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Highly diastereoselective synthesis of 2-substituted-1,3-diols catalyzed by ketoreductases

Dimitris Kalaitzakis, Ioulia Smonou *

Department of Chemistry, University of Crete, Heraklio 71003, Crete, Greece

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ABSTRACT

The stereoselective reduction of α-substituted-β-hydroxy ketones for the preparation of the corresponding optically pure 2-monosubstituted or 2-disubstituted-1,3-diols is described. These transformations proceed in high optical purities and yields. Ketoreductases were able to catalyze the formation of either the *syn* or the *anti* diol, depending on the enzyme. By replacing the α-alkyl substituent for an OAc moiety, in low conversion time (≤24 h), ketoreductases catalyzed the formation of the OAc-protected 1,2,3-triol, in high yield and with high optical purity (>99% de, >99% ee). This is a simple and highly stereoselective method for the synthesis of different diastereomers of chiral diols.

1. Introduction

Optically active 1,3-diols are very important compounds in asymmetric synthesis, since they represent chiral building blocks for many polyketide-derived natural products, and have frequently been used as valuable intermediates in the synthesis of drugs and natural products with important biological activity.[1–8] Several synthetic methods have been developed for the stereoselective synthesis of 1,3-diols. In most of them, chiral catalysts or chiral synthons were applied, usually the heavy metal catalysts or the extreme conditions lead to low product yields or low optical purities.[9–26] These methods are frequently not generally applicable for the synthesis of other structurally related compounds, or different diastereomers of the same compound. Therefore, the direct assembly of chiral molecules with all possible 1,3-diol configurations remains virtually unexplored, despite its significant synthetic challenge. Consequently, it is highly demanding to develop synthetic methodologies for the production of 1,3-diol chiral synthons in all possible configurations.

Biocatalytic approaches have led to the synthesis of chiral 1,3-diols using enzymes, such as oxidoreductases, hydrolases, and lyases, either isolated or in the form of whole cells.[9,27–34] In all these examples, the stereoselective formation of 1,3-diols is accomplished through enzymatic reductions or enzymatic resolutions. However, the number of stereoisomers formed is limited, and the substrates, which were used rarely bear a substituent at the 2-carbon. Even in the very limited cases where an α-substituent exists, this substituent is mainly methyl and most importantly the yield is very low due to kinetic resolution.[27,30]

In particular, the synthesis of optically active 1,3-diols can be accomplished through enzymatic stereoselective reduction of 1,3-diketones or β-hydroxy ketones. However, the enzymatic reduction of 1,3-diketones in a single reduction step, rarely leads to 1,3-diols. The major product from this reaction is usually a β-hydroxy ketone, as we and others have recently shown.[28,35–38] These results indicate that β-hydroxy ketones are generally poor substrates for the synthesis of diols catalyzed by dehydrogenases.

2. Results and discussion

Isolated ketoreductases have been proved to be excellent catalysts for the stereoselective synthesis of α-alkyl-β-hydroxy ketones. We have recently demonstrated that a wide range of hydroxy ketones can be accessed by using a variety of ketoreductases. Starting from α-alkyl-1,3-diketones, we achieved the formation of useful chiral synthons, such as α-alkyl-β-hydroxy ketones, in high stereoselectivity and regioselectivity.[38–40] Representative examples are shown in Scheme 1.

* Corresponding author. Tel.: +30 2810 545010; fax: +30 2810 545001; e-mail address: smonou@chemistry.uoc.gr (I. Smonou).

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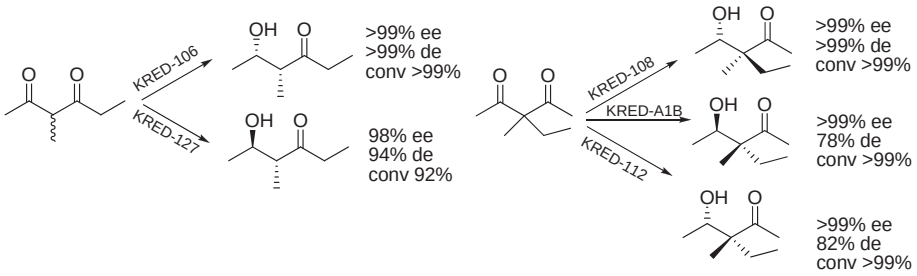


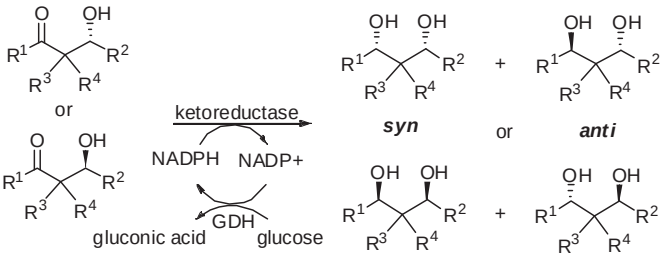
Scheme 1. Enzymatic reduction of 2-substituted and 2-disubstituted-1,3-diketones with NADPH-dependent ketoreductases.

It is possible to prepare single, different diastereomers of the hydroxy ketones by tailoring the choice of enzyme. In addition, the products are frequently formed in high yields. In most of the cases, no diol was observed, whereas in a few cases, it was formed with low optical purity.

Our continuing interest in the preparation of useful optically pure synthons by biocatalytic methods led us to report herein a new methodology that utilizes the enzymatic reduction of optically pure α-substituted-β-hydroxy ketones, for the direct stereoselective synthesis of the corresponding 2-substituted-1,3-diols. We also demonstrate that, under the proper enzyme selection, the stereoisomeric 1,3-diol of choice is formed in high optical purity and high conversion. The general path of this synthetically useful reaction is shown in Scheme 2.

