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Asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones. Part 1: 3-Hydroxylation of 3-alkyl-1,2-cyclopentanediones

Anne Paju,[a] Tõnis Kanger,[a] Tõnis Pehk,[b] Aleksander-Mati Müürisepp[a] and Margus Lopp[a,*]

[a]*Department of Chemistry, Faculty of Natural Sciences, Tallinn Technical University, Ehitajate tee 5, Tallinn 19086, Estonia*
[b]*National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, Tallinn 12618, Estonia*

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Abstract—3-Alkyl-1,2-cyclopentanediones undergo asymmetric 3-hydroxylation with the Sharpless Ti-complex resulting in enantiomeric 3-hydroxy carbonyl compounds with ee up to 95% in yields of 22–40%. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Chiral α-hydroxy carbonyl compounds are widely spread among natural products (sugars, α-hydroxy acids, etc.). Some analogues of those oxygenated compounds have interesting biological properties and are used in a number of medical preparations (e.g. monosaccharide carba-analogues as components for anti-viral medicines,[1–10] hydroxycyclopentenones as anti-cancer drugs,[11] etc.)

An attractive route to enantiomerically enriched α-hydroxy ketones is the direct asymmetric oxidation of the parent carbonyl compounds. A non-asymmetric version of α-hydroxylation of ketones (as their Ti-enolates using *tert*-BuOOH) is known in the literature.[12] The asymmetric α-hydroxylation of ketones has been achieved by the oxidation of enol ethers and/or enolates using (salen)manganese(III)-complexes together with mild oxidants (NaOCl, *N*-oxides or iodosylbenzene)[13–15] enantiomerically pure oxaziridines[16–18] and dioxiranes.[19,20] Sharpless and co-workers found that enol ethers are excellent substrates for dihydroxylation, giving rise to α-hydroxy ketones with high enantiomeric purity.[21,22]

We have previously reported that the Sharpless catalyst system ($Ti(OiPr)_4$/diethyl tartrate (DET)/*tert*-BuOOH (TBHP))[23] oxidizes cyclobutanones to afford the corresponding lactones with moderate to good stereoselectivity (asymmetric Baeyer–Villiger oxidation)[24,25] and hydroxylates 2-hydroxymethyl ketones (asymmetric α-hydroxylation) to yield α,β-dihydroxy ketones with high enantiomeric purity.[26,27]

Recently, we found that the Sharpless complex also oxidizes different cyclic 3-alkyl-1,2-diones at the position adjacent to the 2-carbonyl group, resulting in 3-hydroxylated products with excellent enantioselectivity.[28] In this study, the results from a detailed investigation of 3-hydroxylation of the cyclic 3-alkyl-1,2-diones **1a**–**e** are presented.[†]

2. Results and discussion

2.1. Substrates

Cyclopentane-1,2-diones are readily available compounds. We obtained the substrates 3-methylcyclopentane-1,2-dione **1a** and 3-ethylcyclopentane-1,2-dione **1b** from Aldrich.

The synthesis of substrates **1c**–**e** is straightforward, from 2-cyclopentene-1-acetic acid **2** by converting the double bond into a 1,2-diol followed by mild oxidation to give the dione functionality. The sequence of reactions is presented in Scheme 1.

The cyclohexane derivatives **1f**[29]and **1g**[30] were synthesized according to the known procedures. Compound **1h** was purchased from Aldrich.

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[*] Corresponding author. E-mail: lopp@chemnet.ee

[†] The ring-cleavage reaction will be discussed in a separate paper.

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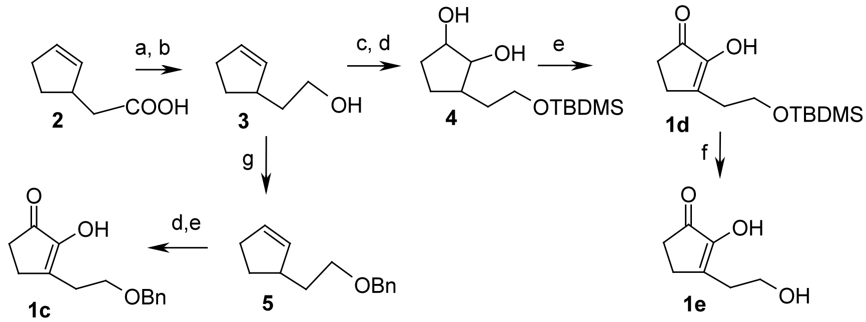


Scheme 1. Synthesis of cyclopentanediones **1c**–**e**. *Reagents and conditions*: (a) MeOH, HCl, 24 h, rt; (b) $LiAlH_4$, 0°C, 1 h, 84% from **2**; (c) TBDMSCl, imidazole, DMF, 20 h, rt, 87%; (d) $KMnO_4$, NaOH, *t*BuOH, 20 min, 0°C, 67%; (e) $(ClCO)_2$, DMSO, CH_2Cl_2, Et_3N, −60°C, 1 h, 48%; (f) HCl/H_2O, THF, 88%; (g) BnCl, NaH, DMF, overnight, rt, 86%.

2.2. 3-Hydroxylation of 3-methyl-1,2-cyclopentanedione

The 3-hydroxylation reaction was investigated in detail, using 3-methyl-1,2-cyclopentanedione **1a** as a model compound. The formation of two major types of oxidation product was observed: The 3-hydroxylation products **6** and **7** and ring cleaved 3-hydroxylated products, derivatives of the diacid **8**[28] (Scheme 2).

The 3-hydroxylation products exist in the reaction mixture in different forms (as free hydroxy diones **6** and/or as acetals **7**), depending on the conditions used for the reaction quench and the work-up procedure. When, in the case of **1a**, the reaction was completed by quenching with methanol, the 3-hydroxylated product appeared in the form of acetal **7a** (a single diastereomer). After purification on silica gel a certain amount of the enol **6a** was always formed. We found that methyl acetal **7a** undergoes reacetalization in isopropanol, resulting in the crystalline isopropyl acetal **9a**. Acetal **9a** hydrolyses in water to the relatively stable hydrate **10a**. Under anhydrous conditions (e.g. chromatography on silica gel), acetals **7a** and **9a** form 3-hydroxy-1,2-diketone **6a** (enol form) (Scheme 3).

It is well known that asymmetric oxidation by the Sharpless complex is sensitive to the reagent/substrate ratio.[31] In order to find the optimal conditions for predominant formation of the 3-hydroxylation products we investigated the oxidation of the model compound at different reagent compositions. The results are presented in Table 1.

