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Regio- and Stereoselective Reduction of Diketones and Oxidation of Diols by Biocatalytic Hydrogen Transfer

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The asymmetric reduction of symmetrical and nonsymmetrical diketones as well as the stereoselective oxidation of various diols by biocatalytic hydrogen transfer was investigated by employing lyophilized cells of *Rhodococcus ruber* DSM 44541 containing alcohol dehydrogense ADH-'A'. Symmetrical and nonsymmetrical diketones at the (ω-1)- and (ω-2)-positions are reduced to the Prelog product with high stereopreference, while sterically more demanding ketone moieties, for example those at the (ω-3)-position, remain unchanged. For the oxidation mode, differentiation between primary and secondary alcohols is achieved, and the (*S*)-configured secondary alcohols at the (ω-1)- and (ω-2)-positions are oxidized preferentially.

Introduction

The regioselective reduction of one specific ketone moiety out of all chemically equivalent ketone moieties within the same molecule cannot easily be achieved by chemical methods without the use of protection strategies.[1] The same is true for the oxidation of one specific hydroxy group out of all chemically equivalent hydroxy groups, although methods that are selective to a certain extent have been reported.[2] Biocatalysts show intrinsic high regio- and stereoselectivity and are therefore ideally suited catalysts for the transformation of complex molecules possessing more than one reactive group, without the need for protection techniques. Chiral keto-alcohols are widespread structural features of many natural products,[3] such as pheromones[3b] or antitumor agents like discodermolide,[3c] and are therefore frequently used chiral building blocks for fine chemicals in the agrochemical-, flavor/fragrance-, and pharmaceutical industry.[4] Furthermore non-racemic short-chain diols serve as starting materials for chiral polymers[5] or as the backbone for chiral ligands[4a] for asymmetric transition-metal catalysis. Enantiopure diols and hydroxy ketones have been biocatalytically synthesized by employing alcohol dehydrogenases from various sources.[4,6] We recently identified an exceptional, solvent-stable alcohol dehydrogenase ADH-'A' from *Rhodococcus ruber* DSM 44541,[7] which is ideally suited for biocatalytic hydrogen-transfer reactions[8] that employ 2-propanol as the hydrogen donor for asymmetric reduction[9] and acetone as the hydrogen acceptor for oxidation.

In order to broaden the applicability of this method to more complex bifunctional substrates, we investigated the regio- and stereoselectivity of the reduction/oxidation of diketones/diols. Special emphasis was placed on the influence of the relative position of the functional groups to each other.

Results and Discussion

Asymmetric Bioreduction of Diketones

The (biocatalytic) reduction of diketones to diols proceeds in a stepwise fashion via the corresponding hydroxy ketone, and the selectivities and reaction rates of both steps determine the outcome of the reduction (Scheme 1). All experiments were performed by employing lyophilized cells of *Rhodococcus ruber* DSM 44541 containing the alcohol dehydrogenase ADH-'A' as the catalyst, while 2-propanol (16% v/v) was used as the hydrogen donor, and also as the co-solvent to improve the solubility of the substrates. The reduction of the vicinal diketone 2,3-pentanedione (**1a**) exclusively yielded the diol (2*S*,3*R*)-**1c** in high isolated yield (93%) with a low *ee* (60%) but a high *de* (97%) (Table 1) – no measurable amounts of the corresponding hydroxy ketone were detected.

Since a low stereoselectivity was previously observed for *R. ruber* ADH-'A' for small substrates,[8a] we assumed that

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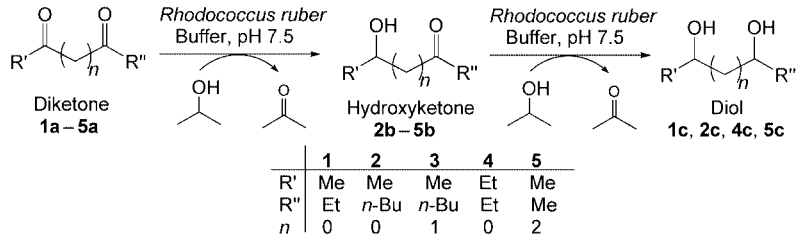


Scheme 1. Reduction of diketones by biocatalytic hydrogen transfer.

