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Tetrahedron: *Asymmetry* 14 (2003) 1565–1573

TETRAHEDRON: *ASYMMETRY*

Asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones. Part 2: Oxidative ring cleavage of 3-alkyl-1,2-cyclopentanediones: synthesis of 2-alkyl-γ-lactone acids

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

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

Received 19 February 2003; accepted 3 April 2003

Abstract—Ti(O*i*Pr)$_4$/diethyl tartrate/*t*BuOOH system oxidizes 3-alkyl-1,2-cyclopentanediones resulting in hydroxylated ring cleavage products 2-alkyl-γ-lactone acids, in high enantioselectivity (~95% ee) and satisfactory isolated yields (up to 55%).

1. Introduction

The unique Ti(O*i*Pr)$_4$/tartaric ester/*t*BuOOH complex introduced by Sharpless for the asymmetric epoxidation of allylic alcohols[1] has found use in the other asymmetric oxidation processes such as oxidation of sulfides,[2,3] Baeyer–Villiger reaction with cyclobutanones[4] and 2-hydroxylation of 3-hydroxyketones.[5,6] We have recently found that the Sharpless system oxidizes readily 3-alkyl-1,2-cyclopentanediones, resulting in enantiomeric 3-hydroxy- and ring cleavage oxidation products in excellent stereoselectivity.[7]

We have already demonstrated that the 3-hydroxylation of 1,2-cyclopentanediones can be used for a preparative synthesis of 3-hydroxy-1,2-cyclopentanediones.[8] The non-asymmetric cleavage of cyclic 3-alkyl-1,2-diones resulting in diacids or keto acids is known earlier.[9–12] We are not aware of any literature references available connected with the asymmetric 3-hydroxylation/ring cleavage of 3-alkyl-cyclopentane-1,2-diones except for our preliminary report:[7] the products of that ring cleavage provide non-racemic lactones and esters which are of importance because of their interesting biological properties.[13,14] Also, the method equips us with several chirons which can be used in asymmetric synthesis.[15–17] Herein, we focus on the possibility of directing the oxidation of 3-alkyl-1,2-cyclopentanediones towards 3-hydroxylation/ring cleavage, and on the synthesis of 2-alkyl-γ-lactonic acids via that reaction.

2. Results and discussion

2.1. Oxidation of 3-methyl-1,2-cyclopentanedione

Our previous experiments revealed that the substrate **1a**, when subjected to the oxidation, using the Ti(O*i*Pr)$_4$-tartaric ester-*tert*-BuOOH (TBHP) system, resulted in up to 40% 3-hydroxylation (mono-oxidation products), and up to 31% 3-hydroxylated ring cleavage products (double-oxidation products–hydroxylation+ring cleavage).[8] In order to shift the reaction towards 3-hydroxylation/ring cleavage we investigated the oxidation of 3-methyl-1,2-cyclopentanedione **1a** as a model compound in different conditions. The main ring cleavage product identified was lactone **2a** with ester **3a** being found as a minor product; Scheme 1. The results obtained are presented in Table 1.

The data from Table 1 show that the amount of double oxidized products **2a** and **3a** varies from 31 to 50%. In each case, a certain amount of the non-cleaved 3-hydroxylation product (mono-oxidized product) was also isolated. The reaction conditions best suited for 3-hydroxylation (40% of the corresponding product **4a**) gave 31% of the ring cleaved products as a sum of **2a** and **3a**; Table 1, no 1.[8] The ee of the isolated compounds **2a**, **3a** and **4a** was ~95% in the best case. In order to increase the amount of ring cleavage products, a larger quantity of Ti(O*i*Pr)$_4$ and oxidant was used.

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

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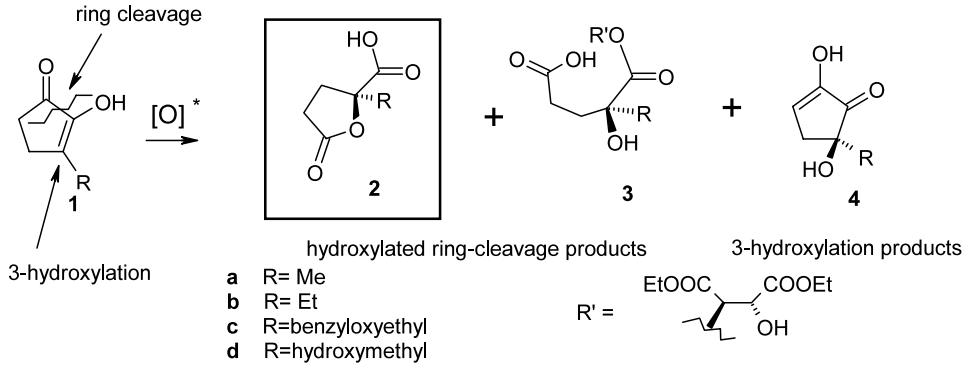
doi:10.1016/S0957-4166(03)00309-4



Scheme 1. 3-Hydroxylation/ring cleavage of 3-alkyl-1,2-cyclopentanediones.

Table 1. Products of the asymmetric oxidation of 3-methyl-1,2-cyclopentanedione **1a***

No	Ti/DET/TBHP time (h)	**2a** yield %	**3a** yield %	Sum isolated ring cleavage products **2a**+**3a**	3-Hydroxylation product **4a**	Sum of isolated oxidation products **2a**+**3a**+**4a**
1[8]	1/1.6/1.5 42	23	8	31	40	71
2	2/2.4/2.5 42	48	2	50	19	69
3	3/3.6/4.0 42	42	5	47	23	70
4	1/1.6/2.5 68	44	6	50	15	65
5	1/3/2.5 68	23	25	48	15	63
6	1/1.6/4 68	31	7	38	13	51
7	1/1.6/2.5 10 days	43	6	49	15	64

* Conditions: reaction temperature –20°C; solvent dichloromethane (see Section 3).

Thus 2- and 3-fold excess of the Ti(O*i*Pr)$_4$ increased the amount of double oxidized (hydroxylated+ring cleaved) products (as a sum of **2a** and **3a**) (Table 1, nos. 2 and 3). The same increase was achieved also with a stoichiometric Ti(O*i*Pr)$_4$ amount (tartaric ester 1.6 equiv.) by increasing only the oxidant ratio in the catalyst (TBHP 2.5 fold excess in respect to Ti(O*i*Pr)$_4$; Table 1, no 4). Additional increase of the Ti(O*i*Pr)$_4$/TBHP ratio in favour of TBHP reduced the amount of the ring cleavage product (Table 1, no 6). The maximum amount of ring cleavage (isolated yield 50%, as a sum of **2a** and **3a**) was obtained at the ratio 1/1.6/2.5 of the reagents.

