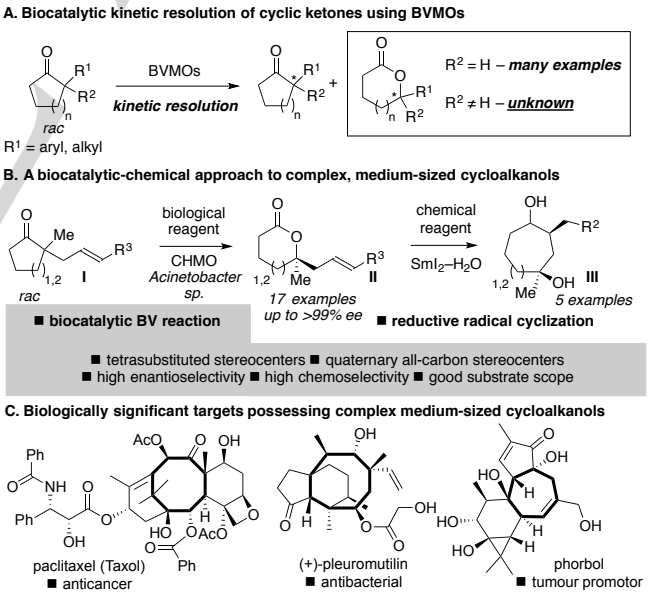
Biocatalytic conversion of cyclic ketones bearing α-quaternary stereocenters to lactones in an enantioselective radical approach to medium-sized carbocycles

Charlotte Morrill,[a] Chantel Jensen,[a] Xavier Just-Baringo,[a] Gideon Grogan,[b] Nicholas J. Turner*[a] and David J. Procter*[a]

Abstract: Cyclic ketones bearing α-quaternary stereocenters undergo efficient kinetic resolution using cyclohexanone monooxygenase (CHMO) from *Acinetobacter calcoaceticus*. Lactones possessing tetrasubstituted stereocenters are obtained with high enantioselectivity (up to >99% ee) and complete chemoselectivity. Preparative scale biotransformations were exploited in conjunction with a SmI_2-mediated cyclization process to access complex, enantiomerically enriched cycloheptan- and cycloctan-1,4-diols. In a parallel approach to structurally distinct products, enantioenriched ketones from the resolution bearing an α-all carbon quaternary stereocenter were used in a SmI_2-mediated cyclization process to give cyclobutanol products (up to >99% ee).

The Baeyer-Villiger (BV) reaction[1] transforms ketones into esters or lactones with predictable regioselectivity and as such is a valuable tool for synthesis. Metal-based catalysts[2] and organocatalysts[3] have been developed for catalytic enantioselective variants of the BV reaction, however, high enantioselectivities are generally limited to the transformation of activated cyclobutanone substrates in which the release of ring strain drives the BV reaction.[4] Baeyer-Villiger monooxygenases (BVMOs) offer an attractive alternative to the use of chemical reagents for enantioselective BV reactions. These flavin-dependent enzymes exploit atmospheric oxygen and catalyze the transformation through an enzyme-bound flavin-(hydro)peroxy intermediate.[5] The use of BVMOs promises distinct advantages in terms of enantioselectivities, substrate scope, and chemoselectivity not possible using chemical reagents.[6]

BV transformations of α,α-dialkyl cyclic ketones have the potential to deliver enantioenriched lactones with tetrasubstituted stereocenters and cyclic ketones bearing α-all-carbon quaternary centers. Such products possess hard-to-build stereocenters[7] and are high value chiral building blocks for synthesis.[8] To our knowledge, there are no reports of the enantioselective BV reaction of α,α-dialkyl cyclic ketones using chemical reagents.[2b, 2g] Furthermore, the ability of BVMOs to catalyze the kinetic resolution of α,α-dialkyl cyclic ketones was, until now, unexplored (Scheme 1A).[9] The synthetic reach of biocatalytic reactions is greatly extended when enzymatic processes are integrated into synthetic sequences involving chemical catalysts and reagents.[10] Herein, we describe a highly enantioselective and chemoselective, biocatalytic Baeyer-Villiger approach to unsaturated lactones **II** bearing tetrasubstituted stereocenters that proceeds by the kinetic resolution of cyclic ketones **I** bearing α-quaternary stereocenters. Crucially, lactones **II** are not easily accessible in enantiomerically enriched form using state-of-the-art chemical methods.[11] Lactones **II** are excellent substrates for SmI_2–H_2O-mediated[12] cyclization reactions that complete an enantioselective biocatalytic-chemical approach to important and complex cycloheptan- and cycloctan-1,4-diols **III** (Scheme 1B): Structural motifs that are notoriously hard to prepare and that are prevalent in many biologically-relevant targets (Schemes 1B and 1C).[13]