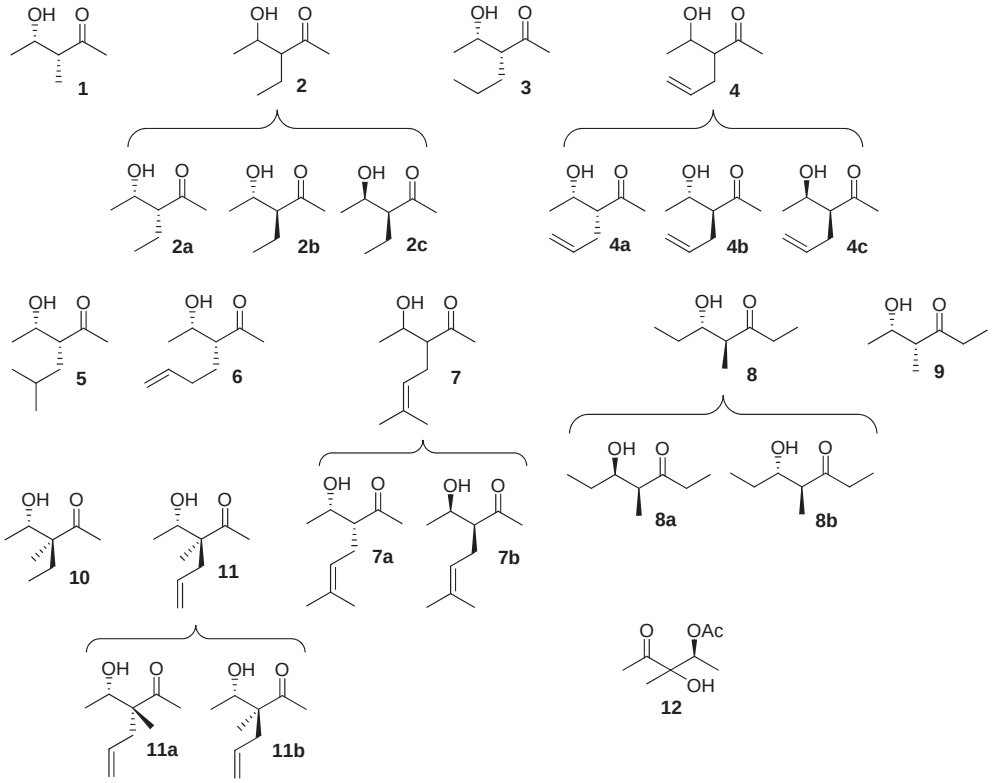
Nine mono-alkyl α-substituted β-hydroxy ketones **1**–**9**, two α-disubstituted β-hydroxy ketones **10**,**11**, and the α-substituted OAc-protected hydroxy ketone **12**, were used as substrates (Scheme 3) for enzymatic reductions. All these optically pure compounds **1**–**11**, were produced by stereoselective reduction of the corresponding 2-substituted-1,3-diketones, utilizing isolated ketoreductases.[38]

The data reported in Table 1 represent the best results obtained after screening thirty-two commercially available ketoreductases.



Scheme 2. Enzymatic reduction of optically pure hydroxy ketones.

As shown in Table 1, for every β-hydroxy ketone tested, a few positive enzymes were found, which were able to catalyze the formation of either the *syn* or *anti* isomer of the corresponding 1,3-diol, in high optical purity, depending on the enzyme. High stereoselectivity in the 1,3-diol formation was achieved even by enzymes that were not highly stereoselective in the first reduction step of the same diketone, as shown previously. The characterization *syn*/*anti* refers to the relative configuration between 1,3-hydroxy groups.



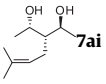
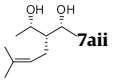
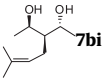
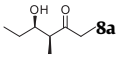
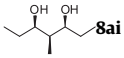
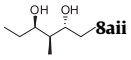
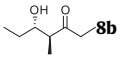
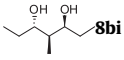
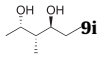
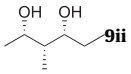
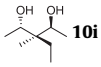
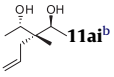
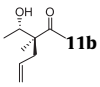
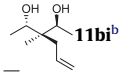
Scheme 3. Optically pure α-substituted-β-hydroxy ketones submitted to enzymatic reduction.

Table 1
Enzyme-catalyzed stereoselective reduction of hydroxy ketones **1**–**11** to 1,3-diols

Substrate	Entry	KRED	Diastereomeric ratio		Conversion	Product
			syn[a]	*anti*[a]		
 **1**	1	101,111	—	>99	>99% (24 h)	 **1i**
	2	112,114,115	—	>99	50–70% (24 h)	
	3	A1B	95	5	>99% (2 h)	 **1ii**
 **2a**	4	101,111,112,114,115	—	>99	90% (24 h)	 **2ai**[b]
	5	A1B	>99	—	95% (24 h)	 **2aii**
 **2b**	6	101	10	90	39% (24 h)	
	7	111,115	—	>99	25–42% (24 h)	
	8	112	5	95	30% (24 h)	
	9	114	2	98	20% (24 h)	 **2bi**[b]
	10	A1B	98	2	>99% (24 h)	 **2bii**
 **2c**	11	101	5	95	53% (24 h)	
	12	111,114,115	—	>99	26–34% (24 h)	
	13	112	4	96	60% (24 h)	 **2ci**
	14	A1B	—	>99	70% (24 h)	
 **3**	15	101	2	98	70% (24 h)	 **3ci**
	16	111	—	>99	10% (24 h)	
	17	112,114,115	—	>99	40–50% (24 h)	
	18	A1B	>99	—	90% (24 h)	 **3cii**
 **4a**	19	101	1	99	90% (24 h)	 **4ai**[b]
	20	111,112,115	—	>99	43–60% (24 h)	
	21	114	3	97	90% (24 h)	
	22	A1B	>99	—	>99% (24 h)	 **4aii**
 **4b**	23	101	4	96	95% (24 h)	 **4bi**[b]
	24	111,114	1	99	>99% (24 h)	
	25	112,115	—	>99	80–90% (24 h)	
	26	A1B	88	12	50% (24 h)	 **4bii**
 **4c**	27	101,114	—	>99	30–45% (24 h)	
	28	111	2	98	10% (24 h)	
	29	112	4	96	65% (24 h)	 **4ci**
	30	115	—	—	<5% (24 h)	
	31	A1B	—	>99	95% (24 h)	
 **5**	32	101	—	>99	15% (24 h)	
	33	111,115	—	—	5% (24 h)	
	34	112	—	>99	35% (24 h)	 **5i**
	35	114	—	>99	60% (24 h)	
	36	A1B	—	—	0% (24 h)	—
 **6**	37	101,111,112	—	>99	98% (24 h)	 **6i**
	38	114	—	>99	38% (24 h)	
	39	115	—	>99	87% (24 h)	
	40	A1B	>99	—	10% (24 h)	 **6ii**

