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Direct asymmetric α-hydroxylation of 2-hydroxymethyl ketones

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Abstract—A direct α-hydroxylation of racemic 2-hydroxymethyl ketones with the Sharpless epoxidation catalyst resulted in α,β-dihydroxy ketones in high ee (up to 97%) and in moderate to good isolated yield (up to 58%).

1. Introduction

Chiral α-hydroxy compounds are widely represented among biologically active natural products.[1–4] Some of those oxygenated compounds have found important applications only recently (monosaccharide carba-analogues,[5] components for anti-viral medicines[6] etc.). Therefore, elaboration of new efficient methods for the synthesis of chiral α-hydroxy ketones in a non-racemic form is of importance.

An attractive route to enantiomerically enriched α-hydroxy ketones is a direct asymmetric oxidation of the parent carbonyl compounds. A non-asymmetric version of α-hydroxylation of ketones (as their enolates) is well known.[7,8] The asymmetric generation of α-hydroxy ketones has been achieved by the chiral auxiliary method, using a chiral organic or organometallic auxiliary which is bound to the ketone group[9] and by the use of enantiomerically pure oxaziridines as oxidizing reagents.[10–12] In efforts to extend the scope of the asymmetric dihydroxylation method, Sharpless and co-workers found that enol ethers are excellent substrates for dihydroxylation, giving rise to α-hydroxy ketones with high enantiomeric purity.[13,14] The asymmetric generation of α-hydroxy ketones has also been achieved by oxidation of silyl enol ethers and ketene acetals using (salen)manganese(III)-complexes together with mild oxidants (NaOCl, *N*-oxides or iodosylbenzene).[15–17] Recently, some metal-free asymmetric oxidation methods were reported where the optically active α-hydroxy ketones have been prepared with moderate to high enantioselectivity by the oxidation of silyl enol ethers with in situ generated chiral dioxirane.[18,19]

We have previously reported that the Sharpless titanium complex can oxidise cyclobutanones into the corresponding lactones in moderate to good stereoselectivity.[20,21] Also, β-hydroxyketones[22] and 3-alkyl-cyclopentane-1,2-diones[23] oxidise readily with the same complex giving rise to different enantiomeric α-hydroxy and ring cleavage oxidation products with excellent enantioselectivity. In the present study we have investigated in detail the use of the Sharpless titanium–tartrate catalyst for the direct oxidation of racemic cyclic and acyclic α-hydroxymethyl ketones.

2. Results and discussion

2.1. Asymmetric α-hydroxylation of 2-hydroxymethyl ketones

When oxidizing cyclobutanones via a Baeyer–Villiger reaction with the Sharpless epoxidation catalyst we found that α-hydroxymethyl cyclobutanone was the most readily oxidised substrate.[20] The oxidation of α-hydroxymethyl cyclopentanone **1a** under the same oxidation conditions, however, afforded α,β-dihydroxy cyclopentanone **2a** in high enantiomeric purity.[22] That preliminary result encouraged us to investigate the oxidation of α-hydroxymethyl alkanones in more detail.

To establish the scope of the reaction, optimal reaction conditions and the product profile a set of different β-hydroxy ketones **1** was subjected to oxidation with the Sharpless complex under various conditions (Table 1).

First we found that the oxidation conditions that were optimal for Baeyer–Villiger reaction (cyclobutanone lactonisation) gave hydroxy ketones **2a** and **2b** in low yield (entries 1 and 8). Use of prolonged reaction time caused only a slight increase in the yield of the product. Also, a slight improvement in yield was observed when the quantity of the catalyst was increased (entries 3 and 4).

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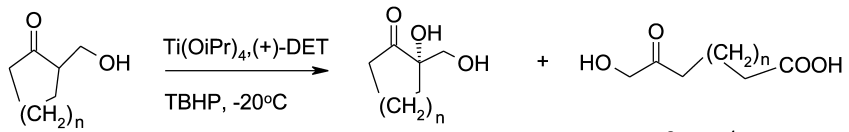
Table 1. Oxidation of cyclic 2-hydroxymethyl ketones under various conditions