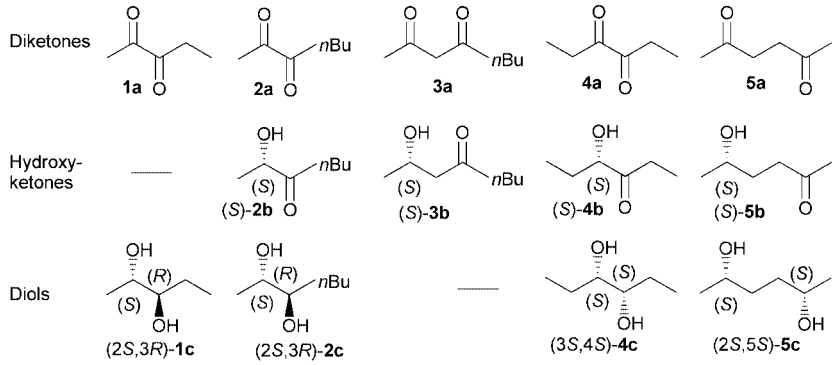


Table 1. Biocatalytic reduction of diketones by hydrogen transfer with the use of *Rhodococcus ruber* DSM 44541.

Substrate	Conversion[a] [%]	Hydroxy ketone	yield[b] [%]	*ee* [%]	Diol	yield[b] [%]	*ee* [%]	*de* [%]
1a	95	**1b**	<0.1	–	(2*S*,3*R*)-**1c**	93	60	97
2a	95	(*S*)-**2b**	39	97	(2*S*,3*R*)-**2c**	52	98	>99
3a	97	(*S*)-**3b**	90	>99	–	<0.1	–	–
4a	85	(*S*)-**4b**	23	95	(3*S*,4*S*)-**4c**	59	>99	>99
5a	65	(*S*)-**5b**	38	>99	(2*S*,5*S*)-**5c**	23	>99	>99

[a] Based on the remaining diketone after 48 h conversion time. [b] isolated yield.

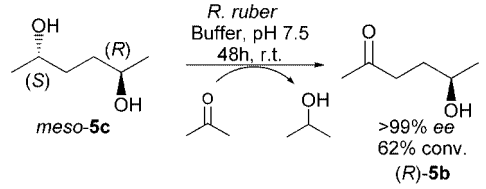
extension of the alkyl chain may lead to a higher selectivity: indeed 2,3-heptanedione (**2a**) was reduced to the diol (2*S*,3*R*)-**2c** with excellent *ee* (98%) and *de* (>99%). For a preparative substrate concentration of 350 mM and a cell/substrate ratio of 1:1, the obtained product mixture contained 39% hydroxy ketone (*S*)-**2b** (97% *ee*) and 52% diol (2*S*,3*R*)-**2c** after 48 h (Table 1). Sterically more demanding keto-moieties, for instance that at the 4-position of 2,4-octanedione (**3a**), were not accepted, therefore the reduction of **3a** proceeded only through a single step to furnish hydroxy ketone (*S*)-**3b** in 90% isolated yield with an *ee* > 99%. In contrast, both keto-moieties of the symmetric diketone **4a** are at the (ω-2)-position and are therefore amenable to bioreduction. The first desymmetrisation reduction step of **4a** occurred with a good stereoselectivity (*ee* 95%), and the second (kinetic resolution) step with a perfect stereo- and enantioselectivity, since only the (*S*)-enantiomer of the hydroxy ketone (*S*)-**4b** was reduced further to yield the optically pure diol (3*S*,4*S*)-**4c** (*ee* and *de* > 99%). From these experiments, we concluded, for the reduction, that (i) ketone moieties at the (ω-1)- or (ω-2)-position can be accepted, (ii) neighboring ketone or hydroxy groups do not diminish the general excellent stereoselectivity of the reduction of a given carbonyl group.

Consequently, the reduction technique was employed for the symmetrical diketone 2,5-hexanedione (**5a**). The corresponding enantiopure 2,5-hexanediol (**5c**) is a versatile building block for the synthesis of various chiral phosphane ligands that are used in chiral Wilkinson catalysts,[10] therefore various chemical[11] and biocatalytic[4a,6c,12] methods for its synthesis have been reported. In line with the observations mentioned above, the first reduction step of **5a** occurred with absolute stereoselectivity to yield the hydroxy ketone (*S*)-**5b** with an *ee* > 99%. In addition, the second reduction step to the corresponding diol (2*S*,5*S*)-**5c** was also performed with absolute stereoselectivity (>99% *ee*, >99% *de*).