Scheme 1. A. BVMOs in the kinetic resolution of cyclic ketones: lack of precedent for the resolution of substrates bearing α-quaternary stereocenters. B. An approach to complex, medium-sized cycloalkanols that exploits the synergy between a biocatalytic and a chemical process. C. The biological importance of molecules containing cycloheptanol and cyclooctanol motifs.

The biocatalytic kinetic resolution was explored using the purified $CHMO_{Actineto}$ enzyme from *Acinetobacter calcoaceticus* (NCIMB 9871). A glucose/glucose dehydrogenase (GDH) recycling system was employed for catalytic regeneration of the NADPH cofactor[14] and the feasibility of the biotransformation was initially

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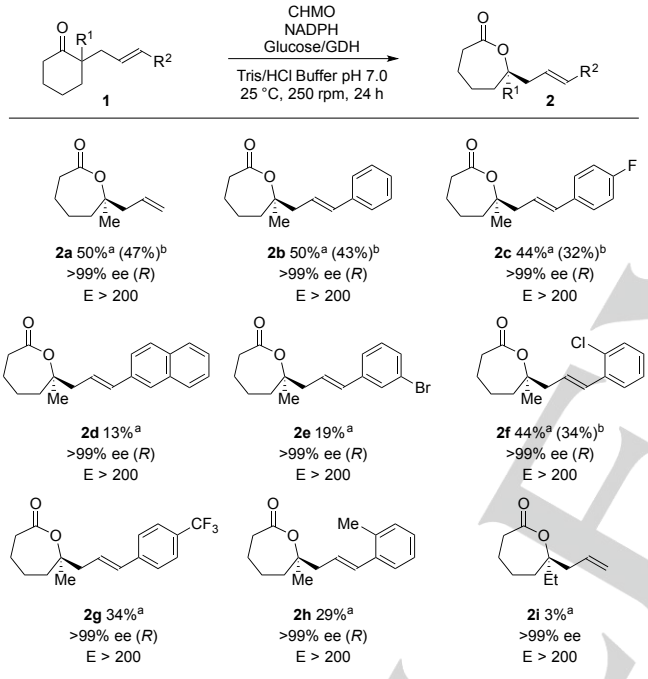
assessed on an analytical scale using ketone **1a** (R^1 = Me, R^2 = H). Pleasingly, despite the lack of precedent for the resolution of substrates bearing α-quaternary centers, lactone **2a** was efficiently formed in >99% ee at a conversion of 50% (Table 1). A control reaction, in which **1a** was exposed to the reaction conditions in the absence of CHMO, resulted in no conversion to the product. In order to assess the scope of the transformation, a range of lactones bearing various aryl groups on the alkene unit was prepared in one straightforward step from **1a** (see Supporting Information). Despite the presence of the bulky aryl substituents and the α-quaternary center, we were pleased to observe unprecedented tolerance on the part of CHMO and all six-membered ketones **1** were transformed to seven-membered lactones **2** with very high enantioselectivities (selectivity factors, E > 200) (Table 1).

Table 1. Biotransformations of six-membered cyclic ketones bearing α-quaternary all-carbon stereocenters catalyzed by $CHMO_{Acineto}$.