1a n=1
1b n=2
1c open chain ketone
4-hydroxy-3-methyl-2-butanone

2a n=1
2b n=2
2c 3,4-dihydroxy-3-methyl-2-butanone

3a n=1
3b n=2

Entry	Ketone	$Ti(OiPr)_4$/DET/TBHP ratio (compared to the substrate)	Time (h)	Hydroxyketone **2**			Acid **3** yield (%)	Recovered **1**		
				Yield (%)	$[\alpha]_D$[a]	ee[b] (%)		Yield (%)	$[\alpha]_D$[c]	ee[d] (%)
1	**1b**	1.5/1.8/1.5	46	20	+101	86	5	54	0	
2	**1b**	1.5/1.8/1.5[e]	46	15	+94		4	56	0	
3	**1b**	1.5/1.8/1.5	160	24	+95		8	35	0	0
4	**1b**	2/2.4/1.5	46	24	+105	87	7	35	0	
5	**1b**	3/3.6/3	46	15	+96	85	9	37	0	
6	**1b**	2.3/2.8/1.15	46	55	+101	86	8	15	0	
7	**1b**	3/3.6/1.2	46	58	+101	86	8	3		
8	**1a**	1.5/1.8/1.5	48	11	+53	75	9	56	+21	10
9	**1a**	2.4/2.9/1.2	46	32	+81	97	12	33	+40	24
10	**1a**	3/3.6/1.2	46	37	+79	97	12	23	+32	21
11	**1c**	3/3.6/1.2	46	29	−10	95	–	49	+5	15
12	**1c**	3/3.6/1.2	92	47	−10	93	–	30	+10	29
13	**1c**	3/3.6/1.2	168	54	−10	91	–	21	+13	35

[a] Measured in 96% ethanol.
[b] Determined using *R*-(−)-α-methoxyphenylacetic acid mono esters of the primary alchols by HPLC (**12a**, **12c**) and by NMR spectroscopy (**12b**) (Scheme 3).
[c] Measured in CH_2Cl_2.
[d] Determined by HPLC from the *R*-(−)-α-methoxyphenylacetic acid esters.
[e] (+)-DIPT (diisopropyl tartrate) was used instead of (+)-DET.

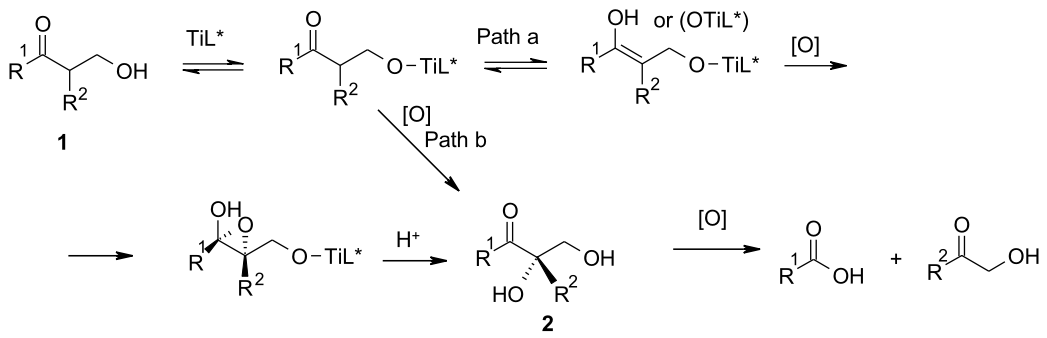
Nevertheless, in all cases a considerable amount of the substrate remained unreacted. Addition of more oxidant to the system (larger excess of tBuOOH (TBHP)) diminished the yield (entry 5). The reaction rate just accelerated when the amount of the oxidant was decreased (entries 6 and 7). The best yield was obtained with a ratio of the substrate/$Ti(OiPr)_4$/(+)-diethyl tartrate (DET)/TBHP 1/3/3.6/1.2 (entry 7).

Reaction conditions had little or no effect on the enantioselectivity. On the other hand, the selectivity of α-hydroxylation depended considerably on the substrate. The highest ee value was obtained in the case of cyclopentanone **1a** (entries 9 and 10), while the oxidation of cyclohexanone derivative **1b** proceeded with slightly lower enantioselectivity. The same tendency has also been observed in the epoxidation of allylic alcohols in the case of cyclohexenols.[24] Analogously to the oxidation of cyclobutanones,[20] the use of (+)-DIPT instead of (+)-DET effected the oxidation in a similar way diminishing both the product yield and enantioselectivity. Thus, cyclohexanone **1b** was oxidised with (+)-DIPT to a lower extent than with (+)-DET resulting in a lower yield of hydroxyketone **2b** under identical reaction conditions (entry 2; compare with entry 1). The α-hydroxylation reaction was accompanied by the formation of a certain amount of achiral ketoacids **3**. As can be seen from Table 1, entry 5 an excess of TBHP diminishes the yield of ketone diol **2b**. At the same time, any substantial increase in the amount of the oxidative cleavage product **3b** was not observed.