(*continued on next page*)

Table 1 (*continued*)

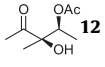
Substrate	Entry	KRED	Diastereomeric ratio		Conversion	Product
			syn[a]	*anti*[a]		
 **7a**	41	101,112	5	95	27–38% (24 h)	 **7ai**
	42	111,114	2	98	10% (24 h)	
	43	115	—	—	<5% (24 h)	
	44	A1B	>99	—	45% (24 h)	 **7aii**
 **7b**	45	101	—	>99	20% (24 h)	 **7bi**
	46	111,112,114,115	—	—	<5% (24 h)	—
	47	A1B	—	—	0% (24 h)	—
 **8a**	48	101,112	>99	—	80–90% (24 h)	 **8ai**
	49	111	>99	—	15% (24 h)	
	50	114,115	—	—	<5% (24 h)	—
	51	A1B	20	80	40% (24 h)	 **8aii**
 **8b**	52	101,115	4	96	33–50% (24 h)	 **8bi**
	53	111	1	99	75% (24 h)	
	54	112,114	—	>99	15–22% (24 h)	
	55	A1B	—	—	0% (24 h)	—
 **9**	56	101,111	—	>99	>99% (24 h)	 **9i**
	57	112,114	—	>99	55–70% (24 h)	
	58	115	—	>99	90% (24 h)	
	59	A1B	98	2	>99% (2 h)	 **9ii**
 **10**	60	101,111,114,115	—	>99	>99% (24 h)	 **10i**
	61	112	—	>99	50% (24 h)	
	62	A1B	—	—	0% (24 h)	—
 **11a**	63	101,111	—	>99	40–52% (24 h)	 **11ai**[b]
	64	112,115	—	>99	25–29% (24 h)	
	65	114	—	>99	>99% (24 h)	
	66	A1B	—	—	0% (24 h)	—
 **11b**	67	101,111,114,115	—	>99	>99% (24 h)	 **11bi**[b]
	68	112	—	>99	65% (24 h)	
	69	A1B	—	—	0% (24 h)	—

[a] The relative configuration between 1,3-hydroxy groups.
[b] Produced diols **2ai** and **2bi** are identical, as well as **4ai** with **4bi** and **11ai** with **11bi**.

The absolute configuration of the products was assigned by analyzing the ^{1}H NMR spectra without any transformation or derivatization, since the absolute configuration of the starting β-hydroxy ketones was already known.[38] Only the product **9i**, derived from the enzymatic reduction of substrate **9**, was converted to its di-MPA ester in order to determine its absolute configuration.

Among all the enzymes screened, KRED-A1B proved to be the most efficient catalyst for the selective formation of the *syn* diol (*meso*-isomers with the exception of compounds **9ii**, entry 59 Table 1, and **12a**, entry 81 Table 2, which are optically active). However, in the cases of substrates **2c**, **4c**, and **8a** KRED-A1B catalyzed the formation of the *anti* isomer (entries 14, 31 and 51, respectively). This result indicates that the selectivity of this enzyme does not depend on the configuration of the hydroxy stereocenter. Speciafically, KRED-A1B always showed high selectivity toward the newly formed stereogenic center with the *R* absolute configuration, regardless of the preexisting *R* or *S* configuration of the OH-stereocenter. This

Table 2
Enzyme-catalyzed stereoselective reduction of (2*S*,3*R*)-2-acetoxy-3-hydroxy-3-methyl-4-pentanone **12**

Substrate	Entry	KRED	Diastereomeric ratio		Conversion
			syn[a] (**12a**)	*anti*[a] (**12b**)	
 **12**	70	101	3	97	>99% (24 h)
	71	102	—	>99	>99% (24 h)
	72	106	—	>99	70% (24 h)
	73	111	8	92	>99% (24 h)
	74	112,113	2	98	>99% (24 h)
	75	114	22	78	>99% (24 h)
	76	115	8	92	90% (24 h)
	77	119	3	97	30% (24 h)
	78	121	20	80	70% (24 h)
	79	123	25	75	46% (24 h)
	80	130,131	—	>99	20–52% (24 h)
	81	A1B	>99	—	>99% (24 h)

[a] The relative configuration between the secondary hydroxy group and the *O*-acetyl group.

result was not a surprise since KRED-A1B has shown anti-Prelog selectivity in our previous studies.[38,40] However, the selectivity of the other positive enzymes was dependent on the hydroxy configuration of the β-hydroxy ketones. When the preexisting hydroxy group was *S*, ketoreductases KRED-101, 111, 112, 114, and 115 showed *S* selectivity, producing the *anti* stereoisomer, whereas in the case of substrates **2c**, **4c**, and **7b**, where the configuration of the already existing hydroxy group was *R*, these enzymes showed *R* selectivity, also producing the *anti* stereoisomer. The only exception to this observation, was recorded in substrate **8a**. Although in this case the preexisting hydroxy group has the *R* configuration, the three positive enzymes for its reduction (KREDs-101, 111, 112), showed *S* selectivity (entries 48 and 49, respectively), producing the *meso* stereoisomer **8ai**.

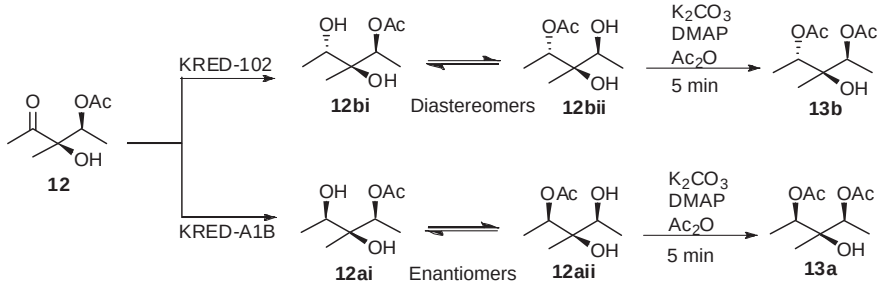
As a general rule, of the 32 enzymes that were screened, only a few of them were able to catalyze the formation of optically pure 1,3-diols, indicating that β-hydroxy ketones are poor substrates for dehydrogenases. Almost every enzyme tested showed lower activity in the reduction of the hydroxy ketone compared to the reduction of the corresponding diketone. The reactivity dependence on absolute stereochemistry was also examined. Most enzymes were either inactive or possessed low activity for the reduction of the hydroxy ketone.