Table 1. 3-Hydroxylation of 3-methyl-1,2-cyclopentanedione **1a** at different Sharpless complex compositions[a]

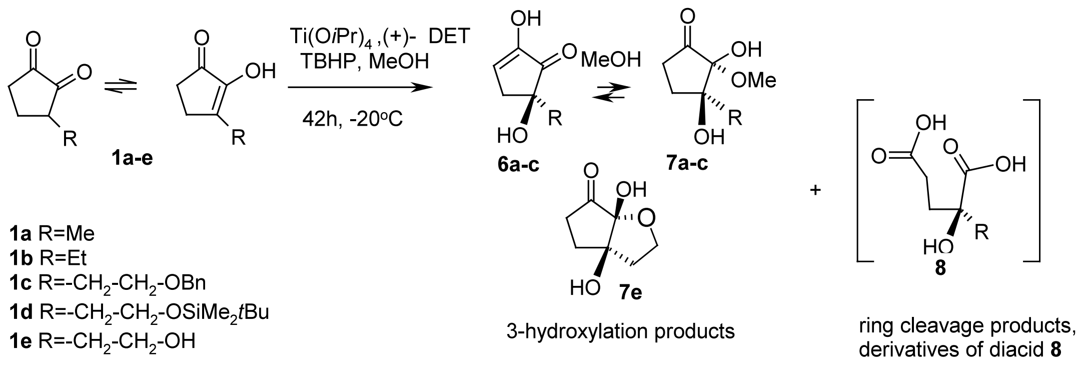
No.	Molar ratio $Ti(OiPr)_4$/(+)-DET/TBHP	Yield **6a** (%)[b]	Ee (%)[c]
1	0.5/1.0/1.5	28	94.7
2	0.8/1.6/1.5	37	95.5
3	1.0/1.5/1.2	37	94.8
4	1.0/1.6/1.5	40	94.3
5	1.5/1.8/1.5	37	92.4
6	2/2.4/1.5	32	89.6
7	2/2.4/2	30	88.8
8	3/3.6/2	25	87.7

[a] Temp.: −20°C, reaction time: 42 h.

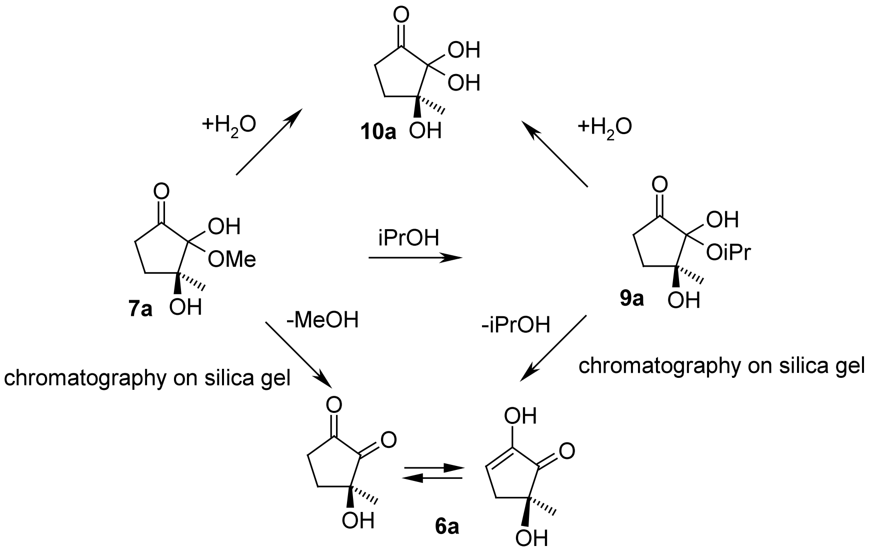
[b] Isolated yields after column chromatography.

[c] Determined by HPLC on chiral column (Daicel Chiralcel ODH) from the corresponding isopropyl acetals **9a** (a single diastereomer, de 100%; the relative configuration established by NMR).

As can be seen from Table 1, the 3-hydroxylation reaction does not require an excess of the catalyst. The best enantioselectivity was observed when 0.8–1.5 equiv. of Ti (based on the substrate) were used at the Ti/DET ratio from 1:1.2 to 1:2.0 (entries 2–5). The optimal ratio is similar to that used in the Sharpless oxidation of allylic alcohols[31] and lower than that used in α-hydroxylation of 2-hydroxymethyl ketones.[26,27] The highest isolated yield (40%) of 3-hydroxylation product was obtained at the ratio of $Ti(OiPr)_4$/(+)-DET/TBHP 1/1.6/1.5. The oxidation of other substrates was performed at this reagent composition. Higher Ti/substrate ratios lead to a reduction in both



Scheme 2. Asymmetric 3-hydroxylation of 3-alkyl-1,2-cyclopentanediones **1a**–**e**.



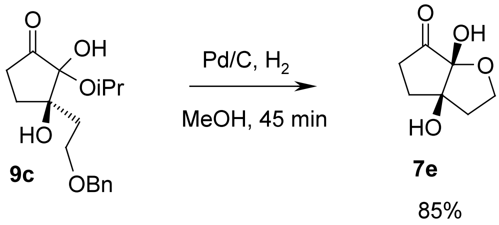
Scheme 3. Reacetalization, hydration and enolization of hydroxylated diketone.

the selectivity and yield of the hydroxylation reaction (entries 6–8).

2.3. 3-Hydroxylation of 3-ethyl-, 3-hydroxyethyl-, and 3-benzyloxyethyl-1,2-cyclopentanediones

The substrates **1b**–**e** were also subjected to oxidation using the optimal conditions found for the model compound **1a**. The results from the 3-hydroxylation reactions of substrates **1b**–**e** are presented in Table 2.

In the case of **1b**, in the course of quenching the reaction with methanol, the initially formed methyl acetal **7b** undergoes deacetalization affording the mixture of enol **6b** and hydrate **10b**. The acetals and hydroxydiones are easily separable by chromatography over silica gel. However, hydrate **10b** usually elutes on silica gel together with deacetalized compounds. The acetals are relatively unstable and transform on standing into the deacetalized products. Thus, 3-hydroxydiketone **6b** was separated in its enol form as a stable crystalline solid. The oxidation of **1c** gave (after quenching the reaction and adding citric acid in the ether–acetone mixture without using methanol) a crystalline isopropyl acetal **9c** as the primary hydroxylation product. It means that acetalization with the participation of isopropyl alcohol (released in the course of formation of the Sharpless complex DET+ Ti(O*i*Pr)$_4$) occurs. However, during purification of **9c** on silica gel, partial deacetalization occurs, affording a mixture of hydrate **10c**, and enol/diketone **6c** (as one fraction; the equilibrium of enol/diketone was well observed in NMR). The primary 3-oxidation product in the case of substrate **1e** was isolated as the stable intramolecular acetal **7e** (the same product was also obtained when deprotecting the benzyl derivative **9c**; see Scheme 4).



Scheme 4. Palladium-catalyzed hydrogenolysis of the benzyl group in acetal **9c**; formation of **7e**.

Table 2. Asymmetric 3-hydroxylation of 3-substituted-cyclopentane-1,2-diones[a]

No.	Cyclic dione **1**	α-Hydroxylated product (sum of products, %)	Ee (%)[b]	Sum of ring cleavage products **8**[e] (%)
1	**1a**	**6a**, **7a** (40)	94.3	31
2	**1b**	**6b**, **7b**, **10b** (22)	>95[c]	44
3	**1c**	**6c**, **9c**, **10c** (31)	>98[d]	34
4	**1d**	**7e** (3)	62	41
5	**1e**	**7e** (25)	>95	58
6	**1e**[f]	**7e** (25)	30	48

[a] *Reagents and conditions*: Ti(O*i*Pr)$_4$/(+)-DET/TBHP ratio 1:1.6:1.5; −20°C, 42 h; the reaction was quenched by adding citric acid in CH$_2$Cl$_2$–MeOH (9:1) in the case of **1b** and **1d**, or by adding acetone–ether (9:1) in the case of **1c** and **1e**.