Oxidation of the α-branched aliphatic α-hydroxymethyl ketone **1c** also results in the corresponding hydroxyketone **2c** with high enantioselectivity (entries 11–13). A finding that open chain ketones which have much more flexible structure than the cyclic compounds are also oxidised under the same reaction conditions in high enantioselectivity is quite remarkable. Such a result hints at the possibility of formation of a *cis*-enolate similar to the corresponding enolates of the cyclic substrates.

Longer reaction times resulted in a higher chemical yield of the product with a slight decrease in the enantiomeric purity of the α-hydroxyketone (entries 12 and 13). The ee of the unreacted starting ketone **1c** also increased steadily in time. The total sum of the recovered and transformed product slightly decreases with prolonged reaction time (78% versus 75%). This result indicates that formation of a certain amount of the other by-products (~22–25%) occurs and these were not isolated from the reaction mixture.

An attractive model for rationalizing a possible mechanism of α-hydroxylation can be drawn by assuming that the reaction proceeds in a similar fashion to the Sharpless asymmetric epoxidation via an allylic intermediate, which forms from the substrates under the influence of the titanium–tartrate complex (Scheme 1, path a). It is very likely the case when cyclohexanone ketone **1b** is used as a substrate. Indeed, the recovered starting compound did not reveal optical activity (entries 1–6) hinting at the possible formation of an allylic enolate from the racemic starting ketone prior to oxidation (continuous in situ racemization of the substrate). In that case the reaction is directed by the enantioface selection of the achiral substrate by the chiral



Scheme 1. Possible mechanistic pathways for the asymmetric oxidation of β-hydroxy ketones.

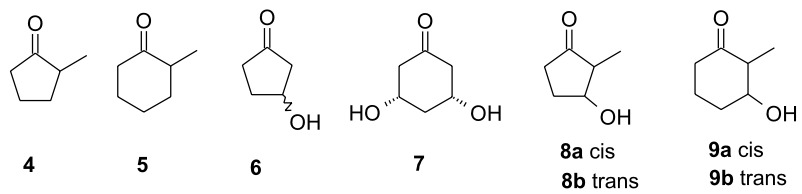


Figure 1. Unreactive substrates under the Sharpless oxidation conditions.

complex rather than by the kinetic resolution. In the case of the substrates **1a** and **1c** the recovered starting ketone revealed optical activity. The ee of the recovered substrate depends on the reaction time (which is characteristic of a kinetic resolution, entries 8, 9 and 11–13). However, the determined enantiomeric purity of the recovered starting compound was at least two times less than expected from the reaction selectivity ($s \approx 140$; estimated from the enantiomeric purity 95% ee of the product at 50% conversion). The result may be explained by assuming that enantioselection also exists in the enolate formation step. It means that the ketone/enolate equilibrium should be shifted towards the ketone, reducing the influence of the kinetic resolution. The other option may be the following: the enolate formation is not taking place prior to oxidation (path b) and the complexation with the ketone oxygen occurs without enol formation or the enolate is formed enantioselectively from one enantiomer only.

The presence of the β-hydroxy group and branching of the substrate at the α-position are essential to achieve α-hydroxylation. Thus, α-branched ketones such as 2-methylcyclopentanone **4** and 2-methylcyclohexanone **5** (Fig. 1) were not oxidised under the ordinary reaction conditions.

Our attempts to extend the scope of the asymmetric α-hydroxylation to other β-hydroxy-substituted cyclic carbonyl compounds (Fig. 1, compounds **6**–**9**) failed—these compounds did not oxidise under the usual oxidation conditions (the relative stereochemistry of the substrates **8** and **9** did not influence the result: both diastereomers were inactive).

The α-hydroxy cyclopentanone **10** (Scheme 2) undergoes non-asymmetric oxidation and was completely converted (no starting ketone left) to the achiral oxidative cleavage product **11** (isolated in 63% yield) under the usual oxidation conditions.

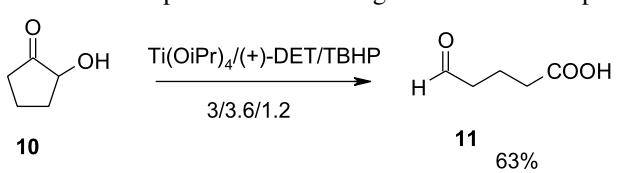
2.2. Determination of the enantiomeric excess and the absolute configuration of the products

The enantiomeric purity of the α,β-dihydroxy ketones was determined by HPLC from the diastereomeric ratio of their mono-*R*-(−)-α-methoxyphenylacetic acid esters (Scheme 3). The obtained ratio was confirmed by the ^{1}H and ^{13}C NMR data and was used as a measure of ee of the diols.