Besides being stereoselective, the positive enzymes showed good to excellent activity. In some cases the reaction was complete in only 2 h (entries 3 and 59), but predominantly, the maximum reaction time was 24 h. In some cases, the activity of enzymes was affected by the structure of the β-hydroxy ketone. For example, KRED-A1B did not catalyze the reduction of disubstituted substrates **10** and **11a**, **11b**. Furthermore, the enzyme activities with substrates **3**, **2b**, **4c**, **5**, and **8b** were relatively low (<75% conversion) with the lowest observed in the case of **7a**, **7b** (entries 41–47).

Quantitative yields of product were obtained in 2 h of reaction time, using 10% (w/w) of enzyme relative to substrate. For example, hydroxy ketone **9** (50 mM, 507 mg) was reduced in larger scale (78 mL) with KRED-101 affording optically pure diol (**9i**) in high isolated yield and optical purities (95% yield, >99% ee). It is important to note here, that this specific product (**9i**) bears three stereogenic centers. In every reaction discussed in this report, the NADPH cofactor was used in catalytic amounts (1% relative to the substrate) and was recycled in situ using glucose dehydrogenase (GDH) and glucose as co-substrate.[41]

Finally, we examined the enzymatic reduction of substrate **12** (Table 2), which has different structure than all the previous substrates utilized in this work. Many of the previously mentioned enzymes (fourteen of them) showed good to excellent activity toward the reduction of compound **12** (Table 2), leading to products with the *anti* relative configuration (refers to the relative configuration between the newly formed hydroxy group and the *O*-acetyl group). The observed *anti* diastereoselectivity was excellent (>97%) in most cases (Table 2). However, KRED-A1B was able to catalyze the formation of the *syn* stereoisomer, in high stereoselectivity (>99%, entry 81) and conversion (>99%).

The diastereomeric ratio of the products *syn*, **12a** or *anti*, **12b** could not be assigned directly from their ^{1}H NMR spectra, as for those in Table 1, because the structure is not symmetrical and bears three stereogenic centers. The ^{1}H NMR spectra, as well as the GC chromatograms of the mixture derived from the reduction of **12** by KRED-102 (entry 71), showed two products. However, reduction of **12** by KRED-A1B led to one product, which was not identical to any of the two previous products derived from KRED-102. This observation was unexpected, because the only possible products from the reduction of **12** should be two. This can be rationalized by the fact that the produced isomer **12bi**, from the reduction catalyzed by KRED-102, is in equilibrium with its diastereomer **12bii**, while the produced isomer **12ai**, from the reaction with KRED-A1B, is in equilibrium with its enantiomer **12aii**, which is not identical to the previous two diastereomers **12bi** and **12bii**. This is clearly illustrated in Scheme 4. Further acetylation of the two secondary hydroxy groups led to the production of only one isomer in both cases, **13a** (*meso*) and **13b** (Scheme 4). This result clarifies the above mentioned equilibria and the absolute configuration of the products.



Scheme 4. Enzymatic reduction of (2*S*,3*R*)-2-acetoxy-3-hydroxy-3-methyl-4-pentanone **12**.

3. Conclusion

In conclusion, we have developed a straightforward enzymatic method for the direct, stereoselective synthesis of 2-monosubstituted or 2-disubstituted-1,3-diols in high optical purity and yield. For this purpose, NADPH-dependent ketoreductases were utilized for the stereoselective reduction of α-substituted-β-hydroxy ketones. By this method either the *syn* or the *anti* diol can be prepared dependent on the enzyme, demonstrating its significance in asymmetric organic synthesis. Furthermore, ketoreductases catalyzed the formation of OAc-protected 1,2,3-triol (**12a** or **12b**) in high yield, high optical purity (>99% de, >99% ee), and low conversion time (≤24 h). All the enzymatic transformations were clean, leading to pure products with the absence of any byproducts. The isolation of the produced diols was accomplished easily and no chromatographic separation was necessary in the case of quantitative reactions.

4. Experimental

4.1. General

Unless otherwise noted, solvents and reagents were reagent grade from commercial suppliers (Sigma–Aldrich) and used without any further purification. The progress of the enzymatic reactions and the selectivities were determined by gas chromatographical analysis of crude EtOAc extracts (for the small scale reactions) and of isolated

products, using HP5890II gas chromatograph equipped with an FID detector; (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated (*R*)-cyclodextrin HP Part No 19091G-8233). ^{1}H and ^{13}C NMR spectra were recorded on 300 and 500 MHz Bruker spectrometers in $CDCl_3$ solutions, by using Me_4Si as an internal standard. Chemical shifts are reported in parts per million downfield from Me_4Si. The enzymes-ketoreductases and glucose dehydrogenase-and NADPH are commercially available (Codexis).

4.2. Enzymatic reduction of hydroxy ketones (small scale)

In every enzymatic reaction the isolated and optically pure α-substituted-β-hydroxy ketone was used as substrate.[38] The second reduction was performed as follows: in a phosphate buffer solution (1 mL, 200 mM, pH 6.9), the α-substituted-β-hydroxy ketones (25 mM), the corresponding ketoreductase (3–5 mg), glucose dehydrogenase (2 mg), NADPH (2 mg), and glucose (18 mg) were added. The reactions were incubated at 37 °C and reaction aliquots were taken at various time points. After extraction with ethyl acetate (3×1 mL), they were analyzed by GC chromatography and ^{1}H NMR spectroscopy.

4.2.1. (2S,4S)-3-Methyl-2,4-pentanediol (diol ***1i****)*[42]. δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.08–4.14 (1H, m, C*H*OH), 3.83–3.89 (1H, m, C*H*OH), 2.81 (2H, br s, OH), 1.54–1.61 (1H, m, CH), 1.24 (3H, d, *J* 6.5, Me), 1.19 (3H, d, *J* 6.5, Me), 0.88 (3H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 71.0, 69.7, 44.5, 22.1, 19.0, 12.2; HRMS (ESI): calcd for $C_6H_{14}O_2$ *m*/*z* (M+H) 119.1072, obsd 119.1064; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.73 min (diol **1i**).