[b] Determined by HPLC using a chiral column (Daicel Chiralcel ODH).

[c] Methyl acetal **7b** was converted to the corresponding isopropyl acetal **9b** prior to chiral chromatography.

[d] Isopropyl acetal **9c** was converted into an intramolecular acetal **7e** (Scheme 4) prior chiral chromatography.

[e] The oxidative cleavage products are presented in Ref. 28.

[f] 2 equiv. of the complex in respect of the substrate were used.

In the case of the silyl protected substrate **1d**, only 3% of the intramolecular acetal **7e** with moderate ee was isolated after chromatographic separation on silica gel. It is possible that the protecting group is cleaved during the oxidation process, resulting in a complex mixture that does not give a predominant product on oxidation.

2.4. Oxidation of 3-methyl-1,2-cyclohexanediones and 2-methylcyclopentane-1,3-dione

In order to establish the scope of the reaction, 3-methyl-1,2-cyclohexanediones **1f** and **1g** were oxidized using the optimal conditions found for the cyclopentane derivative **1a**. Surprisingly enough, the oxidation reaction proceeded very slowly and did not lead to the formation of any expected α-hydroxy compounds **6f** and **6g**. Instead, only the ring contraction products **12f** and **12g**, respectively, were detected in small amounts (5–9%, 140 h, −20°C) (Scheme 5).

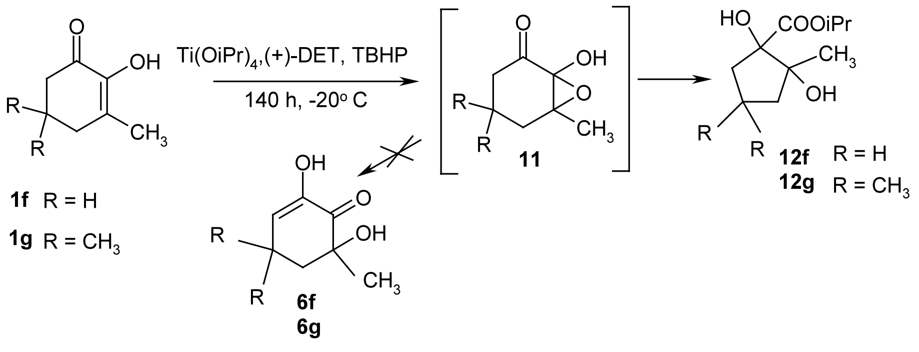
This result implies the existence of the intermediate **11** that undergoes ring contraction (observed in the case of α-hydroxy ketones[32] and α,β-epoxy ketones,[33,34] in our case, the rearrangement of the α-hydroxy-α,β-epoxy ketone occurs).

We also made attempts to oxidize a cyclic 1,3-dione (2-methyl-1,3-cyclopentanedione, **1h**) under the usual reaction conditions. However, after a long incubation time (186 h), we were able to isolate 8% of 4,5-dioxohexanoic acid **13** as the only reaction product together with 82% of the unreacted starting diketone **1h** (Scheme 6).

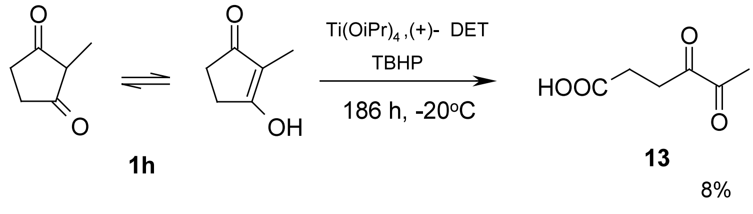
2.5. A model of the 3-hydroxylation reaction

The high enantioselectivity of the process may be rationalized by using a simplified model of the Sharpless intermediate complex.[35] It can be assumed that in the course of the oxidation, the Ti-catalyst forms first an enolate-type complex with the substrate in planar conformation (alternatively, the complexation of Ti to ketone group may be considered). The face of the oxidation is directed by the structure of the complex. According to the Ti-enolate model (Scheme 7) we can distinguish ‘favoured’ and ‘unfavoured’ conformations of the substrate–catalyst complex. The formation of a planar conformation of the enolized substrate in the complex supports the high enantioselectivity of the oxidation.

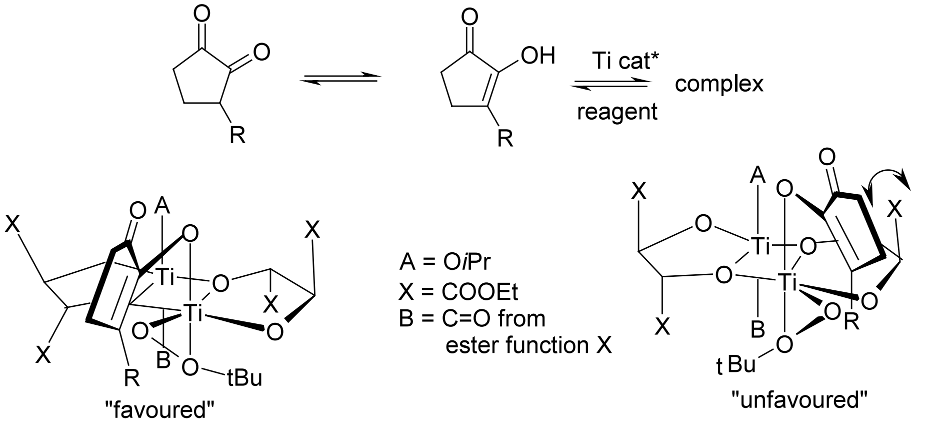
It is noteworthy that the enantioselectivity of the oxidation is significantly dependant on the substrate/complex ratio in the case of the free-OH substrate **1e**. The ee of product **7e** is high when the ratio is 1/1 (Table 2, entry 5; the same enantioselectivity as observed in the oxidation of other cyclopentanediones **1a**–**c**) and relatively low when 2 equiv. of the complex were used in the oxidation (Table 2, entry 6). This result indicates that in the latter case a complex with two chiral catalyst molecules attached to the substrate is formed (one attached to the enol moiety and the other to the primary alcohol moiety). Indeed, as the substrate **1e** exists predominantly in the enol form, the hydroxyethyl substituent may be regarded as a homoallylic alcohol. It is possible that the Ti-complex is formed preferentially (first) with the enol function when 1 equiv. of the



Scheme 5. Oxidation of 3-methyl-1,2-cyclohexanediones.



Scheme 6. Titanium tartrate-catalyzed oxidation of 1,3-cyclopentanedione.



Scheme 7. Enantioface selection. Formation of favoured and unfavoured intermediate complexes of the opposite face selection.