We were concerned about the considerable quantity of 3-hydroxylation product **4a** that remained un-cleaved in these experiments (13–23%; Table 1, nos 2–7). If you assume that the oxidation proceeds via the 3-hydroxylation process, two reasons can be considered for the incomplete oxidation: the quantity of the oxidant is not sufficient or, the reaction time is not sufficient. In checking these assumptions, however, we found that a considerable increase of the oxidant (up to Ti(O*i*Pr)$_4$/TBHP ratio 1:4) had no substantial influence on the quantity of the hydroxylated product **4a** (15% versus 13%; Table 1, no 4 and no 6, respectively). On the contrary, the yield of the ring cleavage as well as the total amount of the asymmetric oxidation products (**2a**+**3a**+**4a**) reduced. The prolonged reaction time did not reduce the relative quantity of the 3-hydroxylation product **4a** among the reaction products either (Table 1, no 7). The observed quite stable ratio of the 3-hydroxylation product towards ring cleaved products (**4a** versus **2a**+**3a**) in all experiments implies that part of the intermediate 3-hydroxylated product does not participate in the following oxidation and does not enter the subsequent oxidation step. It might be possible that only the primary 3-hydroxylation product in the form of acetal **5a (**after the first oxidation step) is capable of further oxidation: The corresponding enolic form **4a** remains un-oxidized (or vice versa). The slow transformation of the initial isopropyl acetal **5a** in the chloroform solution to **4a** has been observed by us already previously.[7]

To verify this assumption, **4a** and **5a** were oxidized separately under the Sharpless conditions. The oxidation of **4a** did not lead to the expected ring cleavage product lactone acid **2a** (different products formed), while the acetal **5a** resulted in the ring cleavage product **2a** (the isolated yield, however, was quite moderate). Also, when **4a** and **5a** were oxidized with achiral oxidants such as Jones' reagent, peracetic acid or Ti(O*i*Pr)$_4$/TBHP, different types of oxidation products were obtained. Thus, from **5a** the lactone acid **2a** was

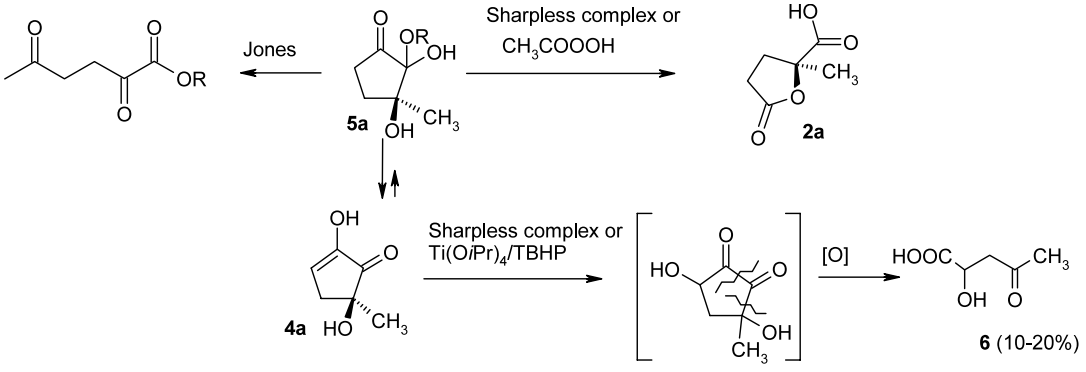
easily obtained with peracetic acid. Compound **4a** remained unchanged with peracetic acid, however, with Ti(O*i*Pr)$_4$/TBHP, hydroxy ketoacid **6** was isolated in low yield. The latter finding indicates that during the oxidation α-hydroxylation at non-branched carbon also occurs to a certain extent. This pathway, leading to a chiral hydroxylated compound **6**, is, however, marginal (Scheme 2).

The results obtained support the proposed assumption that **5a** (or a similar intermediate) is the substrate for the second oxidation step resulting in the ring cleavage products while the enol **4a** is further oxidized in a smaller amount. The oxidative ring cleavage product also contains a certain amount of monoester **3a** coming from the esterification of **2a** with the hydroxyl moiety of tartaric acid diethyl ester component of the catalyst system. The extent of formation of the esters depends on the relative amount of the diethyl tartrate in respect to the substrate (Table 1, nos 4 and 5; **3a**: 6% versus 25%). However, the amount of the tartaric acid ester did not influence greatly the overall yield of the ring cleavage product (Table 1, no 5: **2a**+**3a** 48% versus no 4: **2a**+**3a** 50%).

2.2. Oxidation of 3-ethyl-, 3-benzyloxyethyl- and 3-hydroxymethyl-1,2-cyclopentanediones

The optimum reaction conditions found for double oxidation were used in the case of the substrates **1b–d**. Thus, the substrates **1b–d** were subjected to the oxidation at the catalyst ratio Ti(O*i*Pr)$_4$/DET/TBHP 1/1.6/2.5 and Ti(O*i*Pr)$_4$/substrate ratio 1:1 (in some cases 2:1, depending on the presence of alcohol functionalities in the substrate). The results obtained are presented in Table 2.

The oxidation of the substrates **1b–d** resulted in a product profile similar to that of **1a**. Also, the yields of the reaction products were quite similar. The total yield of the ring cleavage products (presented as a sum of products **2** and **3**) was about 50% (Table 2). Only in the case of hydroxymethyl substrate **1d** was the yield of oxidation lower when one equivalent of the Ti-complex towards substrate was used (Table 2, no 6 versus no 4: 55% versus 42%). It is noteworthy that the enantioselectivity of the oxidation was also higher when two equivalents of the catalyst were used (Table 2, no 6 versus no



Scheme 2. Ring cleavage of acetal **5a** and enol **4a**.