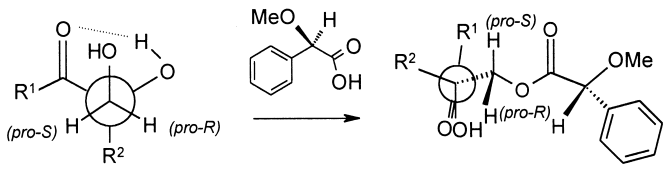
2.2.1. NMR spectra of *R*-(−)-α-methoxyphenylacetic acid esters. The ^{1}H and ^{13}C NMR spectra of the diastereomeric mono-*R*-(−)-α-methoxyphenylacetic acid primary alcohol esters of diols **2a**–**c** differ considerably from each other—nearly all ^{1}H and ^{13}C nuclei give different chemical shifts for the corresponding atoms (Section 4). These differences can in principle be used for the assignment of absolute configuration of the parent chiral alcohols. That method is generally accepted for the determination of absolute configurations of secondary alcohols.[25,26]

For chiral primary alcohols the differences that are caused by the anisotropy effects of phenyl ring are usually too small to be observed and, therefore, 9-anthrylmethoxyacetic acid as a more powerful source of aromatic shielding effects has been usually introduced.[27]

In the present case the phenyl ring induced differences are still remarkable and the largest effect is observed on the protons α-to the carbonyl group. In all major diastereoisomers of compounds **12** these signals are shifted up to



Scheme 2. Titanium–tartrate catalysed oxidation of 2-hydroxycyclopentanone.



2a $R^1 = R^2 =$ $-(CH_2)_3-$
2b $R^1 = R^2 =$ $-(CH_2)_4-$
2c $R^1 = R^2 =$ $-CH_3$

12a $R^1 = R^2 =$ $-(CH_2)_3-$
12b $R^1 = R^2 =$ $-(CH_2)_4-$
12c $R^1 = R^2 =$ $-CH_3$

Scheme 3. *R*-Methoxyphenylacetic acid monoesters of ketodiols **2**.

0.37 ppm towards higher field. Despite a large number of bonds between the phenyl ring and the above-mentioned protons we made an attempt to explain the observed differences on the basis of the widely accepted model of preferred conformation of α-methoxyphenylacetic acid ester. According to that model the ether and carbonyl oxygen atoms and the carbinol hydrogen atoms should be in a coplanar conformation. The preferred conformation of the remaining part of the molecules was assigned by using calculations according to Merck MM, AM1, PM3 and ab initio HF/6-31G* methods[28] using **2c** as a model compound. All these calculations suggest that the most stable conformation is such where the carbonyl and 3-hydroxyl oxygen atoms are nearly eclipsed, and the terminal hydroxyl group is *trans*-oriented to the 3-methyl group. Only that conformation where the *pro-S* carbinol H_a hydrogen–carbon bond (see Scheme 3) is coplanar with the CO bond results in a remarkable anisotropy effects of the phenyl ring on the alcohol part of the molecule. These effects depend on the absolute configuration of alcohol. From that model we can suggest the 3*S* configuration of the stereogenic centre because that configuration should give larger shielding effect on α-protons. This result is in accordance with the absolute configuration predicted by the Sharpless oxidation face selection rule.

3. Conclusions

The proposed novel α-hydroxylation method provides a valuable way to obtain important enantiomeric 2,3-keto-diols, that are frequently found in the structural units of several biologically active natural products. The method produces chiral α,β-dihydroxy ketones in a straightforward manner from cyclic and acyclic β-hydroxy ketones with high enantioselectivity (86–97% ee) and in satisfactory isolated yield (37–58%). However, the method is limited to α-hydroxymethyl substituted ketones.