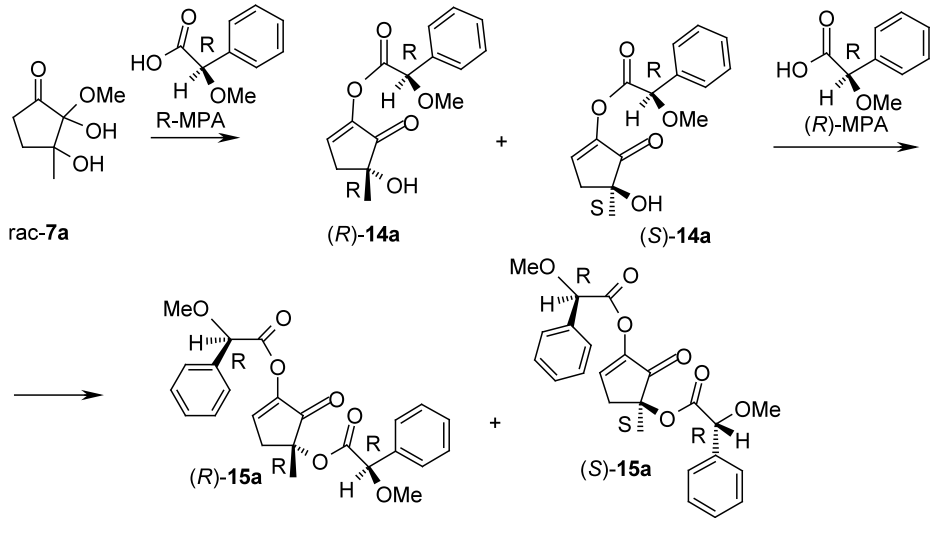
catalyst is used, affording a complex in planar 'favoured' conformation (which supports the high enantioselectivity of the oxidation). When the second molecule of catalyst is added, a homoallylic Ti-complex is also formed. It is known from the Sharpless asymmetric epoxidation of homoallylic alcohols that the oxidation of homoallylic structures proceeds with moderate selectivity and with the opposite facial selectivity as compared to that of allylic alcohols.[36] This means that in our case each of the complexes may have an opposite facial preference and as a result, lower enantioselectivity is obtained.

2.6. Determination of the ee and the absolute configuration of the products

In addition to the chiral HPLC analysis for determination of the enantiomeric purity of **6a**, the 2-mono- and 2,5-di-(*R*)-MPA ester derivatives were prepared, and their ^{1}H and ^{13}C NMR spectra were compared to those from the corresponding diastereomeric ester mixtures formed from (±)-**7a** (Scheme 8).

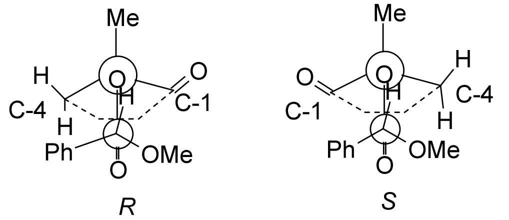
Both pairs of diastereoisomeric esters from the racemic diol gave different ^{1}H and ^{13}C chemical shifts for nearly all atoms, and in the analyzed sample of **6a** esters, only the single diastereoisomeric monoester **14a** and diester **15a** were observed.

The NMR spectra from MPA esters of secondary alcohols can be used for the determination of their absolute configurations.[37,38] Compound **14a** is a vinyl as well as a tertiary alcohol. Comparison of differential effects in ^{1}H and ^{13}C chemical shifts of diastereoisomeric vinyl esters **14a** separated by 2 bonds from the stereogenic centre did not reveal any regularities, which can be interpreted as phenyl ring anisotropy effects. Formation of the second MPA ester **15a** at the stereogenic carbon atom gives a more defined picture: Both H-4 protons as well as C-4 of the (*R*)-MPA ester **15a** are shifted to a low field (^{1}H by 0.11 and 0.18 ppm, ^{13}C by 0.32 ppm). At the same time, C-1 is shifted to a high field by 0.29 ppm. However, there are no known NMR rules for the assignment of absolute configurations from the differential shieldings of MPA esters of chiral tertiary alcohols. The use of a conformational model for secondary alcohols by replacing the carbinol proton with a methyl group[28] is not sufficiently justified. The only report known to us is connected with the use of Mosher esters



Scheme 8. (*R*)-Methoxyphenylacetic acid diesters from *rac*-**7a**.

for the configurational assignment of enantiomeric tertiary pinanols by the use of MM2 calculations.[39] Our conformational calculations using MM (Merck and Sybyl force fields) and semi-empirical (AM1 and PM3 models) on the (*R*)-MPA esters of (*R*)-**15a** and (*S*)-**15a** with the Spartan 5.0 program[40] indicate that the conformer with *trans*-orientation of carbonyl and methyl carbons is the most stable (Scheme 9).



Scheme 9. The most stable conformations of (*R*)-MPA esters of the *R* and *S* enantiomers of **6a** ((*R*)-**15a** and (*S*)-**15a**) calculated by Merck FF.

The conformations obtained were used to calculate *z* and *ρ* parameters of the Johnson–Bovey model for the estimation of phenyl ring anisotropy effects.[41] These calculations result in *S* configuration for **15a** (compound (*S*)-**15a**) and consequently for **6a** also. Taking into account the fact that the oxidative ring cleavage should not affect the stereochemistry at the tertiary carbon formed by hydroxylation, the absolute configuration of the compound **6a** was also determined by converting **7a** to the known lactone **8a** (Scheme 10). The ring cleavage was accomplished by using peracetic acid. The sign of the specific rotation of the obtained **8a** was found to be (–) ($[\alpha]_D^{22} = -15.2$; *c* 1.78, water), which corresponds to (*S*)-(–)-2-hydroxypentane-1,5-dienoic acid 2,5-lactone ($[\alpha]_D^{23} = -16.2$; *c* 1.86, water).[42] This means that the absolute configuration of **6a** is *S*, and according to the specific rotation value its ee is at least 93%.

3. Experimental

3.1. Materials and methods

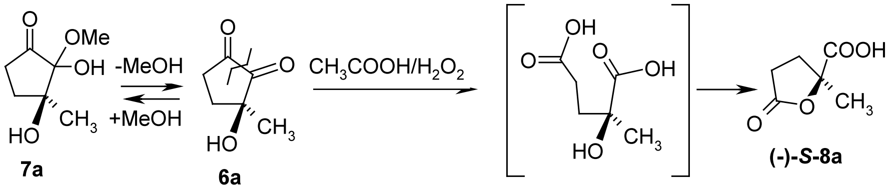
^{1}H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker AMX-500 spectrometer. The solvent peaks $CHCl_3$ (δ 7.26 ppm), CH_3OH (δ 3.30 ppm), $(CH_3)_2SO$ (δ 2.50 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm), CD_3OD (δ 49.0 ppm) $(CD_3)_2SO$ (δ 39.50 ppm) for ^{13}C were used as internal references. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra were measured on a Hitachi M80B spectrometer using the EI (70 eV) mode and HRMS 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) or Silufol® UV 254 silica gel plates. Merck Silica gel 60 (0.063–0.200 mm) or Chemapol silica gel L 40/100 was used for column chromatography. All reactions 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, DMF and Et_3N from CaH_2.