4.2.2. (2S,4R)-3-Methyl-2,4-pentanediol (meso-diol ***1ii****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.08–4.14 (2H, m, 2×C*H*OH), 2.35 (2H, br s, 2×OH), 1.36–1.42 (1H, m, CH), 1.20 (6H, d, *J* 6.5, 2×Me), 0.94 (3H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 72.7, 43.5, 21.5, 3.8; HRMS (ESI): calcd for $C_6H_{14}O_2$ *m*/*z* (M+H) 119.1072, obsd 119.1068; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.43 min (*meso*-diol **1ii**).

4.2.3. (2S,4S)-3-Ethyl-2,4-pentanediol (diol ***2ai****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.21–4.26 (1H, m, C*H*OH), 4.00–4.05 (1H, m, C*H*OH), 2.83 (1H, br s, OH), 2.65 (1H, br s, OH), 1.40–1.49 (1H, m, CH), 1.29–1.37 (1H, m, CH_2), 1.24–1.29 (1H, m, CH_2), 1.27 (3H, d, *J* 6.5, Me), 1.22 (3H, d, *J* 6.5, Me), 0.96 (3H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 69.1, 68.0, 51.0, 22.4, 19.2, 19.0, 12.6; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.1218; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.85 min (diol **2ai**).

4.2.4. (2S,4R)-3-Ethyl-2,4-pentanediol (meso-diol ***2aii****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.09–4.14 (2H, m, 2×C*H*OH), 2.33 (2H, br s, 2×OH), 1.48–1.54 (2H, m, CH_2), 1.23 (6H, d, *J* 6.5, 2×Me), 1.14–1.18 (1H, m, CH), 1.02 (3H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 72.4, 51.4, 21.7, 15.8, 14.5; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.1219; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.50 min (*meso*-diol **2aii**).

4.2.5. (2S,4S)-3-Ethyl-2,4-pentanediol (diol ***2bi****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.21–4.26 (1H, m, C*H*OH), 4.00–4.05 (1H, m, C*H*OH), 2.83 (1H, br s, OH), 2.65 (1H, br s, OH), 1.40–1.49 (1H, m, CH), 1.29–1.37 (1H, m, CH_2), 1.24–1.29 (1H, m, CH_2), 1.27 (3H, d, *J* 6.5, Me), 1.22 (3H, d, *J* 6.5, Me), 0.96 (3H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 69.1, 68.0, 51.0, 22.4, 19.2, 19.0, 12.6; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.1225; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.85 min (diol **2bi**).

4.2.6. (2S,4R)-3-Ethyl-2,4-pentanediol (meso-diol ***2bii****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 3.95–4.02 (2H, m, 2×C*H*OH), 2.91 (2H, br s, 2×OH), 1.38–1.45 (2H, m, CH_2), 1.24–1.30 (1H, m, CH), 1.27 (6H, d, *J* 6.5, 2×Me), 0.86 (3H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 71.0, 52.1, 22.2, 17.1, 15.1; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.1223; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.85 min (diol **2bii**).

4.2.7. (2R,4R)-3-Ethyl-2,4-pentanediol (diol ***2ci****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.21–4.26 (1H, m, C*H*OH), 4.00–4.05 (1H, m, C*H*OH), 2.83 (1H, br s, OH), 2.65 (1H, br s, OH), 1.40–1.49 (1H, m, CH), 1.29–1.37 (1H, m, CH_2), 1.24–1.29 (1H, m, CH_2), 1.27 (3H, d, *J* 6.5, Me), 1.22 (3H, d, *J* 6.5, Me), 0.96 (3H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 69.1, 68.0, 51.0, 22.4, 19.2, 19.0, 12.6; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.1215; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.85 min (diol **2ci**).

4.2.8. (2S,4S)-3-Propyl-2,4-pentanediol (diol ***3ci****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.19–4.25 (1H, m, C*H*OH), 3.96–4.03 (1H, m, C*H*OH), 2.81 (1H, br s, OH), 2.61 (1H, br s, OH), 1.23–1.45 (5H, m, C*H*CH_2CH_2), 1.27 (3H, d, *J* 6.5, Me), 1.21 (3H, d, *J* 6.5, Me), 0.92 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 69.5, 68.2, 49.0, 28.5, 22.4, 21.2, 19.3, 14.4; HRMS (ESI) calcd for $C_8H_{18}O_2$ *m*/*z* (M+H) 147.1385, obsd 147.1380; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.85 min (diol **3ci**).

4.2.9. (2S,4R)-3-Propyl-2,4-pentanediol (meso-diol ***3cii****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.09–4.15 (2H, m, 2×C*H*OH), 2.34 (2H, br s, 2×OH), 1.37–1.46 (5H, m, C*H*CH_2CH_2), 1.22 (6H, d, *J* 6.5, 2×Me), 0.94 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 72.6, 49.2, 24.4, 23.6, 21.7, 14.6; HRMS (ESI) calcd for $C_8H_{18}O_2$ *m*/*z* (M+H) 147.1385, obsd 147.1376; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.62 min (*meso*-diol **2ci**).

4.2.10. (2S,4S)-3-Allyl-2,4-pentanediol (diol ***4ai****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.77–5.86 (1H, m, C*H*=CH_2), 5.02–5.11 (2H, m, CH=CH_2), 4.23–4.28 (1H, m, C*H*OH), 4.01–4.06 (1H, m, C*H*OH), 2.90 (1H, br s, OH), 2.57 (1H, br s, OH), 2.21–2.28 (1H, m, CH_2), 2.08–2.14 (1H, m, CH_2), 1.44–1.48 (1H, m, CH), 1.28 (3H, d, *J* 6.5, Me), 1.22 (3H, d, *J* 6.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 137.4, 116.3, 69.1, 67.7, 48.8, 30.8, 22.1, 19.4; HRMS (ESI) calcd for $C_8H_{16}O_2$ *m*/*z* (M+H) 145.1229, obsd 145.1219; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.82 min (diol **4ai**).

4.2.11. (2S,4R)-3-Allyl-2,4-pentanediol (meso-diol ***4aii****).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.92–6.00 (1H, m, C*H*=CH_2), 4.97–5.12 (2H, m, CH=CH_2), 4.01–4.17 (2H, m, 2×C*H*OH), 2.81 (2H, br s, 2×OH), 2.28–2.36 (2H, m, CH_2), 1.39–1.44 (1H, m, CH), 1.25 (6H, d, *J* 6.5, 2×Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 139.9, 115.2, 72.2, 49.2, 26.7, 21.8; HRMS (ESI) calcd for $C_8H_{16}O_2$ *m*/*z* (M+H) 145.1229, obsd 145.1221; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20%

permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.69 min (*meso*-diol **4aii**).