4. Experimental

^1H and ^{13}C NMR spectra were determined in $CDCl_3$ solution on a Bruker AMX-500 spectrometer. Residual ^1H signal from of $CDCl_3$ (δ 7.27 ppm) was used for ^1H and δ 77.0 ppm for ^{13}C as internal references. IR spectra were recorded on a Hitachi 270-30 Infrared Spectrophotometer. Mass spectra were measured on a Hitachi M80B spectrometer using EI (70 eV) and CI (isobutane) mode. Optical rotations were obtained using a Polamat A polarimeter or a Krüss Optronic GmbH Polarimeter P 3002. TLC was performed using DC-Alufolien Kieselgel 60 F_{254} (Merck). Merck Silica gel 60 (0.063–0.200 mm) or Chemapol silica gel L 40/100 was used for column chromatography. HPLC was performed on a LKB liquid chromatograph equipped with a UV spectrometric detector (2158 Uvicord SD, 254 nm) and a column Waters Spherisorb 3 μm Silica (4.6×100 mm). All reactions that were sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Commercial reagents were generally used as received. CH_2Cl_2 was distilled from CaH_2 and stored over 3 Å molecular sieve pellets. THF and ether were distilled from $LiAlH_4$ before use. Petroleum ether (40–65) was distilled before use as the chromatography solvent.

The substrates **1a** and **1b** were prepared according to the reported procedure[29] (from commercially available ethyl 2-oxocyclopentanecarboxylate and from methyl 2-oxo-cyclohexanecarboxylate[30] respectively); **1c**, **4** and **5** were purchased from Aldrich. Compound **6** was made from 1,3-cyclopentanediol by Jones mono-oxidation; compound **7** was made from *cis*,*cis*-1,3,5-cyclohexanetriol (Aldrich) by protecting it with phenyl boronic acid followed by Jones oxidation and deprotection; compound **8** was made from 2-methylcyclopentane-1,3-dione by convering it to ethyleneglycol diacetal, followed by selective deprotection of one of the protecting groups and reduction with $NaBH_4$; *cis*- and *trans*-isomers were separated on silica gel, deprotected and used in the subsequent oxidation separately; compound **9** was prepared and the diastereomers separated analogously to compound **8**.

4.1. General procedure for the asymmetric oxidation of α-hydroxymethyl ketones

To a solution of $Ti(OiPr)_4$ (0.89 mL, 3 mmol) in CH_2Cl_2 (6 mL), (+)-DET (0.6 mL, 3.6 mmol) was added at −20°C and the mixture was stirred for 15 min. After addition of a substrate (1 mmol) in CH_2Cl_2 (2 mL) the mixture was stirred for 30 min. Then TBHP (0.35 mL, 1.2 mmol, 3.4 M solution in toluene) was added and the mixture was kept at −20°C for 46 h. The reaction was quenched by stirring with a solution of citric acid monohydrate (630 mg, 3 mmol in a mixture of 10% acetone in ether, 30 mL) at room temperature for 1 h. The reaction mixture was filtered through a path of Celite, the Celite layer was washed with acetone and methanol. The solutes were concentrated and the residue was purified on silica gel.

4.1.1. 2-Hydroxy-2-hydroxymethyl-cyclopentanone (2a) and 6-hydroxy-5-oxohexanoic acid (3a). Cyclopentanone **1a** was oxidised according to the general procedure and

purified by column chromatography (petroleum ether/acetone 10/2–10/5) affording the compounds **2a** (48 mg, 37%) and **3a** (18 mg, 12%). **2a**: colourless oil; R_f (petroleum ether/acetone 10/4) 0.16; ee 97%; $[\alpha]_D^{19}=+79$ (*c* 3.02, ethanol); ν_{max} (liquid film) 3370, 2960, 2880, 1740, 1455, 1400, 1165, 1060 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.67 (1H d, J=11.9 Hz, CH_2OH), 3.62 (1H d, J=11.9 Hz, CH_2OH), 3.18 (1H bs, O*H*); 2.38 (2H t, J=8.1 Hz, 5-H), 2.07 (2H m, 3-H), 1.93 (1H m, 4-H), 1.87 (1H m, 4-H); δ_C (125 MHz, $CDCl_3$) 219.55 (C-1), 78.78 (C-2), 64.95 (CH_2OH), 35.29 (C-5), 32.43 (C-3), 17.23 (C-4); *m/z* (EI) 130 (1.1, M^+), 112 (9.7, $[M-H_2O]^+$), 100 (6.3), 84 (25.8), 74 (89.6), 56 (100%); HRMS (EI): M^+, found 130.0669. $C_6H_{10}O_3$ requires 130.0629; $(M-H_2O)^+$, found 112.0538. $C_6H_8O_2$ requires 112.0524. **3a**: white solid, mp 45–46°C; R_f (petroleum ether/acetone 10/4) 0.11; δ_H (500 MHz, $CDCl_3$) 4.27 (2H s, 6-H), 2.53 (2H t, J=7.1 Hz, 4-H), 2.43 (2H t, J=7.1 Hz, 2-H), 1.98 (2H quin, J=7.1 Hz, 3-H); δ_C (125 MHz, $CDCl_3$) 208.90 (C-5), 178.19 (C-1), 68.03 (C-6), 36.99 (C-4), 32.72 (C-2), 18.30 (C-3); *m/z* (CI) 147 (100, MH^+); *m/z* (EI) 129 (3.2, $[M-OH]^+$), 115 (74.9), 97 (7.1), 87 (72.9%); HRMS (EI): $[M-OH]^+$, found 129.0554. $C_6H_9O_3$ requires 129.0551.