3.2. Substrates

3.2.1. 2-Hydroxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-cyclopent-2-en-1-one, 1d and 2-hydroxy-3-(2-hydroxy-ethyl)cyclopent-2-en-1-one, 1e. 2-Cyclopentene-1-acetic acid **2** (1.26 g, 10 mmol) was dissolved in MeOH (10 mL), followed by conc. HCl (0.1 mL). After stirring at rt for 24 h the mixture was diluted with ether (150 mL), washed with satd $NaHCO_3$ solution, brine and dried ($MgSO_4$). The extract was then concentrated to ~5 mL and added at 0°C to a suspension of $LiAlH_4$ (380 mg, 10 mmol) in dry ether (10 mL). The mixture was stirred at 0°C for 1 h and water (1.9 mL) was added dropwise. After stirring at rt for 0.5 h and filtration with ether, the filtrate was dried ($MgSO_4$) and ether evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether/acetone 10:1) giving 0.94 g (84%) of 2-cyclopentene-1-ethanol **3**.

The solution of **3** (0.94 g, 8.39 mmol), TBDMSCl (1.9 g, 12.58 mmol) and imidazole (1.14 g, 16.78 mmol) in dry DMF (37 mL) was stirred at rt for 20 h. Ether (200 mL) was then added, the mixture was washed with water, with 5% $NaHCO_3$ solution, water, brine, dried (Na_2SO_4) and ether evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether/acetone 100:1) to give silyl-protected 2-cyclopentene-1-ethanol (1.642 g, 87%).

To a stirred solution of cyclopentene–1-ethanol (1.642 g, 7.26 mmol) in *tert*-BuOH (44 mL) and water (30 mL), cooled in an ice bath, was added over a 20-min period a cooled solution of $KMnO_4$ (1.264 g, 8 mmol) and NaOH (0.436 g, 10.9 mmol) in water (50 mL). After completion of the addition, the solution was stirred at 0°C for 20 min, and then Na_2SO_3 (0.365 g, 2.9 mmol) in water (8 mL) was added. The reaction mixture was filtered and the filtrate was extracted three



Scheme 10. Determination of the absolute configuration of **6a**.

times with EtOAc. The combined extracts were washed with water, brine, dried (Na_2SO_4) and the solvents evaporated. Flash chromatography (silica gel, petroleum ether/acetone 10:1) yielded the diol **4** (1.262 g, 67%).

To a solution of oxalyl chloride (1.27 mL, 14.55 mmol) in CH_2Cl_2 (33 mL) DMSO (2.25 mL, 31.8 mmol) in CH_2Cl_2 (7 mL) was dropwise added at −60°C. The mixture was stirred for 10 min, followed by addition of diol **4** (1.262 g, 4.85 mmol) in CH_2Cl_2 (10 mL). After stirring at −60°C for 1 h, Et_3N (6.75 mL, 48.5 mmol) was added at −60°C. The reaction mixture was then allowed to warm to rt, poured into a cold 1N HCl solution (100 mL) and extracted twice with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel, petroleum ether/EtOAc 10:1 to 10:1.5) to give 594 mg (48%) of **1d** as a white solid.

To a solution of **1d** (272 mg, 1.06 mmol) in THF (6 mL) 1.5N HCl solution (2.4 mL) was added. After stirring at rt for 2 h the mixture was diluted with water (20 mL) and extracted 12 times with dry EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, petroleum ether/acetone 10:5) yielding 132 mg (88%) of **1e** as a white solid; ^1H NMR (500 MHz, $CDCl_3$+ΔCD_3OD): δ 2.24 (m, 2H, H-5), 2.33 (m, 2H, H-4), 2.46 (t, J=6.0 Hz, 2H, H-1′), 3.69 (t, J=6.0 Hz, 2H, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$+ΔCD_3OD): δ 204.01 (C-1), 149.69 (C-2), 145.73 (C-3), 25.71 (C-4), 31.96 (C-5), 32.26 (C-1′), 59.13 (C-2′).

3.2.2. 2-Hydroxy-3-(2-benzyloxyethyl)-2-cyclopenten-1-one, 1c. To a solution of 2-cyclopentene-1-ethanol **3** (0.906 g, 8.1 mmol) in DMF (12 mL) NaH (467 mg, 12.2 mmol, 60–65% in mineral oil) was added at 0°C. After the reaction subsided, benzyl chloride (1.7 mL, 14.6 mmol) was added. The reaction was stirred overnight, then quenched with water (5 mL) and extracted three times with CH_2Cl_2. The combined extracts were washed with water, brine, dried (Na_2SO_4) and the solvents evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether/acetone 100:1) affording benzyl ether **5** (1.38 g, 86%). This compound was dihydroxylated with $KMnO_4$, followed by Swern oxidation according to the procedures for synthesis of **1c**. Chromatography (silica gel, petroleum ether/EtOAc 10:2 to 10:2.5) gave diketone **1c** as a white solid (708 mg, 31% from 2-(2-benzyloxyethyl)-1-cyclopentene); ^1H NMR (500 MHz, $CDCl_3$): δ 2.40 (m, 2H, H-5), 2.47 (m, 2H, H-4), 2.71 (t, J=6.2 Hz, 2H, H-1′), 3.74 (t, J=6.2 Hz, 2H, H-2′), 4.52 (s, 2H, Bn-CH_2), 6.80 (s, 1H, OH), 7.30–7.35 (m, 5H, Bn-Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.06 (C-1), 149.67 (C-2), 144.18 (C-3), 25.89 (C-4), 32.01 (C-5), 29.47 (C-1′), 67.44 (C-2′), 73.02 (Bn-CH_2), 137.50 (Bn-Ph *s*), 127.75 (Bn-Ph *o*), 128.40 (Bn-Ph *m*), 127.78 (Bn-Ph *p*); EIMS (*m*/*z*, %): 232 (M$^+$, 4.4), 201 (4.3), 141 (10.6), 126 (41.6), 91 (100).

3.3. Oxidation of 3-alkyl-1.2-cyclopentanediones

3.3.1. Typical procedure for asymmetric 3-hydroxylation of 3-alkyl-1.2-cyclopentanediones. To a solution of $Ti(OiPr)_4$ (0.3 mL, 1 mmol) and 4 Å powdered molecular sieves (100 mg) in CH_2Cl_2 (6 mL) (+)-DET (0.27 mL, 1.6 mmol) were added and the mixture was stirred for 15 min at −20°C. After addition of cyclopentanedione (1 mmol) in CH_2Cl_2 (2 mL) the mixture was stirred for 30 min. Then TBHP (0.44 mL, 1.5 mmol, 3.4 M solution in toluene) was added and the mixture was kept at −20°C for 42 h. The reaction was quenched by stirring with a solution of citric acid monohydrate (210 mg, 1 mmol in a mixture of 10% MeOH in CH_2Cl_2) at rt for 1 h. The reaction mixture was filtered through a path of Celite and purified by column chromatography on silica gel.