Table 2. Products of the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones **1a–d**

No	Substrate	Ti/DET/TBHP time (h)	Sum, ring cleavage products **2** and **3** (%)	**2**		**3**	**4** yield %	**7** yield %
				Yield (%)	Ee%	Yield (%)		
1	**1a**	1/1.6/2.5 68	50	44	>95[a]	6	15	6
2	**1b**	1/1.6/2.5 68	51	44	>95[a]	7	15	6
3	**1c**	1/1.6/2.5 68	53[b]	28	98[c]	16	18	9
4	**1d**	1/1.6/2.5 68	42	42	69[d]	N.d.[e]	N.d.	Traces
5	**1d**	2/3/1.5 42	31	31	97[d]	N.d.[e]	N.d.	Traces
6	**1d**	2/3/2.5 68	55	55	94[d]	N.d.[e]	N.d.	Traces

[a] Determined by NMR from the (–)-menthol esters **9**, the other diastereomer was not observed (Scheme 4).
[b] Dimeric ester **8c** (Fig. 2) in 9% yield was also separated, and that amount added to the sum of ring cleavage products.
[c] Determined by HPLC as spirodilactone **11** using a chiral column (Daicel Chiralcel ODH; Scheme 5).
[d] Determined by HPLC as *p*-bromophenacyl esters of **2d** using a chiral column (Daicel Chiralcel ODH).
[e] Not detected.

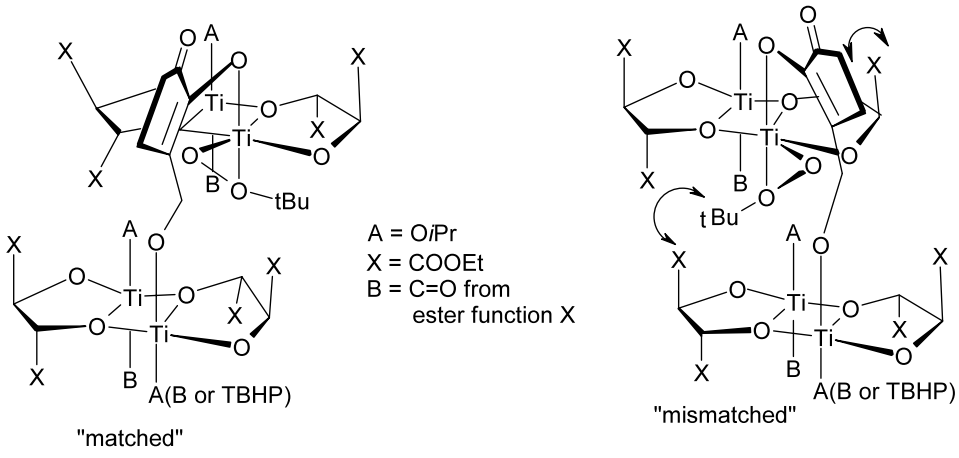


Figure 1. Simplified model of the double co-ordinated complex (see also Part 1.[8])

4: ee 69% versus 94%). It means that both chiral complex molecules that are bound to the two hydroxyl groups of the substrate are favouring the same oxidation face in the first hydroxylation step (i.e. they are a 'matched' pair) (Fig. 1). When a smaller amount of the oxidant was used the isolated yield of ring-cleavage product was lower, however, the enantioselectivity was slightly higher (Table 2, no 5).

In the case of the substrate **1c**, together with other esterified ring cleaved oxidation product **3c**, the formation of triacid monoester **8c** was observed (Fig. 2).

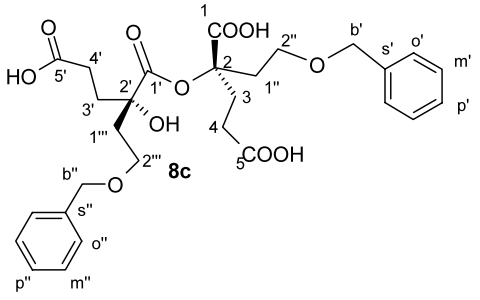
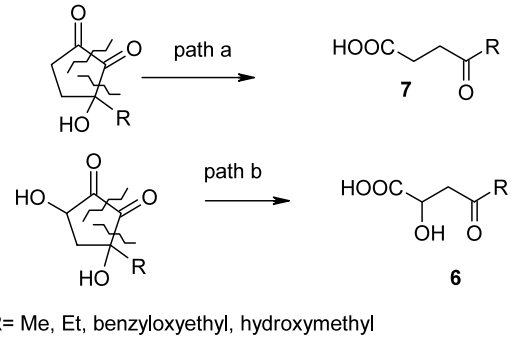


Figure 2.

The formation of the quite unusual dimeric ester **8c**, and also the finding that in most cases monoesters **3** (easily lactonize on standing) are formed during the oxidation (depending on the ratio of the tartaric acid in the reaction media, Table 1, no 5) refer to the catalytic ability of the Sharpless complex in the esterification reaction (analogous to that described in[18] for a TADDOL complex).

In all cases, the decarbonylated products were detected among the reaction products. Thus, the achiral 4-oxocarboxylic acids **7** were isolated in 6–9% yield (Scheme 3). The highest amount (9%) of the decarbonylated product was observed in the case of the substrate **1c**. Another decarbonylated product **6** was also detected among the reaction products in the case of substrate **1a** (discussed in Section 2.1).

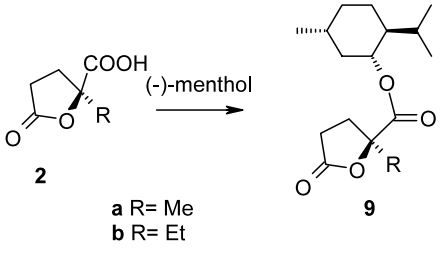


Scheme 3. By-products of the oxidative cleavage of 3-alkyl-1,2-cyclopentanediones.

2.3. Determination of enantiomeric purity and the absolute configuration of the products

The enantiomeric purity of the compounds was determined by use of different techniques.

Thus, lactones **2a** and **2b** were converted to (1*R*,2*S*,5*R*)-(−)-menthol esters **9** and the ee was determined by NMR from the diastereomeric ratio of the corresponding esters (Scheme 4).



Scheme 4. Diastereomeric (−)-menthol esters from ring cleaved products.