4.1.2. 2-Hydroxy-2-hydroxymethyl-cyclohexanone (2b) and 7-hydroxy-6-oxoheptanoic acid (3b). Cyclohexanone **1b** was oxidised according to the general procedure and purified by column chromatography (petroleum ether/acetone 10/3–10/5) affording the compounds **2b** (84 mg, 58%) and **3b** (13 mg, 8%). **2b**: colourless oil; R_f (petroleum ether/acetone 10/4) 0.26; ee: 86%; $[\alpha]_D^{19}=+101$ (*c* 4.76, ethanol); ν_{max} (liquid film) 3420, 2950, 2870, 1718, 1458, 1248, 1122, 1050 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.31 (1H bs, OH), 3.96 (1H d, J=11.7 Hz, 7-H), 3.66 (1H d, J=11.7 Hz, 7-H), 2.77 (1H bs, OH), 2.55–2.53 (2H m, 6-H), 2.16 (1H m, 3-H_e), 2.09 (1H m, 5-H_e), 1.81 (1H m, 4-H_e), 1.68 (1H m, 5-H_a), 1.67 (1H m, 4-H_a), 1.60 (1H m, 3-H_a); δ_C (125 MHz, $CDCl_3$) 212.59 (C-1), 80.01 (C-2), 66.71 (C-7), 38.27 (C-6), 37.40 (C-3), 27.70 (C-5), 22.38 (C-4); *m/z* (EI) 144 (4.5, M^+), 126 (12.5, $[M-H_2O]^+$), 114 (47.3), 100 (20.4), 85 (100), 67 (48.8%); HRMS (EI): M^+, found 144.0831. $C_7H_{12}O_3$ requires 144.0785; $(M-H_2O)^+$, found 126.0677. $C_7H_{10}O_2$ requires 126.0680. **3b**: white solid; mp 97–98°C; R_f (petroleum ether/acetone 10/4) 0.12; δ_H (500 MHz, $CDCl_3$) 4.26 (2H s, 7-H), 2.46 (2H t, J=7.1 Hz, 5-H), 2.40 (2H t, J=7.1 Hz, 2-H), 1.72 (2H m, 4-H), 1.68 (2H m, 3-H); δ_C (125 MHz, $CDCl_3$) 209.19 (C-6), 178.04 (C-1), 68.07 (C-7), 37.89 (C-5), 33.39 (C-2), 24.05 (C-3), 22.85 (C-4); *m/z* (CI) 161 (27, MH^+), *m/z* (EI) 160 (0.1, M^+), 143 (1.1, $[M-OH]^+$), 129 (36.2), 111 (29.5), 101 (32.5%); HRMS (EI): $[M-OH]^+$, found 143.0718. $C_7H_{11}O_3$ requires 143.0707.

4.1.3. 3,4-Dihydroxy-3-methyl-2-butanone (2c). 4-Hydroxy-3-methyl-2-butanone **1c** was oxidised according to the general procedure and purified by column chromatography (petroleum ether/acetone 10/3) affording **2c** (64 mg, 54%) as a colourless oil; R_f (petroleum ether/acetone 10/3) 0.19; ee 91%; $[\alpha]_D^{20}=-10$ (*c* 4.12, ethanol); $[\alpha]_D^{20}=+4$ (*c* 4.20, CH_2Cl_2); ν_{max} (liquid film) 3420, 2980, 2940, 2880, 1710, 1452, 1360, 1125, 1045 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.85 (1H d, J=11.7 Hz, 4-H); 3.64 (1H d, J=11.7 Hz, 4-H); 2.28 (3H s, 1-H), 1.29 (3H s, 3-CH_3); δ_C (125 MHz, $CDCl_3$) 210.96 (C-2), 79.82 (C-3), 67.78 (C-4), 23.82 (C-1), 21.20 (3-CH_3); *m/z* (CI) 119 (41, MH^+); *m/z* (EI) 88 (16.8, $[M-H_2CO]^+$), 75 (100), 57 (98.5), 43 (58.4%); HRMS (EI): $[M-H_2CO]^+$, found 88.0516. $C_4H_8O_2$ requires 88.0524.