3.3.2. 2,5-Dihydroxy-5-methylcyclopent-2-en-1-one, 6a, and 2,3-dihydroxy-2-methoxy-3-methylcyclopentanone, 7a. Diketone **1a** was oxidized according to the typical procedure and purified by column chromatography (CH_2Cl_2/MeOH 60:1 to 20:1) to afford **6a** as a colourless oil (19 mg, 15%); ee 94%; $[\alpha]_D^{18}=-49$ (*c* 0.71, CH_2Cl_2). Unlike the starting **1a**, which exists predominantly (>97%) in enol form in chloroform or in DMSO solution, both forms of **6a** can be distinguished in NMR spectra without any indication of exchange at rt; ^1H NMR (500 MHz, DMSO-d_6) from the ~2:1 mixture of enol and keto forms: enol δ, ppm: 1.16 (s, 3H, 5-Me), 2.37 and 2.42 (dd, J=3.2, J_{gem}=17.3 Hz, 2H, H-4), 6.32 (t, J=3.2 Hz, 1H, H-3), ketone δ 1.27 (s, 3H, 3-Me); 2.10 (m, 2H, H-4), 2.41 and 2.45 (m, 2H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) enol δ 204.69 (C-1), 150.89 (C-2), 127.08 (C-3), 39.43 (C-4), 71.90 (C-5), 25.06 (5-Me), ketone δ 200.84 (C-1), 204.41 (C-2), 71.73 (C-3), 30.75 (C-4), 32.73 (C-5), 21.37 (3-Me); IR (film, cm^{-1}): 3332, 2980, 2932, 1714, 1648, 1628, 1394, 1280, 1210, 1078, 1024; EIMS (*m*/*z*, %): 128 (M$^+$, 11.8), 100 (4.1), 86 (4.9), 72 (12.4), 58 (26.6), 57 (28.3), 55 (21.6), 43 (100); HRMS calcd for $C_6H_8O_3$: 128.0473; found: 128.0482. Compound **7a**: Separated as a reddish oil (40 mg, 25%); ee 94%; $[\alpha]_D^{18}=+35$ (*c* 1.12, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H, 3-Me), 1.95 and 2.02 (m, 2H, H-4), 2.38 (m, 2H, H-5), 2.43 (bs, 1H, OH), 3.19 (s, 3H, 2-OMe), 4.31 (bs, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.12 (C-1), 98.37 (C-2), 76.67 (C-3), 30.30 (C-4), 31.20 (C-5), 19.73 (3-Me), 50.36 (2-OMe); IR (film, cm^{-1}): 3464, 2972, 2946, 2840, 1756, 1454, 1378, 1264 1196, 1100, 1072; EIMS (*m*/*z*, %): 160 (M$^+$, 0.8), 128 (14.1), 104 (78.5), 100 (11), 89 (9.4), 87 (9.4), 72 (28.4), 71 (11.1), 58 (57.7), 55 (44.1), 43 (100).

3.3.3. 2,3-Dihydroxy-2-isopropoxy-3-methylcyclopentanone, 9a. Methyl acetal **7a** (38 mg, 0.24 mmol) was dissolved in *i*PrOH (1.5 mL) and allowed to stand at rt for 5 days. The mixture was concentrated and purified by flash chromatography (silica gel, petroleum ether/*i*PrOH 10:1) to afford **9a** as white crystals (22 mg, 49%); mp 58–61°C; ee 95%; $[\alpha]_D^{21}=+75$ (*c* 1.22, *i*PrOH); ^1H NMR (500 MHz, $CDCl_3$): δ 0.98 and 1.15 (2d, J=6.2Hz, 6H, 2-*i*Pr Me), 1.31 (s, 3H, 3-Me), 1.92 and

2.04 (m, 2H, H-4), 2.39 (m, 2H, H-5), 3.91 (sept., *J*=6.2 Hz, 1H, 2-*i*Pr CHO), 4.10 (bs, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.58 (C-1), 98.08 (C-2), 76.80 (C-3), 30.02 (C-4), 31.27 (C-5), 65.96, 23.14 and 24.56 (2-*i*PrO), 19.69 (3-Me); EIMS (*m*/*z*, %): 160 (0.9), 146 (1.2), 132 (11.2), 128 (3.8), 100 (6.1), 99 (7.0), 90 (62.7), 72 (10.7), 58 (19.6), 43 (100); HRMS calcd for $C_9H_{16}O_4$:188.1047; found: 188.1087.

3.3.4. 3-Methyl-2,2,3-trihydroxycyclopentanone, 10a. Isopropyl acetal **9a** (22 mg, 0.117 mmol) was dissolved in water (1 mL) and *i*PrOH was removed under reduced pressure to afford 17 mg of hydrate **10a** (100% yield), which crystallized on standing. ee 95%; $[\alpha]_D^{22}=+40$ (*c* 0.92, acetone); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14 (s, 3H, 3-Me); 1.71 (ddd, *J*=3.9, 8.7, 12.6 Hz, 1H, H-4), 1.81 (ddd, *J*=8.7, 9.6, 12.6 Hz, 1H, H-4), 2.13 (dt, *J*=19.0, 8.7 Hz, 1H, H-5), 2.18 (ddd, *J*=3.9, 9.6, 19.0 Hz, 1H, H-5), ^{13}C NMR (125 MHz, DMSO-d_6): δ 213.75 (C-1), 95.80 (C-2), 75.64 (C-3), 31.24 (C-4), 31.08 (C-5), 20.05 (3-Me); EIMS (*m*/*z*, %): 146 (M^+, 0.3), 128 (17.5), 112 (7.0), 100 (29.7), 90 (48.1), 72 (51.2), 58 (100), 43 (79.4).

3.3.5. 5-Ethyl-2,5-dihydroxycyclopent-2-en-1-one, 6b, 3-ethyl-2,3-dihydroxy-2-methoxycyclopentanone, 7b, and 3-ethyl-2,2,3-trihydroxycyclopentanone, 10b. Diketone **1b** was oxidized according to the typical procedure and purified by column chromatography (CH_2Cl_2/MeOH 80:1 to 30:1) to afford **6b** as a colourless oil which crystallized on standing (11 mg, 8%); ee >95%; $[\alpha]_D^{21}=-146$ (*c* 0.73, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, *J*=7.5 Hz, 3H, H-5″), 1.65 and 1.70 (qd, *J*=7.5, 13.7 Hz, 2H, H-5′), 2.53 (dd, *J*=3.1, 17.7 Hz, 1H, H-4), 2.63 (dd, *J*=3.3, 17.7 Hz, 1H, H-4), 2.8 (bs, 1H, OH), 6.2 (bs, 1H, OH), 6.57 (t, *J*=3.2 Hz, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.27 (C-1), 150.42 (C-2), 129.63 (C-3), 36.29 (C-4), 75.95 (C-5), 31.15 (C-5′), 7.66 (C-5″); IR (film, cm^{-1}): 3356, 2976, 2932, 1712, 1650, 1628, 1396, 1268, 1204, 1056, 1030; EIMS (*m*/*z*, %): 142 (M^+, 18.5), 113 (10.3), 86 (12.0), 72 (10.9), 57 (100); HRMS calcd for $C_7H_{10}O_3$: 142.0629; found: 142.0622. Compound **7b**: Separated as a reddish oil (25 mg, 14% yield, in NMR spectra also **6b** and **10b** are observed); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (t, *J*=7.5 Hz, 3H, H-3″), 1.67–1.69 (m, 2H, H-3′), 1.95 (m, 2H, H-4), 2.41 (m, 2H, H-5), 3.18 (s, 3H, 2-OMe); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.54 (C-1), 98.78 (C-2), 77.00 (C-3), 28.38 (C-4), 31.24 (C-5), 50.26 (2-OMe), 25.75 (C-3′), 6.73 (C-3″). Compound **10b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (t, *J*=7.5 Hz, 3H, H-3″), 1.67–1.69 (m, 2H, H-3′), 1.96 (m, 2H, H-4), 2.38 (m, 2H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.07 (C-1), 96.05 (C-2), 78.84 (C-3), 28.29 (C-4), 31.04 (C-5), 25.54 (C-3′), 6.87 (C-3″).