In ^{1}H NMR spectra from these diastereomeric esters, different chemical shifts are clearly seen from menthol

carbinol proton and from some of its methyl groups. Differences in the shieldings of the remaining protons were obtained using the 2D FT correlation diagrams. In ^{13}C NMR spectra from racemic **2** nearly all lines from the corresponding atoms of the diastereoisomers **9a** and **9b** are resolved. These differences are only in the range of tens of ppb, as a rule, however, in few cases the differences exceed 100 ppb. There are no known rules to use these differences for the assignment of the absolute configuration of the menthol esters. It is remarkable that in the present case for the esters of **2a** and **2b** the ^{13}C chemical shieldings are about 0.5 ppm less than in their corresponding diastereoisomers. The high field ^{13}C chemical shifts generally indicate a higher role of the nonbonded interactions that is characteristic to the thermodynamically less stable isomer. The molecular mechanics (MM, Merck and Sybyl force fields) and semiempirical (AM1) calculations (Spartan 5.0, Wavefunction, Inc.) of diastereoisomeric (–)-menthol esters of **2a** and **2b** reveal that *S*-**2a** and *S*-**2b** are less stable and, thus, ^{13}C chemical shifts support the proposed *S* configuration of the lactones.

The enantiomeric purity of the compound **2c** was determined by chiral HPLC after converting it to the spirodilactone **11** (Scheme 5).

The lactone acid **2c** was deprotected using H_2 and Pd/C. The resulting hydroxyethyl carboxylic acid **10** was lactonized with *p*-TsOH to afford spirodilactone **11**. The enantiomers of the spirodilactone are separable on a HPLC chiral column that enables us to estimate the ee of the initial **2c** (ee of **11** was found 98%). The ee of the compound **2d** was determined directly by HPLC after it was converted into *p*-bromophenacyl ester by *p*-bromophenacyl bromide which provides excellent resolution of enantiomers on a Chiralcel ODH column (Daicel). The enantiomeric purity of the obtained ring cleavage products was high in all cases. Only in the case of **1d**, does the oxidation enantioselectivity depends on the Ti(O*i*Pr)$_4$/substrate ratio (Table 2, nos 4–6).

The absolute configuration of the compounds was determined from the ring cleavage product **2a** that has (–) optical rotation, which is identical with the sign of the known (*S*)-(–)-2-hydroxypentane-1,5-dienoic acid 2,5-lactone.[15] It means that the absolute configuration of **2a** is *S* and according to the specific rotation its ee is ~95%. The value of the specific rotation of the **2a** was $[\alpha]_D^{25}$ –15.5; *c* 2.35, water ($[\alpha]_D^{23}$ –16.2; *c* 1.86, water[15]). The obtained compound **2a** has the same absolute configuration that the compound obtained from 3-hydroxylation product **4a** by non-asymmetric oxidation (see Part 1[8]). It proves the assumption that the 3-hydroxylation reaction (generation of an asymmetry) occurs before the ring cleavage reaction.

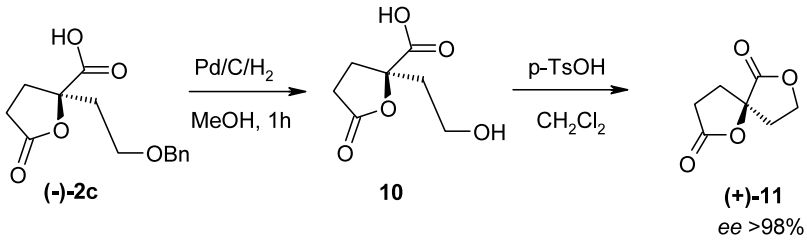
The absolute configurations of other ring cleaved products were assigned by analogy. The enantioselectivity (presented as ee) of the obtained ring cleavage oxidation reaction was high (ee ~95%, comparable with that of the corresponding 3-hydroxylated products). This means that the ring cleavage reaction may proceed via 3-hydroxylation without any loss in enantiomeric excess in the second oxidation step.

3. Experimental

^1H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker AMX-500 spectrometer. Full assignment of all ^1H and ^{13}C chemical shifts are based on 2D FT NMR and selective INEPT experiments. The solvent peaks of $CHCl_3$ (δ 7.27 ppm for ^1H) and $CDCl_3$ (δ 77.0 ppm for ^{13}C) were used as internal references. Mass spectra were measured on a Hitachi M80B spectrometer using the EI (70 eV), CI (isobutane) and HRMS mode. Optical rotations were obtained using a 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 the 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.

3.1. Substrates

The synthesis (or origin) of the substrates **1a**–**c** is described in the Part 1.[8] Compound **1d** was prepared from 2-cyclopentene-1-methanol[19] by protecting the hydroxy group as a *tert*-butyldimethylsilyl ether, dihydroxylating the double bond with $KMnO_4$, oxidising the vicinal diols according to Amon et al.,[20] followed by deprotection.



Scheme 5. Conversion of lactone acid **2c** to spirodilactone **11**.

3.1.1. 2-Hydroxy-3-(hydroxymethyl)-cyclopent-2-en-1-one, 1d. A solution of 2-cyclopentene-1-methanol (373 mg, 2.8 mmol), TBDMSCl (630 mg, 4.2 mmol) and imidazole (378 mg, 5.6 mmol) in dry DMF (9 mL) was stirred at rt for 22 h. Ether (100 mL) was then added, the mixture was washed with water, with 5% $NaHCO_3$ solution, water, brine, dried ($MgSO_4$) and ether evaporated. The residue was purified by flash chromatography (silica gel, hexanes/acetone 100:1) to give of silyl-protected 2-cyclopentene-1-methanol (574 mg, 96%).

To a stirred solution of protected 2-cyclopentene-1-methanol (574 mg, 2.7 mmol) in *t*-BuOH (16 mL) and water (11 mL), cooled in an ice bath, was added over a 15 min period a cooled solution of $KMnO_4$ (469 mg, 3 mmol) and NaOH (162 mg, 4 mmol) in water (18 mL). After completion of the addition, the solution was stirred at 0°C for 20 min, and then Na_2SO_3 (136 mg, 1.1 mmol) in water (3 mL) was added. The reaction mixture was filtered and the filtrate was extracted three times with EtOAc. The combined extracts were washed with water, brine, dried ($MgSO_4$) and the solvents evaporated. Flash chromatography (silica gel, hexanes/acetone 10:1.5) yielded 3-(*tert*-butyldimethylsilyloxymethyl)-1,2-cyclopentanediols (420 mg, 63%).

To a solution of DMSO (0.71 mL, 10.1 mmol) in CH_2Cl_2 (43 mL) TFAA (1.28 mL, 9.1 mmol) was added dropwise at −60°C. The mixture was stirred for 10 min, followed by addition of the above diol (777 mg, 3.16 mmol) in CH_2Cl_2 (4 mL). After stirring at −60°C for 1.5 h, Et_3N (2.9 mL, 21 mmol) was added at −60°C and the mixture was stirred for 1.5 h at that temperature. The reaction mixture was allowed to warm up to ca. 5°C, poured into a cold 1N HCl solution (100 mL) and extracted twice with CH_2Cl_2. The extract was washed with water, brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, hexanes/EtOAc 10:1) to give 371 mg (48.5%) of 3-(*tert*-butyldimethylsilyloxymethyl)-1,2-cyclopentanedione.