*4.2.12. (2S,4S)-3-Allyl-2,4-pentanediol (diol **4bi**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.76–5.86 (1H, m, C*H*=CH_2), 5.02–5.11 (2H, m, CH=CH_2), 4.23–4.28 (1H, m, C*H*OH), 4.01–4.06 (1H, m, C*H*OH), 2.97 (1H, br s, OH), 2.67 (1H, br s, OH), 2.21–2.28 (1H, m, CH_2), 2.07–2.14 (1H, m, CH_2), 1.43–1.49 (1H, m, CH), 1.27 (3H, d, *J* 6.5, Me), 1.22 (3H, d, *J* 6.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 137.4, 116.3, 69.1, 67.7, 48.8, 30.8, 22.1, 19.4; HRMS (ESI) calcd for $C_8H_{16}O_2$ *m*/*z* (M+H) 145.1229, obsd 145.1216; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.82 min (diol **4bi**).

*4.2.13. (2S,4R)-3-Allyl-2,4-pentanediol (meso-diol **4bii**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.68–5.80 (1H, m, C*H*=CH_2), 5.02–5.12 (2H, m, CH=CH_2), 3.93–4.01 (2H, m, 2×C*H*OH), 2.81 (2H, br s, 2×OH), 2.15–2.22 (2H, m, CH_2), 1.44–1.50 (1H, m, CH), 1.28 (6H, d, *J* 6.5, 2×Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 135.5, 116.8, 70.9, 50.9, 33.0, 22.3; HRMS (ESI) calcd for $C_8H_{16}O_2$ *m*/*z* (M+H) 145.1229, obsd 145.1218; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.10 min (*meso*-diol **4bii**).

*4.2.14. (2R,4R)-3-Allyl-2,4-pentanediol (diol **4ci**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.76–5.86 (1H, m, C*H*=CH_2), 5.02–5.11 (2H, m, CH=CH_2), 4.23–4.29 (1H, m, C*H*OH), 4.00–4.07 (1H, m, C*H*OH), 2.87 (1H, br s, OH), 2.53 (1H, br s, OH), 2.21–2.28 (1H, m, CH_2), 2.07–2.14 (1H, m, CH_2), 1.43–1.49 (1H, m, CH), 1.27 (3H, d, *J* 6.5, Me), 1.22 (3H, d, *J* 6.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 137.4, 116.3, 69.1, 67.7, 48.8, 30.8, 22.1, 19.4; HRMS (ESI) calcd for $C_8H_{16}O_2$ *m*/*z* (M+H) 145.1229, obsd 145.1221; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.79 min (diol **4ci**).

*4.2.15. (2S,4S)-3-(3-Butenyl)-2,4-pentanediol (diol **6i**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.76–5.84 (1H, m, C*H*=CH_2), 4.95–5.05 (2H, m, CH=CH_2), 4.22–4.27 (1H, m, C*H*OH), 3.99–4.04 (1H, m, C*H*OH), 2.88 (1H, br s, OH), 2.69 (1H, br s, OH), 2.12–2.20 (1H, m, CH_2CH=CH_2), 2.02–2.10 (1H, m, CH_2CH=CH_2), 1.47–1.55 (1H, m, CH), 1.33–1.44 (2H, m, CHCH_2CH_2), 1.28 (3H, d, *J* 6.5, Me), 1.21 (3H, d, *J* 6.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 138.5, 114.9, 69.2, 67.9, 48.3, 32.0, 25.2, 22.3, 19.4; HRMS (ESI) calcd for $C_9H_{18}O_2$ *m*/*z* (M+H) 159.1385, obsd 159.1378; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=8.01 min (diol **6i**).

*4.2.16. (2S,4R)-3-(3-Methyl-2-butenyl)-2,4-pentanediol (meso-diol **7aii**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.18–5.23 (1H, m, C*H*=C$(CH_3)_2$), 4.08–4.14 (2H, m, 2×C*H*OH), 2.20–2.26 (2H, m, CH_2), 1.69 (3H, s, Me), 1.67 (3H, s, Me), 1.33–1.38 (1H, m, CH), 1.23 (6H, d, *J* 6.5, 2×Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 129.0, 120.0, 72.1, 50.3, 25.8, 21.8, 21.0, 17.8; HRMS (ESI) calcd for $C_{10}H_{20}O_2$ *m*/*z* (M+H) 173.1542, obsd 173.1538; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=8.79 min (*meso*-diol **7aii**).

*4.2.17. (3R,5S)-4-Methyl-3,5-heptanediol (meso-diol **8ai**)*[43]. δ_H (500 MHz; $CDCl_3$; Me_4Si): 3.73–3.79 (2H, m, 2×C*H*OH), 2.63 (2H, br s, 2×OH), 1.41–1.61 (5H, m, 2×CH_3CH_2, C*H*), 0.93 (6H, t, *J* 7.5, 2×Me), 0.88 (3H, d, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 78.9, 39.3, 28.1, 10.4, 3.9; HRMS (ESI) calcd for $C_8H_{18}O_2$ *m*/*z* (M+H) 147.1385, obsd 147.1377; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.72 min (*meso*-diol **8ai**).

*4.2.18. (3S,5S)-4-Methyl-3,5-heptanediol (diol **8bi**)*[43]. δ_H (500 MHz; $CDCl_3$; Me_4Si): 3.82–3.87 (1H, m, C*H*OH), 3.55–3.60 (1H, m, C*H*OH), 2.52 (1H, br s, OH), 2.42 (1H, br s, OH), 1.39–1.66 (5H, m, 2×CH_3CH_2, C*H*), 0.97 (3H, t, *J* 7.0, Me), 0.96 (3H, t, *J* 7.0, Me), 0.95 (3H, d, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 77.5, 74.1, 40.2, 28.2, 26.9, 11.3, 10.7, 10.0; HRMS (ESI) calcd for $C_8H_{18}O_2$ *m*/*z* (M+H) 147.1385, obsd 147.1380; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.55 min (diol **8bi**).