Asymmetric Oxidation of 2,*n*-Alkane Diols

By switching from the hydrogen donor 2-propanol to the hydrogen acceptor acetone, stereoselective oxidations can be performed. Biocatalytic oxidation of the prochiral diol

meso-**5c** with *R. ruber* yielded the enantiopure hydroxy ketone (*R*)-**5b** (>99% *ee*) (Scheme 2), which indicates that ADH-'A' showed an exclusive preference for the (*S*)-configured center of the two hydroxy moieties at the (ω-1) position.



Scheme 2. Biocatalytic oxidation by hydrogen transfer of *meso*-2,5-hexanediol **5c**.

By performing the oxidation for the racemic diol (2*R**,5*R**)-**5c**, the picture becomes more complex, since we deal with a sequential oxidative kinetic resolution.[13] Under the reaction conditions employed, the biocatalytic oxidation of racemic diol *rac*-(2*R**,5*R**)-**5c** yielded enantiopure hydroxy ketone (*S*)-**5b** (>99% *ee*), a small amount of diketone (5%), and the remaining diol (2*R*,5*R*)-**5c** (97% *ee*) at 47% conversion (Table 2). From these data, the enantioselectivity of the first kinetic resolution step (E_1) can be estimated to be greater than 200.[14] As to be expected, for the oxidation of (2*R**,5*R**)-**5c**, we obtained the (*S*)-configured hydroxy ketone **5b**, which is in contrast to the oxidation of *meso*-**5c**, where (*R*)-**5b** was obtained. Because of the strong preference of ADH-'A' for (*S*)-configured alcohols, the intermediate (*S*)-hydroxy ketone (*S*)-**5b** was further converted to diketone **5a**.

For nonsymmetric substituted diols a high regioselectivity in addition to the high recognition of (*S*)-centers was observed, for instance, racemic (2*R**,4*R**)-**3c** was exclusively oxidized at the (*S*)-configured (ω-1)-position to yield the 4-hydroxy-2-octanone (*S*)-**3d**, thus no 2-hydroxy-4-octanone **3b** was detectable. However, the close vicinity of the two hydroxy groups led to a significant decrease in enantioselectivity (*E*) of the oxidation step ($E = 3$). A similar low enantioselectivity was obtained for the oxidation of (2*R**,4*S**)-**3c** ($E = 4$); however, in this case only hydroxy ketone was found as the oxidation product, and no diketone was detectable. For the vicinal diol (2*R**,3*R**)-**6c** similar results were obtained, thus the (*S*)-configured alcohol at the (ω-1)-position was oxidized first to give (*S*)-**6d** as the major isomer. The intermediate hydroxy ketone **6d** was oxidized further to yield a significant amount of diketone **6a** (18% GC yield). The oxidative kinetic resolution of (2*R**,3*S**)-**6c** resulted in (*R*)-3-hydroxy-2-octanone (*R*)-**6d** as the mayor isomer, which is the male sex pheromone of the longhorn beetle *Anaglyptus subfasciatus*.[3b] Nevertheless, the enantioselectivity of the first oxidation step was very low ($E < 4$). In summary, (i) hydroxy moieties at either the (ω-1)- or the