To a solution of the above diketone (371 mg, 1.53 mmol) in THF (15 mL) 1N HCl solution (6 mL) was added. After stirring at rt for 1.5 h the mixture was diluted with water (12 mL) and THF was removed at 25°C under vacuum. The water phase was 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, hexanes/acetone 10:5), yielding 174 mg (89%) of 2-hydroxy-3-(hydroxymethyl)cyclopent-2-en-1-one **1d** as a white solid; ^{1}H NMR (500 MHz $CDCl_3$+CD_3OD): δ 2.21 (m, 2H, H-5), 2.31 (m, 2H, H-4), 4.30 (s, 2H, 3′-CH_2O); ^{13}C NMR (125 MHz $CDCl_3$+CD_3OD): δ 22.25 (C-4), 31.77 (C-5), 58.58 (C-3′), 145.47 (C-3), 148.65 (C-2), 204.06 (C-1); EI (*m*/*z*, %): 128 (M^+, 12.3), 111 (3.2), 110 (3.2), 100 (8.4), 99 (100); HRMS calcd. for $C_6H_8O_3$: 128.0473; found: 128.0463.

3.2. Oxidative ring cleavage of 3-alkyl-1,2-cyclopentanediones

3.2.1. Typical procedure for synthesis of lactone-acids by asymmetric oxidation 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 (0.27mL, 1.6 mmol) was 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 (0.4 mL, 2.5 mmol, 6.25 M solution in decane) was added and the mixture was kept at −20°C for 68 h. The reaction was quenched by stirring with a solution of citric acid (192 mg, 1 mmol in a mixture of 10% MeOH in CH_2Cl_2 or 10% acetone in ether) at rt for 1 h. The reaction mixture was filtered through a path of Celite and purified by column chromatography on silica gel (Chemapol silica gel L40/100).

3.2.2. (*S*)-2-Methyl-5-oxotetrahydrofuran-2-carboxylic acid, 2a. Diketone **1a** was oxidized according to the typical procedure and purified by column chromatography (petroleum ether/acetone 10:3 to 10:6) to afford compounds **2a** together with minor amounts of **3a** and **7a**. Compound **2a** as a white solid (63 mg, 44%); ee 95%, $[\alpha]_D^{20} = -15$ (*c* 1.66, CH_2Cl_2). ^{1}H NMR (500 MHz $CDCl_3$): δ 1.66 (s, 3H, 2-Me), 2.20 (dt, J=13.3, 9.8, 9.8 Hz, 1H, H-3), 2.60 (ddd, J=13.3, 9.8, 3.6 Hz, 1H, H-3), 2.62 (ddd, J=18.0, 9.8, 3.6 Hz, 1H, H-4), 2.70 (dt, J=18.0, 9.8, 9.8 Hz, 1H, H-4), 10.37 (bs, 1H, COOH); ^{13}C NMR (125 MHz $CDCl_3$): δ 23.44 (2-Me), 28.32 (C-4), 32.90 (C-3), 83.55 (C-2), 176.31 (2-COOH), 176.71 (C-5); EI (*m*/*z*, %): 145 ($M+H^+$, 0.34), 127 (0.27), 100 (5.6), 99 ($M-COOH^+$, 90.1), 71 (12.7), 43 (100); CI (*m*/*z*, %): 145 ($M+H^+$, 90); HRMS calcd. for $(M-OH)^+$ $C_6H_7O_3$: 127.0394; found: 127.0397.

(*S*)-2-Hydroxy-2-methylpentanedioic acid (+)-diethyltartrate ester **3a** as colourless oil (21 mg, 6%). ^{1}H NMR (500 MHz $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, 4′-Et Me), 1.31 (t, J=7.2 Hz, 3H, 1′-Et Me), 2.04 (ddd, J=14.0, 10.1, 6.1 Hz, 1H, H-3), 2.12 (ddd, J=14.0, 10.0, 5.6 Hz, 1H, H-3), 2.29 (ddd, J=16.4, 10.1, 5.6 Hz, H-4), 2.53 (ddd, J=16.4, 10.0, 6.1 Hz, H-4), 4.26 (m, 2H, 4′-Et CH_2), 4.28 (m, 2H, 1′-Et CH_2), 4.80 (d, J=2.1 Hz, 1H, H-3′), 5.51 (d, J=2.1 Hz, 1H, H-2′); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.98 (1′-Et Me), 14.03 (4′-Et Me), 26.03 (2-Me), 28.56 (C-4), 33.93 (C-3), 62.46 (1′-Et CH_2), 62.85 (4′-Et CH_2), 70.53 (C-3′), 73.84 (C-2′), 74.29 (C-2), 166.10 (C-1′), 170.69 (C-4′), 174.88 (C-1), 178.24 (C-5).

4-Oxopentanoic acid **7a** (7 mg, 6%). ^{1}H NMR (500 MHz $CDCl_3$): δ 2.19 (s, 3H, Me), 2.62 (t, J=6.4 Hz, 2H, H-2), 2.75 (t, J=6.4 Hz, 2H, H-3); ^{13}C NMR (125 MHz $CDCl_3$): δ 27.78 (C-2), 29.75 (Me), 37.63 (C-3), 178.60 (C-1), 206.77 (C-4).

3.2.3. (*S*)-2-Ethyl-5-oxotetrahydrofuran-2-carboxylic acid, 2b. Diketone **1b** was oxidized according to the

typical procedure and purified by column chromatography (CH_2Cl_2/MeOH 10:0.2 to 10:1) to afford **2b** together with minor amounts of **3b** and **7b**. Compound **2b** as a white solid (70 mg, 44%); ee 95%, $[\alpha]_D^{22}=-23$ (*c* 1.49, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (t, $J=7.5$ Hz, 3H, 2-Me), 1.89 and 2.12 (both dq, $J=14.3$, 7.5 Hz, 2H, 2-CH_2), 2.23 (dt, $J=13.5$, 9.8 Hz, 1H, H-3), 2.53 (ddd, $J=13.5$, 9.9, 3.9 Hz, 1H, H-3), 2.58–2.72 (m, 2H, H-4), 9.90 (bs, 1H, COOH); ^{13}C NMR (125 MHz $CDCl_3$): δ 8.03 (C-2″), 28.08 (C-4), 30.33 (C-2′), 30.97 (C-3), 86.97 (C-2), 176.11 (C-1), 176.39 (C-5); EI (*m*/*z*, %): 159 ($M+H^+$, 0.33), 141 (0.41), 129 (1.8), 114 (7.9), 113 ($M-COOH^+$, 100); CI (*m*/*z*, %): 159 ($M+H^+$, 100); HRMS calcd for $(M-OH)^+$ $C_7H_9O_3$: 141.0551; found: 141.0580.