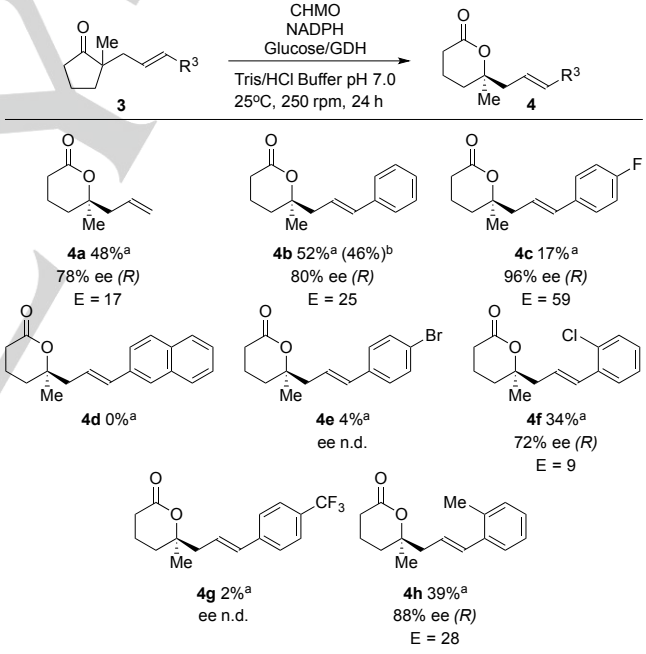


Conditions for analytical scale biotransformations: Ketone 1 mg mL^{-1}, CHMO 0.25 mg mL^{-1}, NADPH 0.7 mM, GDH 0.25 mg mL^{-1}, glucose 5.5 mM, Tris/HCl buffer 100 mM. [a] Values shown are conversions determined by GC or ^{1}H NMR analysis of crude reaction mixtures. [b] Isolated yields in brackets for preparative scale transformations. For a detailed description of the procedure for the preparative scale biotransformations see the Supporting Information. Enantiomeric excesses determined by chiral stationary phase GC or HPLC analysis.

Selective formation of the *(R)* enantiomer of the lactone products was confirmed for **2a-c** and inferred for the remainder.[15] For substrates bearing a methyl substituent at the α-quaternary center, conversions up to 50% (the maximum theoretical value for an ideal kinetic resolution) were observed. In stark contrast to chemical oxidation of **1b** to **2b**, no side products resulting from competing oxidation of the alkene in the starting material and product were observed.[16] Thus, the biocatalytic process exhibits complete chemoselectivity. Substitution was tolerated at all positions on the aromatic ring, with halogen, methyl and trifluoromethyl substituents all accepted by the enzyme active site. Substrates **1d** and **1e**, bearing bulky naphthyl and 3-bromo substituents, were transformed less efficiently by the enzyme and lower conversions were exhibited, however, enantioselectivity remained high. Variation of the reaction pH and use of an alternative biocatalyst, cyclododecanone monooxygenase ($CDMO_{Rhodo}$) from *Rhodococcus*, did not lead to improved conversions.[17] Ketone **1i**, in which the R^1 group was an ethyl rather than a methyl substituent, was transformed inefficiently, although a small amount of product was formed with high enantiocontrol. Following assessment of the process on an analytical scale, transformations were performed on a preparative scale (0.2 mmol) (formation of **2a-c**, **2f**). Facile separation of the product from the ketone afforded pure samples of the enantioenriched lactone products. For substrates, **1a-c, 1f**, high value ketones bearing α- all carbon quaternary stereocenters **2a-c**, **2f** were obtained in high enantiopurity after the kinetic resolution (*vide infra*).

We also explored the scope of the biocatalytic kinetic resolution with respect to the formation of six-membered lactones. A range of five-membered ketones **3** was prepared and subjected to the CHMO-catalysed transformation (Table 2). Although the biotransformations were typically less efficient than those involving

Table 2. Biotransformations of five-membered cyclic ketones bearing α-quaternary all-carbon stereocenters catalyzed by $CHMO_{Acineto}$.