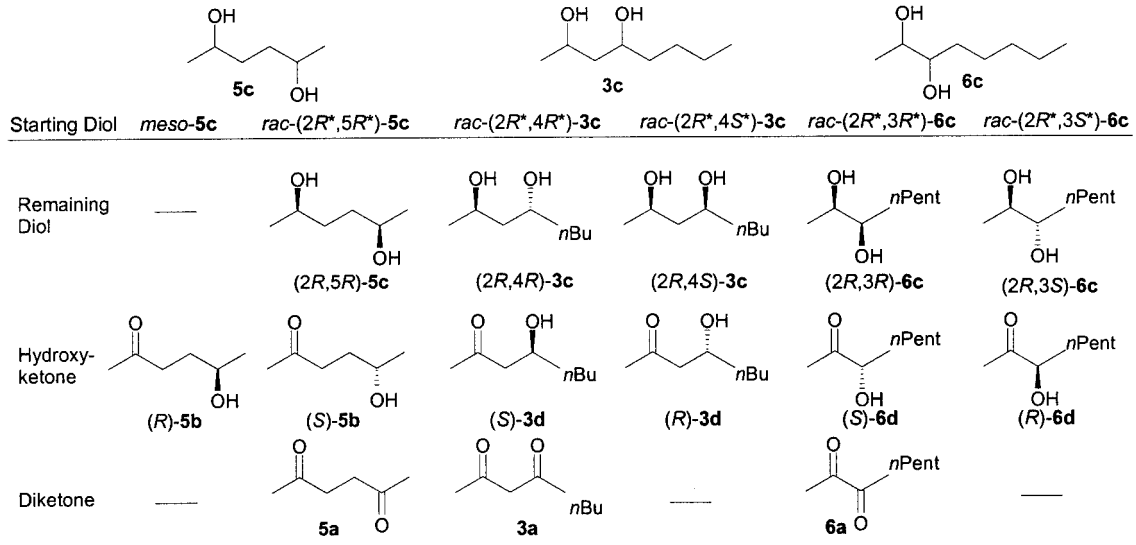


Table 2. Biocatalytic oxidation of 1,2-alkane diols by hydrogen transfer with the use of *Rhodococcus ruber* DSM 44541.

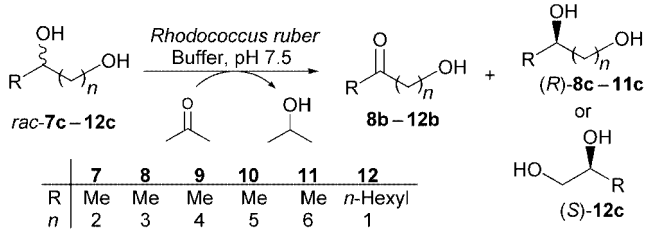
Substrate	Conversion[a] [%]		Diketone yield[b] [%]		Hydroxy ketone yield[b] [%]	*ee* [%]		Remaining diol yield[b] [%]	*ee* [%]
(2*R**,4*R**)-**3c**	42	**3a**	1	(*S*)-**3d**	41	41	(2*R*,4*R*)-**3c**	58	25
(2*R**,4*S**)-**3c**	56	**3a**	<0.1	(*R*)-**3d**	56	55	(2*R*,4*S*)-**3c**	44	24
meso-**5c**	62	**5a**	<0.1	(*R*)-**5b**	62	>99	*meso*-**5c**	38	n.a.
(2*R**,5*R**)-**5c**	47	**5a**	5	(*S*)-**5b**	42	>99	(2*R*,5*R*)-**5c**	53	97
(2*R**,3*R**)-**6c**	46	**6a**	18	(*S*)-**6d**	28	66	(2*R*,3*R*)-**6c**	54	51
(2*R**,3*S**)-**6c**	27	**6a**	<0.1	(*R*)-**6d**	27	31	(2*R*,3*S*)-**6c**	73	8

[a] Based on remaining diol after 48 h conversion time. [b] GC yield; n.a. = not applicable.

(ω-2)-position are accepted, and (ii) in contrast to the reduction mode, a neighboring hydroxy moiety diminishes the enantioselectivity of the first oxidation step.

Regio- and Enantioselective Oxidation of 1,*n*-Alkane Diols

Enantioselective oxidation by biocatalytic hydrogen transfer of diols *rac*-**7c**–**12c** bearing a secondary and primary alcohol moiety showed an exclusive selectivity for the secondary alcohol moiety, while the primary hydroxy group remained unchanged (Scheme 3). This offers a highly selective method to distinguish between primary and secondary alcohols. While *rac*-**7c** turned out to be a nonsubstrate, the other substrates underwent oxidative kinetic resolution. The substrate structure/ enantioselectivity pattern was similar to that of the *sec*,*sec*-diols described above; whereas low *E* values were obtained when the hydroxy moieties are in close proximity (*rac*-**8c**, **9c**, **12c**), good to excellent *E* values were obtained for substrates with distant groups (*rac*-**10c**, **11c**) (Table 3). As a rule of thumb, the minimum requirement for the spacer moiety between both hydroxy groups is at least four to five methylene groups. In general, going in line with internal diols, (*S*) enantiomers are preferentially oxidized. For substrate **12c**, the apparent opposite enantiopreference can be explained by a switch of the CIP priority.



Scheme 3. Regio- and enantioselective oxidation of a *sec*-alcohol moiety in the presence of a primary alcohol by biocatalytic hydrogen transfer.