*4.2.19. (2S,3R,4S)-3-Methyl-2,4-hexanediol (diol **9i**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.09–4.17 (1H, m, C*H*OH), 3.55–3.63 (1H, m, C*H*OH), 2.84 (1H, br s, OH), 2.72 (1H, br s, OH), 1.48–1.66 (3H, m, CH_3CH_2, C*H*), 1.18 (3H, d, *J* 7.0, Me), 0.96 (3H, t, *J* 7.5, Me), 0.91 (3H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 76.7, 69.2, 41.9, 28.1, 19.5, 11.9, 9.8; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.0758; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.35 min (diol **9i**).

*4.2.20. (2S,3R,4R)-3-Methyl-2,4-hexanediol (diol **9ii**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.06–4.13 (1H, m, C*H*OH), 3.75–3.80 (1H, m, C*H*OH), 2.55 (1H, br s, OH), 2.40 (1H, br s, OH), 1.41–1.60 (3H, m, CH_3CH_2, C*H*), 1.20 (3H, d, *J* 6.5, Me), 0.93 (3H, t, *J* 7.5, Me), 0.91 (3H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 78.7, 72.9, 41.4, 28.2, 21.5, 10.4, 3.8; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m*/*z* (M+H) 133.1229, obsd 133.1220; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=6.83 min (diol **9ii**).

*4.2.21. (2S,4S)-3-Ethyl-3-methyl-2,4-pentanediol (diol **10i**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 3.95–3.99 (1H, m, C*H*OH), 3.90–3.94 (1H, m, C*H*OH), 3.02 (1H, br s, OH), 2.97 (1H, br s, OH), 1.59–1.66 (2H, m, C$H_2$$CH_3$), 1.18 (3H, d, *J* 6.5, Me), 1.16 (3H, d, *J* 6.5, Me), 0.88 (3H, t, *J* 7.5, CH_2CH_3), 0.80 (3H, s, CCH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si): 73.0, 72.4, 41.9, 24.5, 18.2, 17.7, 17.6, 7.6; HRMS (ESI) calcd for $C_8H_{18}O_2$ *m*/*z* (M+H) 147.1385, obsd 147.1378; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.15 min (diol **10i**).

*4.2.22. (2S,4S)-3-Allyl-3-methyl-2,4-pentanediol (diol **11ai**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.87–5.96 (1H, m, C*H*=CH_2), 5.08–5.16 (2H, m, CH=CH_2), 3.94–4.00 (1H, m, C*H*OH), 3.85–3.92 (1H, m, C*H*OH), 3.16 (1H, br s, OH), 2.74 (1H, br s, OH), 2.41–2.47 (1H, m, CH_2), 1.92–1.98 (1H, m, CH_2), 1.21 (3H, d, *J* 6.5, Me), 1.17 (3H, d, *J* 6.5, Me), 0.82 (3H, s, CCH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si): 134.9, 117.7, 73.0, 72.6, 42.7, 36.9, 19.1, 17.5, 17.4; HRMS (ESI) calcd for $C_9H_{18}O_2$ *m*/*z* (M+H) 159.1385, obsd 159.1377; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.89 min (diol **11ai**).

*4.2.23. (2S,4S)-3-Allyl-3-methyl-2,4-pentanediol (diol **11bi**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.86–5.95 (1H, m, C*H*=CH_2), 5.07–5.15 (2H, m, CH=CH_2), 3.94–3.99 (1H, m, C*H*OH), 3.85–3.90 (1H, m, C*H*OH), 3.28 (1H, br s, OH), 2.91 (1H, br s, OH), 2.40–2.46 (1H, m, CH_2), 1.91–1.96 (1H, m, CH_2), 1.20 (3H, d, *J* 6.5, Me), 1.17 (3H, d, *J* 6.5, Me), 0.82 (3H, s, CCH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si): 134.9, 117.7, 73.0, 72.6, 42.7, 36.9,

19.1, 17.5, 17.4; HRMS (ESI) calcd for $C_9H_{18}O_2$ *m/z* (M+H) 159.1385, obsd 159.1379; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.87 min (diol **11bi**).

*4.2.24. Reduction of (2S,3R)-2-acetoxy-3-hydroxy-3-methyl-4-pentanone **12** catalyzed by KRED-102 (diol **12bi** in equilibrium with **12bii**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.10 (1H, q, *J* 6.5, C*H*OAc), 5.00 (1H, q, *J* 6.5, C*H*OAc), 3.61–3.67 (1H, m, C*H*OH), 3.55–3.61 (1H, m, C*H*OH), 2.11 (3H, s, COMe), 2.09 (3H, s, COMe), 1.26 (3H, d, *J* 6.0, Me), 1.25 (3H, d, *J* 6.0, Me), 1.21 (3H, d, *J* 6.5, Me), 1.16 (3H, d, *J* 6.5, Me), 1.14 (3H, s, CC*H*$_3$), 1.06 (3H, s, CC*H*$_3$); HRMS (ESI) calcd for $C_8H_{16}O_4$ *m/z* (M+H) 178.1205, obsd 178.1195; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=8.76 min (diol **12bi**), t_R=9.26 min (diol **12bii**).

*4.2.25. Reduction of (2S,3R)-2-acetoxy-3-hydroxy-3-methyl-4-pentanone **12** catalyzed by KRED-A1B (diol **12ai** in equilibrium with **12aii**).* δ_H (500 MHz; $CDCl_3$; Me_4Si): 5.05 (1H, q, *J* 6.5, C*H*OAc), 3.72–3.78 (H, m, C*H*OH), 2.08 (3H, s, COMe), 1.25 (3H, d, *J* 6.5, Me), 1.14 (3H, d, *J* 6.5, Me), 1.08 (3H, s, CC*H*$_3$); HRMS (ESI) calcd for $C_8H_{16}O_4$ *m/z* (M+H) 178.1205, obsd 178.1199; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=9.71 min (diol **12ai** and **12aii**).

4.3. Acetylation of diols 12ai, 12aii and 12bi, 12bii

In EtOAc (5 mL) were added the product from the enzymatic reduction of keto alcohol **12** catalyzed by KRED-102 or by KRED-A1B (7 mg, 0.04 mmol), small quantities of K_2CO_3 (0.06 mmol, 8 mg), Ac_2O (0.1 mmol, 10 μL), and DMAP (cat.) and the mixture was stirred at 0 °C for 10 min. After the completion of the reaction, water (5 mL) was added to the mixture and the aquatic phase was extracted with EtOAC (2×5 mL). The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to dryness (8 mg, 90%).