Conditions for analytical scale biotransformations: Ketone 1 mg mL^{-1}, CHMO 0.25 mg mL^{-1}, NADPH 0.7 mM, GDH 0.25 mg mL^{-1}, glucose 5.5 mM, Tris/HCl buffer 100 mM. [a] Values shown are conversions determined by GC or ^{1}H NMR analysis of crude reaction mixtures. [b] Isolated yields in brackets for preparative scale transformations. For a detailed description of the procedure for the preparative scale biotransformations see Supporting Information. Enantiomeric excesses determined by chiral phase GC or HPLC analysis.

six-membered cyclic ketones, in some cases lactone products **4** were formed with selectivity factors (E 17-59) indicative of useful synthetic procedures. For example, cyclopentanones **3c** and **3h** underwent significant conversion and lactones **4c** and **4h** were obtained in 96% ee and 88% ee, respectively. Five-membered cyclic ketones **3d**, **3e** and **3g**, containing larger aromatic substituents, showed very little or no conversion to lactone products (Table 2).

Selective formation of the *(R)* enantiomer of the lactone products was confirmed for **4a-c** and inferred for the remainder.[15] Analogous seven-membered ketone substrates were incompatible with the biocatalytic process.[15]

Berghuis and co-workers have previously determined the structure of $CHMO_{Rhodo}$, a homolog of $CHMO_{Actineto}$, in its 'tight' conformation in complex with ε-caprolactone, the product of BV oxidation of cyclohexanone (PDB code 4RG3)[18] and suggest that this is the conformation of the enzyme in which stereoselectivity of the reaction is determined. $CHMO_{Acineto}$ used here, shares 55% amino acid sequence identity with $CHMO_{Rhodo}$ and the majority of residues within the active site are conserved, allowing the construction of a model of $CHMO_{Acineto}$ such as that previously presented by Reetz and co-workers.[19] The model was used as the input for an *in silico* docking experiment with the enantiomers of lactone product **2a**. Figure 1 shows the (*R*)-enantiomer of **2a**, the preferred product of reaction, beneath the FAD coenzyme with its alkenyl substituent accommodated in the hydrophobic pocket formed by the side chains of L435, F505, and F432, the latter having been shown through mutation to have a profound influence on the enantioselectivity of CHMO $_{Acineto}$ catalyzed reactions.[20] The pose would also permit the accommodation of larger side chains such as those in the (*R*)-lactone products **2b** and **2c**. The role of this region in the accommodation of bulky side chains, such as that of 2-phenyl cyclohexanone, has previously been demonstrated.[19] Interestingly, the **2a** lactone carbonyl in the top pose superimposes well with the equivalent atom in the 4RG3-ε caprolactone complex, at a distance of 3.3 Å from the ribose 1- hydroxyl and 2.7 Å from the side chain of R327, which is thought to stabilise the oxyanion in the Criegee intermediate in the same position.