4.1.4. 5-Oxopentanoic acid (11). Cyclopentanone **10** was oxidised according to the general procedure and purified by column chromatography (petroleum ether/acetone 10/2) affording the compound **11** (73 mg, 63%) as a colourless oil; R_f (petroleum ether/acetone 10/3) 0.22; ν_{max} (liquid film) 3100, 2950, 2730, 1720, 1415, 1245, 1165, 1078 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.77 (1H d, J=0.9 Hz, 5-H), 2.56 (2H td, J=7.3, 0.9 Hz, 4-H), 2.42 (2H t, J=7.3 Hz, 2-H), 1.95 (2H quin, J=7.3 Hz, 3-H); δ_C (125 MHz, $CDCl_3$) 201.58 (C-5), 179.10 (C-1), 42.66 (C-4), 32.79 (C-2), 16.89 (C-3); *m/z* (CI) 117 (100, MH^+); *m/z* (EI)115 (0.3, $[M-H]^+$), 98 (5.4), 88 (18.3), 60 (100%); HRMS (EI): $[M-H]^+$, found 115.0382. $C_5H_7O_3$ requires 115.0394.

4.2. Preparation of primary (*R*)-(−)-α-methoxyphenyl-acetic acid mono esters

*Preparation of compounds (**12**).* To a mixture of (*R*)-(−)-MPA (21.6 mg, 0.13 mmol) and DCC (26.8 mg, 0.13 mmol) in dry THF (0.6 mL) α,β-dihydroxyketone (0.1 mmol) in THF (0.5 mL) and DMAP (6.7 mg) were added. After stirring at rt for 2.5 h the mixture was diluted with ether (5 mL) and water (1 mL) was added. Then additional amount of ether (25 mL) was added and the mixture was washed with 1 M HCl solution, with saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel (petroleum ether/EtOAc 10/3) gave the primary *R*-MPA mono-esters of the corresponding dihydroxy ketone.

4.2.1. Compound 12a major isomer. δ_H (500 MHz, $CDCl_3$) 7.41–7.35 (5H m, Ph), 4.77 (1H s, C*H*OCH_3), 4.32 (1H d, J=11.5 Hz, 6-H), 4.08 (1H d, J=11.5 Hz, 6-H), 3.42 (3H s, OCH_3), 2.27–2.25 (2H m, 5-H), 1.94 (1H m, 4-H), 1.89–1.87 (2H m, 3-H), 1.73 (1H m, 4-H); δ_C (125 MHz, $CDCl_3$) 216.41 (C-1), 170.45 (COO), 135.82 (*s*-Ph), 128.87 (*p*-Ph), 128.64 (*m*-Ph), 127.18 (*o*-Ph), 82.28 (CHO), 77.34 (C-2), 66.18 (C-6), 57.42 (OCH_3), 34.95 (C-5), 32.84 (C-3), 16.91 (C-4); HPLC (hexane/*i*-PrOH 97/3, flow rate 0.7 mL/min) t_R 10.09 min.

4.2.2. Compound 12a minor isomer. δ_H (500 MHz, $CDCl_3$) 7.41–7.35 (5H m, Ph), 4.79 (1H s, C*H*OCH_3), 4.34 (1H d, J=11.6 Hz, 6-H), 4.06 (1H d, J=11.6 Hz, 6-H), 3.40 (3H s, OCH_3), 2.35 (1H m, 5-H), 2.31 (1H m, 5-H), 1.96 (1H m, 4-H), 1.89–1.87 (2H m, 3-H), 1.71 (1H m, 4-H); δ_C (125 MHz, $CDCl_3$) 216.44 (C-1), 170.54 (COO), 135.89 (*s*-Ph), 128.88 (*p*-Ph), 128.68 (*m*-Ph), 127.17 (*o*-Ph), 82.19 (CHO), 77.67 (C-2), 66.29 (C-6), 57.41 (OCH_3), 34.73 (C-5), 32.86 (C-3), 16.89 (C-4); HPLC (hexane/*i*-PrOH 97/3, flow rate 0.7 mL/min) t_R 10.54 min.