Table 3. Biocatalytic oxidation of 1,*n*-alkane diols by hydrogen transfer with the use of *Rhodococcus ruber* DSM 44541.

Substrate	Conversion [%]	*ee*[c] [%]	*E*[d]
rac-**7c**	n.c.[a]	n.d.	n.d.
rac-**8c**	9[a]	20 (*R*)	n.d.
rac-**9c**	42[a]	34 (*R*)	4
rac-**10c**	51[b]	99 (*R*)	>200
rac-**11c**	50[b]	90 (*R*)	58
rac-**12c**	21[a]	11 (*S*)	3

[a] After 48 h conversion time. [b] After 24 h conversion time. [c] *ee* of remaining alcohol. [d] Enantioselectivity calculated from conversion and *ee*; n.d. = not determined because of too low conversion; n.c. = no conversion.

Conclusions

Symmetrical and nonsymmetrical diketones can be reduced with high stereopreference, whereby ketone moieties at the (ω-1)-position are reduced faster than those at the (ω-2)-position. Sterically more demanding ketone moieties, for example those at the (ω-3)-position, remained unchanged. For the oxidation mode, differentiation between primary and secondary alcohols is achieved, and the (*S*)-configured secondary alcohols at the (ω-1) and (ω-2)-positions are oxidized preferentially.

Experimental Section

Diketones **1a**–**5a**, as well as diols **5c**, *rac*-**7c**–**12c**, and the precursors (*R*)-ethyl-3-hydroxybutyrate and (*S*)-ethyl-lactate were available commercially either from Sigma–Aldrich–Fluka (Vienna, Austria) or Lancaster (Frankfurt am Main, Germany). The commercial mixture of *meso*-2,5-hexanediol (*meso*-**5c**) and *rac*-2,5-hexanediol [(2*R**,5*R**)-**5c**] was separated by silica gel chromatography (toluene/EtOAc = 1:1). The following *all*-*rac*-diols were obtained by reduction of the corresponding diketone with the appropriate amount of $NaBH_4$ in EtOH as described previously,[8a] and the products were identified by comparison of the NMR data with that from the literature: 2,3-pentanediol **1c**,[15] 2,3-heptanediol **2c**,[16] and 3,4-hexanediol **4c**.[17] Diols (2*R**,3*R**)-**6c** and (2*R**,3*S**)-**6c** were synthesized as described starting from *E*- and *Z*-2-octene, respectively.[18]

Optical rotations were measured on a Perkin–Elmer Polarimeter 341 in a 1 mL cuvette with a 10 cm pathlength. Column chromatography was performed using Merck 60 silica gel (40–63 μM). ^1H and ^{13}C NMR spectra were recorded on a Bruker 360 MHz spectrometer at 360 and 90 MHz, respectively, using TMS as internal standard. THF was freshly distilled before use from sodium/potassium alloy under argon.

Lyophilized cells of *Rhodococcus ruber* DSM 44541 were obtained by cultivating the organism in 250 mL of a complex medium [10 $g l^{-1}$ yeast extract (Oxoid L21), 10 $g l^{-1}$ bacteriological peptone (Oxoid L37), 10 $g l^{-1}$ glucose (Fluka 49150), 2 $g l^{-1}$ NaCl (Roth 9265.1), 0.15 $g l^{-1}$ $MgSO_4 \cdot 7H_2O$ (Fluka 63140), 1.3 $g l^{-1}$ NaH_2PO_4 (Fluka 71496), 4.4 $g l^{-1}$ K_2HPO_4 (Merck 5101), distilled water] in one liter baffled shake flasks at 30 °C at 120 rpm. After three days, the cells were harvested by centrifugation (6000 rpm, 20 min), washed with phosphate buffer (50 mM, pH 7.5), shock frozen in liquid nitrogen, and lyophilized.

General Procedure for Reduction by Biocatalytic Hydrogen Transfer

Lyophilized cells of *R. ruber* (0.25 g) were rehydrated in tris buffer (5 mL, pH = 8, 50 mM) at 130 rpm for 2 h at 30 °C. The substrate (2.1 mmol) and 2-propanol (1 mL, 16.7 mmol) was added, and the mixture was shaken at 30 °C (130 rpm) for 48 h. The products were extracted with EtOAc and analyzed by GC. The solvent was removed, and the products were purified by silica gel chromatography.