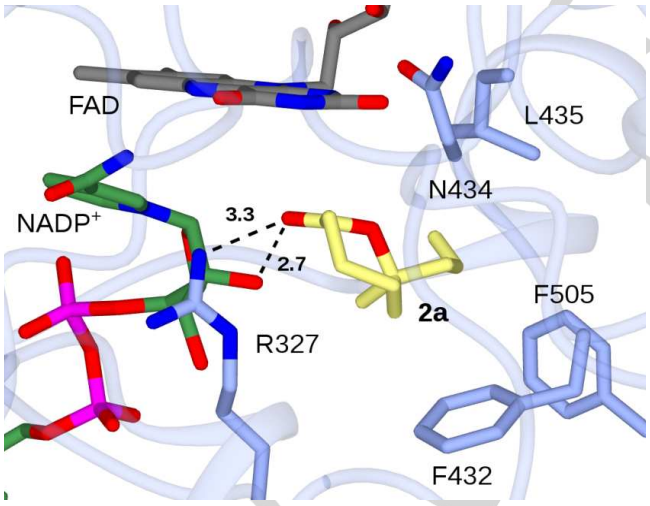


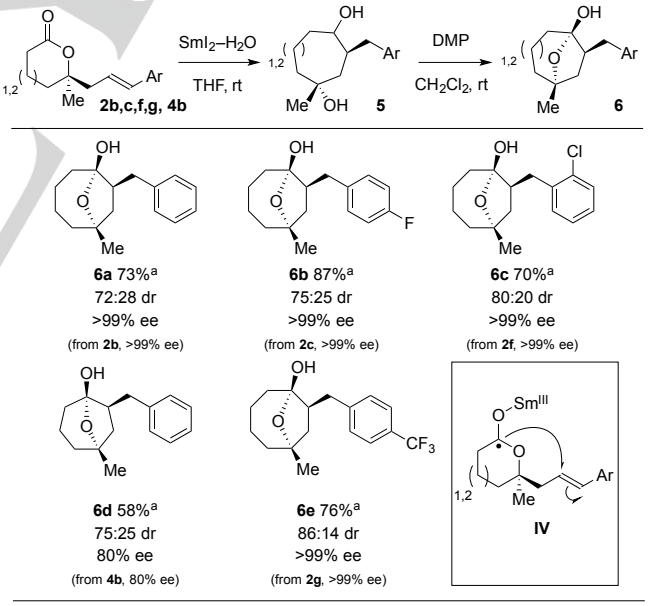
Figure 1. Model of $CHMO_{Acineto}$ in complex with lactone product (*R*)-**2a** created using Autodock-Vina.[21] Backbone and side chains of the enzyme are shown in light blue, carbon atoms of FAD, $NADP^+$ and **2a** are shown in grey, green and yellow, respectively. Selected interactions are indicated by black dashed lines with distance in Ångstroms.

Radical approaches to challenging medium sized carbocycles are highly prized.[22] In particular, radical cyclizations to give cyclooctanes are scarce and are mostly limited to 8-*endo* cyclization modes. We recently reported a 5-*exo*-trig radical cyclization approach that converts unsaturated six and seven-membered lactones to complex seven- and eight-membered cycloalkanols, however, until now the process could only deliver racemic products as enantioenriched starting lactones could not easily be prepared.[12g, 12j] Achieving enantiocontrol in SmI_2-mediated reactions of achiral or racemic substrates is challenging[23] and the use of enantioenriched substrates in diastereoselective processes is a more general approach to access enantioenriched products.

The enantioenriched lactones **2**/**4** formed by the biocatalytic Baeyer-Villiger reaction were excellent substrates for diastereoselective radical cyclizations mediated by SmI_2–H_2O. Upon treatment with SmI_2–H_2O, lactones **2**/**4** underwent efficient 5-*exo*-trig radical cyclization to give seven- and eight-membered cycloalkanols **5** in good yield. Oxidation of the crude product mixtures simplified the diastereoisomeric mixtures and afforded the cycloalkanoid products **6** with up to 6:1 dr. The reaction proceeded with no loss of enantioenrichment and important cyclooctanol motifs were obtained in >99% ee.

The radical cyclization proceeds by electron transfer from Sm(II) to the carbonyl group of the enantioenriched lactones formed by the biocatalytic BV reaction. The resultant radical anions **IV** (see Table 3) undergo intramolecular addition to the alkene acceptor to give hemiketal intermediates that are reduced *in situ* by SmI_2–H_2O to give enantioenriched seven- and eight-membered cycloalkanol products **5** in good yield.

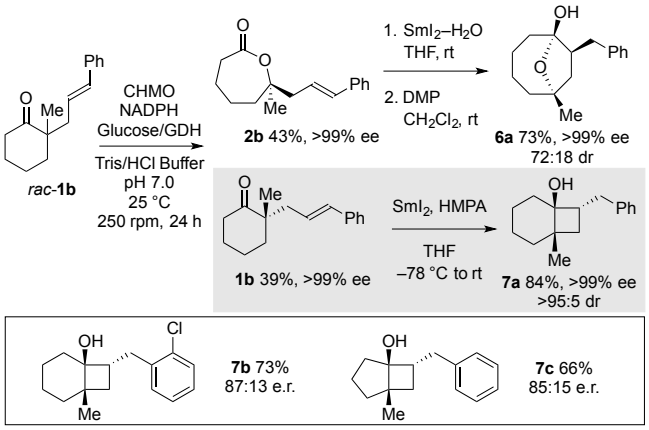
Table 3. Radical cyclization of enantioenriched lactones using SmI_2–H_2O completes an enantioselective approach to cycloheptanols and cyclooctanols.