4.2.3. Compound 12b major isomer. δ_H (500 MHz, $CDCl_3$) 7.37 (2H m, *o*-Ph), 7.36 (2H m, *m*-Ph), 7.34 (1H m, *p*-Ph), 4.76 (1H s, C*H*OCH_3), 4.57 (1H d, J=11.7 Hz, 7-H), 4.18 (1H d, J=11.7 Hz, 7-H), 4.09 (1H s, OH), 3.40 (3H s, OCH_3), 2.31 (1H m, 6-H), 2.17 (1H m, 6-H), 2.13 (1H

m, 3-H), 2.02 (1H m, 5-H), 1.77 (1H m, 4-H), 1.62 (1H m, 4-H), 1.60 (1H m, 3-H), 1.58 (1H m, 5-H); δ_C (125 MHz, $CDCl_3$) δ 210.23 (C-1), 170.51 (COO), 135.87 (*s*-Ph), 128.78 (*p*-Ph), 128.61 (*m*-Ph), 127.01 (*o*-Ph), 82.01 (CHO), 77.88 (C-2), 68.39 (C-7), 57.38 (OCH_3), 38.20 (C-3), 37.89 (C-6), 27.58 (C-5), 22.52 (C-4).

4.2.4. Compound 12b minor isomer. δ_H (500 MHz, $CDCl_3$) 7.41 (2H m, *o*-Ph), 7.37 (2H m, *m*-Ph), 7.35 (1H m, *p*-Ph), 4.76 (1H s, C*H*OCH_3), 4.60 (1H d, J=11.7 Hz, 7-H), 4.16 (1H d, J=11.7 Hz, 7-H), 3.93 (1H s, OH), 3.38 (3H s, OCH_3), 2.54 (2H m, 6-H), 2.13 (1H m, 3-H), 2.09 (1H m, 5-H), 1.77 (1H m, 4-H), 1.64 (1H m, 4-H), 1.64 (1H m, 5-H), 1.61 (1H m, 3-H); δ_C (125 MHz, $CDCl_3$) δ 210.52 (C-1), 170.51 (COO), 135.81 (*s*-Ph), 128.88 (*p*-Ph), 128.65 (*m*-Ph), 127.12 (*o*-Ph), 82.01 (CHO), 77.95 (C-2), 68.18 (C-7), 57.31 (OCH_3), 37.84 (C-3), 38.23 (C-6), 27.52 (C-5), 22.42 (C-4).

4.2.5. Compound 12c major isomer. δ_H (500 MHz, $CDCl_3$) 7.41–7.33 (5H m, Ph); 4.75 (1H s, C*H*OCH_3), 4.34 (1H d, J=11.7 Hz, 4-H), 4.17 (1H d, J=11.7 Hz, 4-H), 3.92 (1H s, OH), 3.40 (3H s, OCH_3), 1.86 (3H s, 1-H), 1.27 (3H s, 3-CH_3); δ_C (125 MHz, $CDCl_3$) 208.76 (C-2), 170.23 (COO); 135.98 (*s*-Ph), 128.89 (*p*-Ph), 128.69 (*m*-Ph), 127.09 (*o*-Ph), 82.09 (CHO), 77.59 (C-3), 68.95 (C-4), 57.38 (OCH_3), 23.45 (C-1), 21.65 (3-CH_3). HPLC (hexane/*i*-PrOH 97/3, flow rate 0.7 mL/min) t_R 10.15 min.

4.2.6. Compound 12c minor isomer. δ_H (500 MHz, $CDCl_3$) 7.41–7.33 (5H m, Ph); 4.75 (1H s, C*H*OCH_3), 4.32 (1H d, J=11.7 Hz, 4-H), 4.22 (1H d, J=11.7 Hz, 4-H), 3.65 (1H s, OH), 3.39 (3H s, OCH_3), 2.13 (3H s, 1-H), 1.29 (3H s, 3-CH_3); δ_C (125 MHz, $CDCl_3$) 209.16 (C-2), 170.31 (COO); 135.87 (*s*-Ph), 128.92 (*p*-Ph), 128.69 (*m*-Ph), 127.09 (*o*-Ph), 82.33 (CHO), 77.76 (C-3), 68.79 (C-4), 57.35 (OCH_3), 24.02 (C-1), 21.50 (3-CH_3). HPLC (hexane/*i*-PrOH 97/3, flow rate 0.7 mL/min) t_R 9.71 min.

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