General Procedure for Oxidation by Biocatalytic Hydrogen Transfer

Lyophilized cells of *R. ruber* (0.25 g) were rehydrated with tris buffer (5 mL, pH = 8, 50 mM) at 130 rpm for 2 h at 30 °C. The substrate (1.4 mmol) and acetone (1 mL, 17 mmol) was added, and the mixture was shaken at 30 °C (130 rpm) for 24/48 h. The products were extracted with EtOAc and analyzed by GC. The solvent was evaporated under reduced pressure, and the crude products were purified by silica gel chromatography.

(2*R,4*R**)-3c and (2*R**,4*S**)-3c:** A diastereomeric mixture of (2*R**,4*S**)-**3c** and (2*R**,4*R**)-**3c** (86/14) was synthesized as reported.[19] In order to obtain a higher amount of the (2*R**,4*R**)-**3c**

diasteromer, 2,4-octanedione **3a** (1.4 g, 9.8 mmol) was dissolved in EtOH (20 mL, 96%), and Pt/C(160 mg, 5%) was added. The mixture was stirred at 20 °C under H_2 (1 atm, 13 d) until complete conversion. The mixture was filtered, and the solvent evaporated under reduced pressure. Silica gel chromatography afforded 0.59 g (4.0 mmol, 41%) of (2*R**,4*S**)-**3c** and 0.44 g (3 mmol, 30%) of (2*R**,4*R**)-**3c**. (2*R**,4*S**)-**3c**: ^{1}H NMR ($CDCl_3$): δ = 4.06 (m, 1 H), 3.86 (m, 1 H), 3.01 (bs, OH), 2.81 (bs, OH), 1.3–1.58 (m, 8 H), 1.21 (d, J = 6.2 Hz, 3 H), 0.92 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 72.7, 68.8, 44.5, 37.8, 27.5, 24.0, 22.7, 14.0 ppm.

(2*R,4*R**)-3c:** ^{1}H NMR ($CDCl_3$): δ = 4.16 (hex, J = 8.8 Hz, 1 H), 3.94 (m, 1 H), 2.64 (bs, 2OH), 1.60 (t, J = 5.6 Hz, 2 H), 1.3–1.58 (m, 6 H), 1.24 (d, J = 6.3 Hz, 3 H), 0.91 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.2, 65.3, 44.1, 37.1, 28.0, 23.5, 22.7, 14.1 ppm.

5-Hydroxy-2-pentanone (8b): 5-Hexenoic acid (115 mg, 1 mmol) dissolved in dry THF (3 mL) was stirred under nitrogen at –30 °C. Triethylamine (121 mg, 1.2 mmol) and 2-chloroethyl-chloro-formiate (172 mg, 1.2 mmol) in THF (1 mL) were added dropwise. The mixture was stirred at –20 °C for 45 min, then filtered and added to a solution of $NaBH_4$ (42 mg, 1.1 mmol) in THF/H_2O (2 mL, 8:1). This mixture was stirred at 0 °C for 3 h, extracted with EtOAc, and purified by flash chromatography to yield 5 mg (5%) of **8b** as reference material. Compound **8b** was identified by comparison of the ^{1}H NMR spectroscopic data with that from the literature.[20] ^{13}C NMR (90 MHz, $CDCl_3$): δ = 207.1, 61.9, 40.2, 30.5, 24.7 ppm.

The following hydroxy ketones were identified after the biocatalytic reduction of the corresponding diketones by comparison of the NMR spectroscopic data with the literature values: 2-hydroxy-3-heptanone (**2b**),[21] 2-hydroxy-4-octanone (**3b**),[22] 4-hydroxy-3-hexanone (**4b**),[23] 5-hydroxy-2-hexanone (**5b**).[6c]

The following compounds were identified after biocatalytic oxidation of the corresponding diols by comparison of the NMR spectroscopic data with that from the literature: 4-hydroxy-2-octanone (**3d**),[22,24] 3-hydroxy-2-octanone (**6d**),[25] 2,3-octanedione (**6a**),[25] 6-hydroxy-2-hexanone (**9b**),[26] 7-hydroxy-2-heptanone (**10b**),[27] 8-hydroxy-2-octanone (**11b**).[28]