3.3.6. 5-[(2-Benzyloxy)ethyl]-2,5-dihydroxy-2-cyclopenten-1-one, 6c, 3-[(2-benzyloxy)ethyl]-2,3-dihydroxy-2-isopropoxycyclopentanone, 9c, and 3-[2-(benzyloxy)ethyl]-2,2,3-trihydroxycyclopentanone, 10c. Diketone **1c** was oxidized according to the typical procedure and purified by column chromatography (petroleum ether/acetone 10:1.5 to 10:4) to afford **9c** as a white solid (52 mg, 17%); ee >98%; $[\alpha]_D^{20}=+38$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.88 (ddd, *J*=3.8, 7.6, 13.2 Hz, 1H, H-4), 2.03 (dt, *J*=13.2, 9.7 Hz, 1H, H-4), 2.37–2.39 (m, 2H, H-5), 1.78 (ddd, *J*=3.5, 5.6, 14.9 Hz, 1H, H-3′), 2.27 (ddd, *J*=4.4, 9.1, 14.9 Hz, 1H, H-3′), 3.74 (ddd, *J*=4.4, 5.6, 9.8 Hz, 1H, H-3″), 3.80 (ddd, *J*=3.5, 9.1, 9.8 Hz, 1H, H-3″), 0.96 and 1.04 (both d, *J*=6.2 Hz, *i*-Pr CH_3), 4.06 (sept., *J*=6.2 Hz, *i*-Pr CH), 4.51 and 4.57 (d, *J*=11.5 Hz, 2H, Bn CH_2), 7.30–7.35 (m, 5H, Bn-Ph), 3.92 and 4.93 (bs, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.37 (C-1), 97.94 (C-2), 78.25 (C-3), 30.30 (C-4), 31.47 (C-5), 32.50 (C-3′), 66.31 (C-3″), 23.10, 24.54, 65.84 (*i*-PrO), 73.40 (Bn CH_2), 137.02 (Bn-Ph *s*), 127.95 (Bn-Ph *o*), 128.51 (Bn-Ph *m*), 128.00 (Bn-Ph *p*); EIMS (*m*/*z*, %): 308 (M^+, 1.0), 291 (14.8), 252 (9.71), 249 (33.9), 231 (9.0), 181 (11.9), 142 (14.5), 141 (23.0), 91 (100); HRMS calcd for $C_7H_{10}O_3$ (M−OBn−O*i*Pr)$^+$: 142.0629; found: 142.0647.

Compounds **6c** (enol form), **6c** (dione form) and **10c** were isolated as a mixture: Compound **6c** (enol form): ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.45 (t, *J*=3.2 Hz, 1H, H-3), 2.59 (dd, *J*=3.1, 17.6 Hz, 1H, H-4), 2.69 (dd, *J*=3.4, 17.6 Hz, 1H, H-4), 1.92 (m, 1H, H-5′), 2.06 (m, 1H, H-5′), 3.65 (m, 1H, H-5″), 3.80 (m, 1H, H-5″); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.08 (C-1), 149.89 (C-2), 127.79 (C-3), 38.05 (C-4), 75.45 (C-5), 37.18 (C-5′), 66.38 (C-5″), 73.47 (Bn CH_2), 137.47 (Bn-Ph *s*), 127.74 (Bn-Ph *o*), 128.44 (Bn-Ph *m*), 127.77 (Bn-Ph *p*); Compound **6c** (dione form): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03 (m, 1H, H-3′), 2.18 (m, 1H, H-3′), 2.29 (m, 2H, H-4), 2.50 (m, 1H, H-5), 2.70 (m, 1H, H-5), 3.63 (m, 1H, H-3″), 3.78 (m, 1H, H-3″); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.42 (C-1), 202.49 (C-2), 76.04 (C-3), 30.00 (C-4), 33.19 (C-5), 36.43 (C-3′), 65.72 (C-3″), 73.24 (Bn CH_2), 136.82 (Bn-Ph *s*), 127.87 (Bn-Ph *o*), 128.49 (Bn-Ph *m*), 127.85 (Bn-Ph *p*); Compound **10c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98 (m, 1H, H-3′), 2.18 (m, 1H, H-3′), 2.01 (m, 2H, H-4), 2.46 (m, 1H, H-5), 2.49 (m, 1H, H-5), 3.73 (m, 1H, H-3″), 3.81 (m, 1H, H-3″); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.19 (C-1), 95.49 (C-2), 78.23 (C-3), 30.24 (C-4), 31.28 (C-5), 33.98 (C-5′), 65.98 (C-5″), 73.47 (Bn CH_2), 136.76 (Bn-Ph *s*), 128.05 (Bn-Ph *o*), 128.60 (Bn-Ph *m*), 127.74 (Bn-Ph *p*).

3.3.7. 1,5-Dihydroxy-2-oxabicyclo[3.3.0]octane-8-one, 7e. Diketone **1e** was oxidized according to the typical procedure and purified by column chromatography (petroleum ether/acetone 10:3) affording **7e** as white crystals (40 mg, 25%); mp 98–101°C; ee >95%; $[\alpha]_D^{20}=-26$ (*c* 1.17, acetone); ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ 1.87 and 1.92 (m, 2H, H-6), 2.05 (m, 2H, H-4), 2.34 and 2.36 (m, 2H, H-7), 3.80 and 4.05 (m, 2H, H-3), 4.06 (bs, 2H, OH); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD): δ 101.06 (C-1), 67.03 (C-3), 36.40 (C-4), 82.88 (C-5), 29.49 (C-6), 33.43 (C-7), 210.83 (C-8); EIMS (*m*/*z*, %): 158 (M^+, 0.2), 130 (7.5), 102 (68.6), 86 (3.7), 71 (3.9), 57 (23.7), 56 (100); HRMS calcd for (M−CO)$^+$ $C_6H_{10}O_3$: 130.0629; found: 130.0621.