(*S*)-2-Hydroxy-2-ethylpentanedioic acid (+)-diethyltartrate ester **3b** as a colourless oil (26 mg, 7%). ^{1}H NMR (500 MHz $CDCl_3$): δ 0.91 (t, $J=7.4$ Hz, 3H, 2-Et Me), 1.27 (t, $J=7.2$ Hz, 3H, 4′-Et Me), 1.29 (t, $J=7.2$ Hz, 3H, 1′-Et Me), 1.71 (dq, $J=14.0$, 3×7.4 Hz, 1H, 2-Et CH_2), 1.86 (dq, $J=14.0$, 3×7.4 Hz, 1H, 2-Et CH_2), 2.03 (m, 1H, H-3), 2.04 (m, 1H, H-3), 2.24 (ddd, $J=16.4$, 10.1, 5.6 Hz, H-4), 2.51 (ddd, $J=16.4$, 9.9, 6.1 Hz, H-4), 4.14 (dq, $J=10.7$, 3×7.2 Hz, 1H, 4′-Et CH_2), 4.27 (q, $J=7.2$ Hz, 2H, 1′-Et CH_2), 4.28 (dq, $J=10.7$, 3×7.2 Hz, 1H, 4′-Et CH_2), 4.79 (d, $J=2.2$ Hz, 1H, H-3′), 5.50 (d, $J=2.2$ Hz, 1H, H-2′); ^{13}C NMR (125 MHz $CDCl_3$): δ 7.40 (2-Et Me), 13.95 (2C, 1′,4′-Et Me), 28.48 (C-4), 32.14 (2-Et CH_2), 33.09 (C-3), 62.40 (1′-Et CH_2), 62.81 (4′-Et CH_2), 70.60 (C-3′), 73.87 (C-2′), 77.59 (C-2), 166.06 (C-1′), 170.63 (C-4′), 174.44 (C-1), 178.44 (C-5).

4-Oxohexanoic acid **7b** (8 mg, 6%). ^{1}H NMR (500 MHz $CDCl_3$): δ 1.08 (t, $J=7.3$ Hz, 3H, H-6), 2.48 (q, $J=7.3$ Hz, 2H, H-5), 2.65 (t, $J=6.4$ Hz, 2H, H-2), 2.74 (t, $J=6.4$ Hz, 2H, H-3); ^{13}C NMR (125 MHz $CDCl_3$): δ 7.72 (C-6), 27.73 (C-2), 35.83 (C-5), 36.36 (C-3), 177.83 (C-1), 209.34 (C-4).

3.2.4. (*R*)-2-Benzyloxyethyl-5-oxotetrahydrofuran-2-carboxylic acid, 2c. Diketone **1c** was oxidized according to a typical procedure (using 195 mg, 0.84 mmol of the substrate) and purified by column chromatography (petroleum ether/acetone 10:1.5 to 10:6) to afford compounds **2c** together with minor amounts of **3c**, **7c** and **8c**. Compound **2c** as a colourless oil (62 mg, 28%); ee 98%, $[\alpha]_D^{20}=-24$ (*c* 2.96, $CHCl_3$). ^{1}H NMR (500 MHz $CDCl_3$): δ 2.12 (dt, $J=14.8$, 2×5.5 Hz, 1H, H-2′), 2.32 (dt, $J=13.5$, 2×9.7 Hz, H-3), 2.46 (m, 1H, H-2′), 2.47 (m, 1H, H-3), 2.54 and 2.56 (m, 2H, H4), 3.67 (m, 2H, H-2″), 4.45 and 4.49 (2d $J=11.8$ Hz, 2H, Bn CH_2), 7.25–7.34 (m, 5H, Bn *o*, *m*, *p*); ^{13}C NMR (125 MHz $CDCl_3$): δ 27.74 (C-4), 31.80 (C-3), 36.78 (C-2′), 65.10 (C-2″), 73.08 (Bn CH_2), 84.27 (C-2), 127.56 (*o*), 127.62 (*p*), 128.29 (*m*), 137.55 (*s*), 175.68 (2-COOH), 176.08 (C-5); EI (*m*/*z*, %): 264 (M^+, 0.4), 219 ($M-COOH^+$, 1.7), 158 (17.1), 140 (26.2), 107 (118.1), 91 (100); CI (*m*/*z*, %): 265 ($M+H^+$, 23); HRMS calcd for $(M-COOH)^+$ $C_{13}H_{15}O_3$: 219.1020; found: 219.1053.

(*R*)-2-Hydroxy-2-benzyloxyethylpentanedioic acid (+)-diethyltartrate ester **3c** as colourless oil (65 mg, 16%). ^{1}H NMR (500 MHz $CDCl_3$): δ 1.28 (t, $J=7.2$ Hz, 3H, 4′-Et Me), 1.29 (t, $J=7.2$ Hz, 3H, 1′-Et Me), 2.06 (m, 2H, H-3), 2.13 (m, 2H, 2-CH_2), 2.23 (m, 1H, H-4), 2.56 (ddd, $J=16.4$, 10.0, 6.1 Hz, 1H, H-4), 3.72 (dt, $J=9.5$, 2×4.7 Hz, 1H, 2-CH_2O), 3.80 (td, $J=2\times9.5$, 4.7 Hz, 1H, 2-CH_2O), 4.18 (dq, $J=10.7$, 3×7.2 Hz, 1H, 4′-Et CH_2), 4.24 (q, $J=7.2$ Hz, 2H, 1′-Et CH_2), 4.28 (dq, $J=10.7$, 3×7.2 Hz, 1H, 4′-Et CH_2), 4.44 and 4.51 (both d, $J=11.7$ Hz, 2H, Bn CH_2), 4.77 (d, $J=2.2$ Hz, 1H, H-3′), 5.49 (d, $J=2.2$ Hz, 1H, H-2′), 7.26–7.35 (m, 5H, Bn *o*, *m*, *p*); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.95 (1′-Et Me), 13.97 (4′-Et Me), 28.18 (C-4), 33.69 (C-3), 37.72 (2-CH_2), 62.21 (1′-Et CH_2), 62.79 (4′-Et CH_2), 66.92 (2-OCH_2), 70.51 (C-3′), 73.31 (Bn CH_2), 73.55 (C-2′), 76.97 (C-2), 127.71 (*p*), 127.74 (*o*), 128.34 (*m*), 137.43 (*s*), 166.09 (C-1′), 170.67 (C-4′), 173.69 (C-1), 178.15 (C-5).