1-Hydroxy-2-octanone (12b): Cetyl pyridiniumchloride (2.0 g, 5.6 mmol) dissolved in 30% H_2O_2 (90 mL) was mixed with 12-tungstophosphoric acid hydrate (5.2 g, 1.8 mmol) in 30% H_2O_2 (28 mL) and stirred at 40 °C for 2 h. The crude product was filtered and washed with water to give peroxotungstophospate (2.2 g, 1.1 mmol, 61%) as a white, waxy solid. Peroxotungstophospate (0.1 g, 0.05 mmol) was dissolved in 30% H_2O_2 (620 mg), and $CHCl_3$ (15 mL) and 1,2-octanediol (0.44 g, 3.0 mmol) was added and heated to reflux for 16 h. The crude product was extracted with EtOAc and purified by silica gel chromatography to yield 55 mg **12b** (0.4 mmol, 13%), which was identified by comparison of the NMR data with the literature data.[29]

Proof of Absolute Configuration: The absolute configuration of the following products was proven by comparison of the optical rotation results with those from the literature (see Supporting Information): **1c**, **2b**, **2c**, **3b**, **4b**, **4c**, **5b**, **5c**, **6d**, **8c**, **9c**, **12c**. The absolute configuration of **3d** was assigned by comparison of the elution order on chiral GC (see Supporting Information).

The absolute configuration of (2*R*,4*S*)-**3c** and (2*R*,4*R*)-**3c** was assigned by independent chemical synthesis of (2*R*,4*R**)-**3c** followed by co-injection with (2*R**,4*R**)-**3c** and (2*R**,4*S**)-**3c**, respectively, on chiral GC. For the synthesis of (2*R*,4*R**)-**3c**, sodium hydride (0.11 g, 4.2 mmol) was added to (*R*)-ethyl-3-hydroxybutyrate (0.55 g, 4.2 mmol) in diethyl ether (20 mL) under nitrogen and stirred for 10 min to deprotonate the hydroxy group. *n*-Butylmagnesium bromide (4.25 mL, 8.5 mmol, 2 M in Et_2O) was added dropwise at 20 °C. The mixture was stirred for 5 h at 20 °C before saturated aqueous NH_4Cl (30 mL) was added, the phases were separated and the organic phase containing (*R*)-2-hydroxy-4-octanone was extracted with diethyl ether, the combined organic layers were dried (Na_2SO_4), and the organic solvent was removed under reduced pressure. Without purification, the crude product was dissolved in diethyl ether (20 mL) and lithium aluminium hydride (70 mg, 1.8 mmol) was added, and the mixture was stirred at 20 °C for 3 h. The reaction was quenched with water, the solution was extracted with EtOAc (3 × 30 mL), the combined organic phase was dried (Na_2SO_4), purified by flash chromatography, and used as reference sample for chiral GC.

The absolute configuration of (2*R*,3*S*)-**6c** and (2*R*,3*R*)-**6c** was assigned by chemical synthesis of (2*S*,3*R**)-**6c** followed by co-injection with (2*R**,3*R**)-**6c** and (2*R**,3*S**)-**6c**, respectively, on chiral GC. The synthesis of (2*S*,3*R**)-**6c** was performed as described above, but by using (*S*)-ethyl-lactate (1 g, 8.5 mmol) and pentylmagnesium bromide, prepared from pentyl bromide (1.2 g, 8.5 mmol) and Mg (0.21 g, 8.5 mmol). After workup, the desired intermediate (*S*)-2-hydroxy-3-octanone was reduced with lithium aluminium hydride as described above. The final product was used as reference sample for chiral GC.

The absolute configuration of (*S*)-**10c** and (*S*)-**11c** was proven by transforming the isolated enantio-enriched diol obtained from the bio-oxidation by chemical methods to the corresponding 2-heptanol/2-octanol, which was then compared by co-injection on chiral GC with racemic and enantiopure 2-heptanol/2-octanol as previously reported.[8a] In a typical procedure, diol **11c** (6 mg, 0.04 mmol) from the bio-oxidation was added to a mixture of pyridine (0.5 mL) and tosyl chloride (7.5 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) and stirred at 20 °C for 5 h. After addition of water, the phases were separated, and the aqueous phase was again extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the organic solvent was removed under reduced pressure. Without further purification, the product was dissolved in THF (3 mL), $LiAlH_4$ (30 mg, 0.8 mmol) was added, and the mixture was stirred at 20 °C for 1 h. After quenching of the reaction by the addition of water, the product was extracted with EtOAc and analyzed by chiral GC.

Supporting Information (see footnote on the first page of this article): Optical rotations, achiral and chiral GC data is available.

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