Conditions: Lactone (1 equiv.), SmI_2 (8 equiv.), H_2O (800 equiv.). Diastereoisomeric ratios were determined from ^1H NMR of crude reaction mixtures. [a]Isolated yields after 2 steps. Enantiomeric excesses were determined by chiral phase GC or HPLC analysis. DMP = Dess-Martin periodinane.

The biocatalytic transformation of α,α-dialkyl cyclic ketones delivers not only enantioenriched lactones **2** but also enantioenriched cyclic ketones **1** recovered from the kinetic resolution (Scheme 2). For example, the biocatalytic transformation to give lactone **2b** (43% isolated yield, >99% ee) also gave ketone **1b** (39% isolated yield,

>99% ee) bearing an α- all-carbon quaternary stereocenter. Pleasingly, SmI_2-mediated radical cyclization of **2b** gave enantiopure cyclobutanol **7a** with complete diastereocontrol in 84% yield.[24] Cyclobutanols **7b** and **7c** could be similarly be obtained from resolved ketones bearing α- all-carbon quaternary stereocenters, **1f** and **3f**. Thus, biocatalytic kinetic resolution of racemic ketones **1** and **3**, when used in combination with metal-mediated radical cyclizations, allows divergent access to important carbocyclic products with very different molecular architectures in enantiopure form.



Scheme 2. Biocatalytic kinetic resolution of *rac*-**1b** in a divergent, metal-mediated radical cyclization approach to structurally distinct, enantiopure molecular architectures.

In summary, racemic cyclic ketones bearing α-quaternary stereocenters undergo efficient kinetic resolution using cyclohexanone monooxygenase (CHMO) from *Acinetobacter calcoaceticus*. The new biocatalytic process has been used in combination with new radical cyclizations to access important enantioenriched carbocyclic scaffolds. In particular, lactones possessing tetrasubstituted stereocenters are obtained with high enantioselectivity (up to >99% ee) and are exploited in SmI_2-mediated cyclization processes to access complex, enantiomerically enriched cycloheptan- and cycloctan-1,4-diols. In a divergent approach to structurally distinct molecular architectures, enantioenriched cyclic ketones from the resolution, bearing an α- all-carbon quaternary stereocenter, were used in a SmI_2-mediated cyclization process to give cyclobutanol products (up to >99% ee).

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Keywords: biocatalysis • lactones • samarium • radical • cyclization

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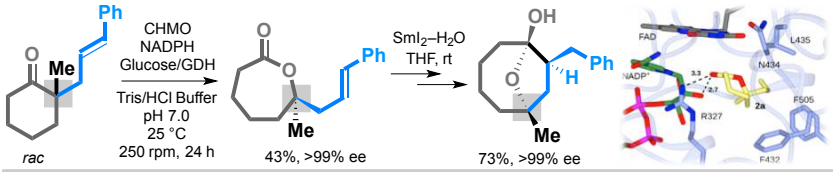

■ combined biocatalytic-chemical approach to complex, medium-sized cycloalkanols

Racemic cyclic ketones bearing α-quaternary stereocenters undergo kinetic resolution using cyclohexanone monooxygenase ($CHMO_{Actineto}$) to give lactones possessing tetrasubstituted stereocenters (up to >99% ee). Preparative scale biotransformations were exploited in conjunction with a SmI_2-mediated cyclization process to access complex, enantiomerically enriched cycloheptan- and cyclooctan-1,4-diols. In a parallel approach to structurally distinct products, enantioenriched cyclic ketones from the resolution were converted to cyclobutanols bearing a quaternary stereocenter (>99% ee) using a SmI_2 cyclization.

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Biocatalytic conversion of cyclic ketones bearing α-quaternary stereocenters to lactones in an enantioselective radical approach to medium-sized carbocycles