Lactone from **3c**—(*R*)-tetrahydro-2-benzyloxyethyl-5-oxo-2-furancarboxylic acid (+)-diethyltartrate ester, atom numbering as in **3c**. ^{1}H NMR (500 MHz $CDCl_3$): δ 1.25 (t, $J=7.2$ Hz, 3H, 4′-Et Me), 1.29 (t, $J=7.2$ Hz, 3H, 1′-Et Me), 2.19 (m, 1H, 2-CH_2), 2.38 (m, 1H, H3), 2.47 (m, 1H, 2-CH_2), 2.52 (m, 1H, H-4), 2.53 (m, 1H, H-3), 2.75 (m, 1H, H-4), 3.64 (t, $J=6.4$ Hz, 2H, 2-CH_2O), 4.18 (dq, $J=10.7$, 3×7.2 Hz, 1H, 4′-Et CH_2), 4.24 (q, $J=7.2$ Hz, 2H, 1′-Et CH_2), 4.28 (dq, $J=10.7$, 3×7.2 Hz, 1H, 4′-Et CH_2), 4.45 and 4.47 (both d, $J=12.3$ Hz, 2H, Bn CH_2), 4.74 (d, $J=2.3$ Hz, 1H, H-3′), 5.42 (d, $J=2.3$ Hz, 1H, H-2′), 7.26–7.35 (m, 5H, Bn *o*, *m*, *p*); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.95 (1′-Et Me), 13.97 (4′-Et Me), 27.74 (C-4), 31.85 (C-3), 36.26 (2-CH_2), 62.34 (1′-Et CH_2), 62.72 (4′-Et CH_2), 64.98 (2-OCH_2), 70.22 (C-3′), 72.99 (Bn CH_2), 73.86 (C-2′), 84.52 (C-2), 127.58 (*o*), 127.62 (*p*), 128.32 (*m*), 137.75 (*s*), 165.84 (C-1′), 170.17 (C-1), 170.20 (C-4′), 176.03 (C-5).

4-Oxo-6-benzyloxyhexanoic acid **7c** (18 mg, 9%). ^{1}H NMR (500 MHz $CDCl_3$): δ 2.64 (t, $J=6.4$ Hz, 2H, H-2), 2.75 (t, $J=6.2$ Hz, 2H, H-5), 2.78 (t, $J=6.4$ Hz, 2H, H-3), 3.76 (t, $J=6.2$ Hz, 2H, H-6), 4.52 (s, 2H, Bn CH_2), 7.27–7.37 (m, 5H, *o*, *m*, *p*); ^{13}C NMR (125 MHz $CDCl_3$): δ 27.57 (C-2), 37.39 (C-3), 42.80 (C-5), 65.11 (C-6), 73.22 (Bn CH_2), 127.68 (*p*), 127.70 (*o*), 128.38 (*m*), 137.91 (*s*), 178.34 (C-1), 207.03 (C-4).

2-{[4-Carboxy-2-hydroxy-2-(2-benzyloxyethyl)butanoyl]oxy}-2-(2-benzyloxyethyl)pentanedioic acid **8c** (21 mg, 9%). ^{1}H NMR (500 MHz $CDCl_3$): δ 1.90 (dt, $J=14.4$, 2×5.1 Hz, 1H, H-1‴), 1.98 (dt, $J=15.5$, 2×9.4 Hz, 1H, H-3′), 2.19 (ddd, $J=14.4$, 8.4, 5.1 Hz, 1H, H-1‴), 2.30 (m, 1H, H-3), 2.35 (m, 1H, H-3), 2.36 (m, 2H, H-3′, H-1″), 2.43 (m, 1H, H-4′), 2.45 (m, 1H, H-4), 2.52 (m, 1H, H-1″), 2.59 (m, 1H, H-4′), 2.60 (m, 1H, H-4), 3.21 (dt, $J=10$, 5, 2×5.3 Hz, 1H, H-2″), 3.47 (m, 1H, H-2‴), 3.50 (m, 1H, H-2″), 3.57 (m, 1H, H-2‴), 4.33 and 4.41 (both d, $J=11.9$ Hz, 2H, *b*′ or *b*″), 4.37 and 4.39 (both d, $J=11.8$ Hz, 2H, *b*′ or *b*″), 7.24–7.35 (m, 10H, *o*′, *o*″, *m*′, *m*″, *p*′, *p*″); ^{13}C NMR (125 MHz $CDCl_3$): δ 27.80 (C-4′), 28.16 (C-4), 30.45 (C-3), 32.03 (C-1″), 33.51 (3′), 38.44 (C-1‴), 64.92 (C-2″), 65.61 (C-2‴), 72.87 and 73.47 (*b*′ and *b*″), 75.80 (C-2′), 82.40 (C-2), 127.56 and 128.01 (*o*′ and *o*″), 127.66 and 127.82

(p' and p''), 128.38 (m' and m'), 137.58 and 137.95 (s' and s''), 174.84 (C-1), 176.59 (C-1′), 179.54 (C-5′), 179.73 (C-5).

3.2.5. (*R*)-2-Hydroxymethyl-5-oxotetrahydrofuran-2-carboxylic acid, 2d. Diketone **1d** was oxidized according to a typical procedure and purified by column chromatography ($CHCl_3$/MeOH 20:1 to 10:1) to afford compound **2d** as a colourless oil (88 mg, 55%); ee 94%, $[\alpha]_D^{19} = +16$ (*c* 1.99, MeOH). ^{1}H NMR (500 MHz $CDCl_3$+CD_3OD): δ 2.36 (m, 2H, H-3), 2.61 (m, 2H, H-4), 3.76 (d, $J = 12.4$ Hz, 1H, H-2′), 3.94 (d, $J = 12.4$ Hz, 1H, H-2′); ^{13}C NMR (125 MHz $CDCl_3$+CD_3OD): δ 27.58 (C-3), 28.65 (C-4), 64.89 (C-2′), 87.78 (C-2), 172.77 (COOH), 178.05 (C-5); EI (*m*/*z*, %): 161 ($M+H^+$, 2.9), 130 (38.9), 129 (22.4), 115 ($M-COOH^+$, 92.3), 101 (46.0); CI (*m*/*z*, %): 161 ($M+H^+$, 100); HRMS calcd for $(M+H)^+$ $C_6H_9O_5$: 161.0449; found: 161.0450.