3.3.8. Isopropyl 1,2-dihydroxy-2-methylcyclopentane-1-carboxylate, 12f. Diketone **1f** was oxidized according to the typical procedure for 140 h and purified by column chromatography (petroleum ether/ethyl acetate 10:2), affording **12f** as a yellow oil (10 mg, 5%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (s, 3H, 2-Me), 1.29 and 1.30 (2d, *J*=6.2 Hz, 6H, *i*Pr Me), 1.70 and 1.92 (m, 2H, H-4), 1.85 and 1.94 (m, 2H, H-5), 1.98 and 2.18 (m, 2H, H-3), 2.84 and 3.72 (bs, OH), 5.11 (sept., *J*=6.2 Hz, 1H, *i*Pr CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.31 (C-1), 80.72 (C-2), 37.50 (C-3), 19.52 (C-4), 34.03 (C-5), 22.69 (2-Me), 174.82 (COO), 70.05 (*i*Pr CH), 21.58 and 21.74 (*i*Pr Me).

3.3.9. Isopropyl 1,2-dihydroxy-2,4,4-trimethylcyclopentane-1-carboxylate, 12g. Diketone **1g** was oxidized according to the typical procedure for 140 h and purified by column chromatography (petroleum ether/ethyl acetate 10:1.5) affording **12g** as a colourless oil (21 mg, 9%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 and 1.24 (s, 6H, 4-Me), 1.15 (s, 3H, 2-Me), 1.31 and 1.32 (2d, *J*=6.1 Hz, 6H, *i*Pr Me), 1.81 and 1.87 (both d, *J*=13.4 Hz, 2H, H-3), 1.86 and 2.31 (both d, *J*=14.3 Hz, 2H, H-5), 2.81 and 3.76 (s, OH), 5.12 (sept., *J*=6.1 Hz, 1H, *i*Pr CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 85.36 (C-1), 81.79 (C-2), 52.45 (C-3), 34.63 (C-4), 48.98 (C-5), 23.74 (2-Me), 31.50 and 32.97 (4-Me), 174.57 (COO), 70.19 (*i*Pr CH), 21.66 and 21.79 (*i*Pr Me).

3.3.10. 4,5-Dioxohexanoic acid, 13. Diketone **1h** was oxidized according to the typical procedure for 186 h and purified by column chromatography (petroleum ether/*i*PrOH 20:1) affording **13** as a yellow solid (11 mg, 8%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, H-6), 2.71 (t, *J*=6.1 Hz, 2H, H-2), 3.04 (t, *J*=6.1 Hz, 2H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.83 (C-1), 27.45 (C-2), 30.56 (C-3), 196.80 (C-4 or C-5), 197.07 (C-5 or C-4), 23.55 (C-6); EIMS (*m*/*z*, %): 127 $(M-OH)^+$, (0.9), 101 (23.2), 73 (8.8), 55 (17.7), 43 (100); HRMS calcd for $(M-OH)^+$ $C_6H_7O_3$: 127.0394; found: 127.0378.

3.4. Preparation of (*R*)-(−)-α-methoxyphenylacetic acid diesters, 15a

A mixture of **7a** (12.4 mg, 0.078 mmol), (*R*)-(−)-MPA (51.5 mg, 0.31 mmol), DCC (64 mg, 0.31 mmol) and DMAP (13 mg) in THF (1.5 mL) was stirred at rt for 2 h. Then the mixture was diluted with ether (5 mL) and water (1 mL) was added. An additional quantity of ether (25 mL) was added, and the mixture was washed sequentially with 1 M HCl solution, satd $NaHCO_3$ solution, brine, dried (Na_2SO_4) and the solvents removed. Flash chromatography (Chemapol silica gel L 40/100, benzene/acetone 30:1) afforded (*S*)-**15a** (32 mg, 97%).

Analogously, the corresponding diastereomeric ester mixture (*R*)-**15a** and (*S*)-**15a** from (±)-**7a** was prepared. (*S*)-**15a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 3H, 5-Me), 2.65 (dd, *J*=3.4, 18.1 Hz, 1H, H-4), 2.89 (dd, *J*=2.9, 18.1 Hz, 1H, H-4), 3.45 and 3.49 (s, 3H, OMe), 4.78 and 4.97 (s, 1H, CHO), 7.24 (t, *J*=3.2 Hz, 1H, H-3), 7.35–7.50 (Ph *o*, *m*, *p*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.67 (C-1), 146.21 (C-2), 139.71 (C-3), 37.53 (C-4), 78.59 (C-5), 167.64 and 169.73 (COO), 82.12 and 82.27 (CHO), 57.54 and 57.70 (OMe), 135.19 and 135.54 (Ph *s*), 127.15 and 127.38 (Ph *o*), 128.65 and 128.78 (Ph *m*), 128.83 and 129.06 (Ph *p*). (*R*)-**15a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (s, 3H, 5-Me), 2.54 (dd, *J*=3.4, 18.2 Hz, 1H, H-4), 2.71 (dd, *J*=2.8, 18.2 Hz, 1H, H-4), 3.41 and 3.49 (s, 3H, OMe), 4.79 and 5.00 (s, 1H, CHO), 7.07 (t, *J*=3 Hz, 1H, H-3), 7.35–7.50 (Ph *o*, *m*, *p*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.96 (C-1), 146.47 (C-2), 140.21 (C-3), 37.21 (C-4), 78.62 (C-5), 167.75 and 169.45 (COO), 81.82 and 81.98 (CHO), 57.50 and 57.67 (OMe), 135.21 and 135.70 (Ph *s*), 127.22 and 127.40 (Ph *o*), 128.72 and 128.82 (Ph *m*), 128.90 and 129.11 (Ph *p*). The assignment of *R* and *S* isomers reported in Ref. 28 should be reversed.

3.5. (*S*)-(−)-2-Hydroxypentane-1,5-dienoic acid 2,5-lactone, (*S*)-8a

A mixture of **7a** (32 mg, 0.2 mmol) and hydrogen peroxide (30% solution in water, 0.2 mL) in acetic acid (3 mL) was stirred at rt for 2.5 h. Then Na_2SO_3 (200 mg) in water (2 mL) was added and the solvents were removed at reduced pressure. The residue was dissolved in water (10 mL), extracted with EtOAc (4×15 mL), dried ($MgSO_4$) and solvents evaporated. Flash chromatography (petroleum ether/acetone 10:3 to 10:4) gave lactone-acid **8a** as a white solid (18 mg, 63%); $[\alpha]_D^{23} = -15.2$ (*c* 1.78, water); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69 (s, 3H, 2-Me), 2.20 (dt, *J*=13.3, 9.8 Hz, 1H, H-3), 2.60 (ddd, *J*=3.7, 9.8, 13.3 Hz, 1H, H-3), 2.63 (ddd, *J*=3.7, 9.8, 18.0 Hz, 1H, H-4), 2.71 (dt, *J*=18.0, 9.8 Hz, 1H, H-4), 8.02 (bs, 1H, COOH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 83.55 (C-2), 32.90 (C-3), 28.32 (C-4), 176.27 (C-5), 23.44 (2-Me), 176.25 (2-COOH).

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