*4.3.1. (2S,4S)-2,4-Diacetoxy-3-methyl-3-pentanol **13b**.* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.97 (1H, q, *J* 6.5, C*H*OAc), 4.92 (1H, q, *J* 6.5, C*H*OAc), 3.04 (1H, s, OH), 2.05 (3H, s, COMe), 2.02 (3H, s, COMe), 1.25 (3H, d, *J* 6.5, Me), 1.24 (3H, d, *J* 6.5, Me), 1.14 (3H, s, CC*H*$_3$); δ_C (75 MHz; $CDCl_3$; Me_4Si): 170.3, 170.2, 74.8, 72.0, 71.5, 21.1, 21.0, 17.3, 14.2, 14.0; HRMS (ESI) calcd for $C_{10}H_{18}O_5$ *m/z* (M+H) 219.1233, obsd 219.1227; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=9.73 min (**13b**).

*4.3.2. (2R,4S)-2,4-Diacetoxy-3-methyl-3-pentanol meso-**13a**.* δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.98 (2H, q, *J* 6.5, 2×C*H*OAc), 3.03 (1H, s, OH), 2.10 (6H, s, 2×COMe), 1.20 (6H, d, *J* 6.5, 2×Me), 1.11 (3H, s, CC*H*$_3$); δ_C (75 MHz; $CDCl_3$; Me_4Si): 170.8, 75.8, 73.0, 21.3, 17.3, 14.8; HRMS (ESI) calcd for $C_{10}H_{18}O_5$ *m/z* (M+H) 219.1233, obsd 219.1225; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=9.82 min (**13a**).

4.4. Preparation of MPA-diester of (2*S*,3*R*,4*S*)-3-methyl-2,4-hexanediol

To a solution of the corresponding diol (0.1 mmol, 13 mg) in dry CH_2Cl_2 (2 mL) were added 2.2 equiv of DCC (0.22 mmol, 46 mg) and 2.2 equiv of the corresponding (*R*) or (*S*) MPA-ester (0.22 mmol, 36 mg), catalytic amount of DMAP and the reaction mixture was stirred at 0 °C for 6 h and at rt for 12 h. After completion of the reaction the produced urea was filtered, the filtrate was evaporated, and then chromatographed with 5/1 (v/v), Hex/EtOAc producing the corresponding MPA-diester (38 mg, 90% isolated yield).

4.4.1. (R,R)-MPA-diester of (2S,3R,4S)-3-methyl-2,4-hexanediol. δ_H (500 MHz; $CDCl_3$; Me_4Si): 7.28–7.45 (10H, m, 2×CHC_6H_5), 5.04–5.09 (1H, m, CHO_2C), 4.77–4.82 (1H, m, CHO_2C), 4.76 (1H, s, C*H*OMe), 4.75 (1H, s, C*H*OMe), 3.45 (3H, s, OMe), 3.44 (3H, s, OMe), 1.72–1.79 (1H, m, C*H*CH$_3$), 1.44–1.53 (1H, m, CH_2), 1.25–1.38 (1H, m, CH_2), 1.02 (3H, d, *J* 6.0, CH_3CHO$_2$C), 0.83 (3H, d, *J* 7.0, CH_3CH), 0.43 (3H, t, *J* 7.5, CH_3CH$_2$).

4.4.2. (S,S)-MPA-diester of (2S,3R,4S)-3-methyl-2,4-hexanediol. δ_H (500 MHz; $CDCl_3$; Me_4Si): 7.29–7.42 (10H, m, 2×CHC_6H_5), 4.67–4.72 (1H, m, CHO_2C), 4.69 (1H, s, C*H*OMe), 4.66 (1H, s, C*H*OMe), 4.45–4.50 (1H, m, CHO_2C), 3.40 (3H, s, OMe), 3.39 (3H, s, OMe), 1.59–1.65 (1H, m, C*H*CH$_3$), 1.23–1.32 (2H, m, CH_2), 1.09 (3H, d, *J* 6.0, CH_3CHO$_2$C), 0.64 (3H, t, *J* 7.5, CH_3CH$_2$), 0.55 (3H, d, *J* 7.0, CH_3CH).

4.5. Enzymatic synthesis of (2*S*,3*R*,4*S*)-3-methyl-2,4-hexanediol (diol 9i) in larger scale

In a phosphate buffer solution (78 mL, 200 mM, pH 6.9) were added (4*R*,5*S*)-5-hydroxy-4-methyl-3-hexanone (**9**) (50 mM, 3.9 mmol, 507 mg), ketoreductase KRED-101 (50 mg), glucose (120 mM, 1.68 g), NADPH (0.5 mM, 0.039 mmol, 34 mg), glucose dehydrogenase (15 mg) and the mixture was stirred at 25 °C. Periodically the pH was readjusted to 6.9 with NaOH (2 M). After the completion of the reaction, the product was isolated by extracting the crude reaction mixture with EtOAc (80 mL×3). The combined organic layers were then dried over $MgSO_4$ and evaporated to dryness to give the corresponding diol (**9i**). Isolated yield 95%, 489 mg.

δ_H (500 MHz; $CDCl_3$; Me_4Si): 4.09–4.17 (1H, m, C*H*OH), 3.55–3.63 (1H, m, C*H*OH), 2.84 (1H, br s, OH), 2.72 (1H, br s, OH), 1.48–1.66 (3H, m, CH$_3$CH_2, C*H*), 1.18 (3H, d, *J* 7.0, Me), 0.96 (3H, t, *J* 7.5, Me), 0.91 (3H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$; Me_4Si): 76.7, 69.2, 41.9, 28.1, 19.5, 11.9, 9.8; HRMS (ESI) calcd for $C_7H_{16}O_2$ *m/z* (M+H) 133.1229, obsd 133.0758; GC data: (column: 30 m×0.25 mm×0.25 μm chiral capillary column, 20% permethylated cyclodextrin 120 °C for 3 min, rate: 10 °C/min, final temp: 210 °C; carrier gas: N_2, press 70 kPa). t_R=7.35 min (diol **9i**).

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Supplementary data

Supplementary data provide the ^{1}H NMR spectra of all the compounds. Supplementary data associated with this article can be found in online version at 10.1016/j.tet.2010.09.096. These data include MOL files and InChIKeys of the most important compounds described in this article.

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