3.3. Determination of the enantiomeric purity of the lactone acids 2

3.3.1. Lactone acids 2a and 2b by NMR as (−)-menthol esters, 9a and 9b. A mixture of **2** (0.1 mmol), (1*R*,2*S*,5*R*)-(−)-menthol (31.2 mg, 0.2 mmol), DCC (24.7 mg, 0.12 mmol) and DMAP (6.2 mg) in THF (1 mL) was stirred at rt for 5 h. The workup was performed as described in Part 1[8] for derivatization of primary hydroxylation products with methoxyphenylacetic acid. Flash chromatography on silica gel (petrol ether/ethyl acetate 15:1 to 10:1) yielded the (−) menthol esters of the corresponding lactone-acids. Analogously the diastereomeric esters from racemic **2a-rac** and **2b-rac** were prepared. NMR chemical shifts of diastereomeric esters in $CDCl_3$ solution are reported from the racemic mixture, values for nonracemic **2a** and **2b** derivatives are given in *italics*.

Compound **9a**. ^{1}H NMR (500 MHz $CDCl_3$): δ acid part: *2.13*/*2.50*, 2.13/2.49 (H-3), *2.58*/*2.63*, 2.56/2.64 (H-4), *1.650*, 1.646 (CH_3), menthyl: *4.74*/4.73 (H-1), *1.45*/1.44 (H-2), *1.05*/1.05, *1.70*/1.69 (H-3), *0.87*/0.87, *1.69*/1.69 (H-4), *1.50*/1.50 (H-5), *1.02*/1.00, *1.96*/1.96 (H-6), *0.906*/0.906 (H-7), *1.79*/1.83 (H-8), *0.749*/0.749 (H-9), *0.894*/0.890 (H-10); ^{13}C NMR (125 MHz $CDCl_3$): δ acid part: *83.86*, 83.92 (C-2), *33.01*, 33.10 (C-3), *28.46*, 28.50 (C-4), *175.82*, 175.89 (C-5), *23.61*, 23.60 (2-Me), *171.18*, 171.18 (COO), menthyl: *76.28*, 76.25 (C-1), *46.78*, 46.81 (C-2), *23.09*, 23.25 (C-3), *34.00*, 34.02 (C-4), *31.32*, 31.32 (C-5), *40.36*, 40.45 (C-6), *21.90*, 21.90 (C-7), *26.29*, 26.26 (C-8), *15.97*, 16.10 (C-9), *20.74*, 20.67 (C-10).

Compound **9b**. ^{1}H NMR (500 MHz $CDCl_3$): δ acid part: *1.88*/*2.10*, 2.17/2.44 (H-3), *2.57*, 2.57 (H-4), *1.88*/*2.10*, 1.87/2.12 (CH_2 of Et), *1.003*, 1.000 (CH_3), menthyl: *4.76*/4.77 (H-1), *1.48*/1.47 (H-2), *1.07*/1.07, *1.72*/1.71 (H-3), *0.89*/0.89, *1.71*/1.71 (H-4), *1.52*/1.52 (H-5), *1.04*/1.02, *2.00*/1.99 (H-6), *0.923*/0.923 (H-7), *1.84*/1.86 (H-8), *0.765*/0.768 (H-9), *0.911*/0.909 (H-10); ^{13}C NMR (125 MHz $CDCl_3$): δ acid part: *87.34*, 87.38 (C-2), *31.19*, 31.49 (C-3), *28.23*, 28.27 (C-4), *175.77*, 175.89 (C-5), *30.59*, 30.54 (2-CH_2), *8.11*, 8.14 (2-Me), *171.07*, 170.96 (COO), menthyl: *76.40*, 76.24 (C-1), *46.73*, 46.78 (C-2), *23.06*, 23.18 (C-3), *34.07*, 34.07 (C-4), *31.38*, 31.38 (C-5), *40.49*, 40.53 (C-6), *21.92*, 21.92 (C-7), *26.22*, 26.25 (C-8), *15.87*, 15.98 (C-9), *20.75*, 20.70 (C-10).

3.3.2. Enantiomeric purity of lactone acid 2c by HPLC via 1,7-dioxaspiro[4.4]nonane-2,6-dione, 11. To a stirred solution of lactone acid **2c** (20 mg, 0.076 mmol) in MeOH (2 mL) 10% Pd/C (10 mg) was added and the mixture was stirred under an atmospheric pressure of H_2 at rt for 1 h. After filtration and removing the solvents the residue was dissolved in CH_2Cl_2 (4 mL) and a crystal of *p*-TsOH was added. After stirring at rt for 3.5 h the mixture was washed with saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, petroleum ether/acetone 10:3) giving 9.4 mg (79%) of spirodilactone **11**. The isolated product was analysed by HPLC (column: Daicel, Chiralcel ODH; hexane/*i*PrOH 7:3; flow rate 0.7 mL/min, detection at 206 nm). The peaks of (+)- and (−)-spirolactones were detected at t_R 14.7 min (major) and 16.5 min (minor), respectively, (compared with the corresponding racemic product).

3.3.3. Lactone acid 2d by HPLC as *p*-Br-phenacyl esters. An analytical sample 0.2–0.5 mg of **2d** in CH_3CN was treated with *p*-Br-phenacyl bromide and *N*,*N*-diisopropylethylamine. The obtained *p*-Br-phenacyl ester was analysed by HPLC (column: Chiralcel ODH, Daicel; hexane/*i*PrOH 6:4; flow rate 0.65 mL/min, detection at 254 nm). The peaks of (+)-**2d** (major) and (−)-**2d** (minor) were detected at t_R 15.1 and 29.2 min, respectively.

Acknowledgements

Support from Estonian Science Foundation (Grants Nos 4976, 5133 and 5628) and from Estonian Ministry of Education (Grant 0350312s01) is acknowledged.

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