Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 2393–2399

TETRAHEDRON: *ASYMMETRY*

Asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones. Part 3: Oxidative ring cleavage of 3-hydroxyethyl-1,2-cyclopentanediones: synthesis of α-hydroxy-γ-lactone acids and spiro-γ-dilactones

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Received 14 May 2003; accepted 10 June 2003

Abstract—A Ti(O*i*Pr)$_4$/diethyl tartrate/*t*BuOOH complex oxidizes 3-hydroxyethyl-1,2-cyclopentanediones, resulting in hydroxylated/ring cleavage products—lactone acids of high enantioselectivity (up to 95% ee) with good yields (up to 75%). These compounds are converted into chiral spiro-γ-dilactones in good yield.

1. Introduction

The methods of synthesis of hydroxy-substituted five-membered carba- and oxa-rings are one of the more important processes for obtaining analogues of natural nucleosides,[1–9] glycopeptides, e.g.[10] and other bioactive compounds.[11–14] We have recently found that different cyclic 3-alkyl-1,2-diones are oxidized by a Ti(O*i*Pr)$_4$/diethyl tartrate (DET)/*t*BuOOH (TBHP) complex[15] asymmetrically at the 3-position, resulting in 3-hydroxylated cyclopentanones with excellent enantioselectivity[16] (Part 1[17]). Additionally, 3-alkyl-, 3-hydroxymethyl- and 3-benzyloxyethyl-1,2-cyclopentanediones undergo asymmetric 3-hydroxylation/ring cleavage reactions, resulting in five-membered lactones and lactone acids in up to 55% yield with excellent enantioselectivity (ee up to 98%; Part 2[18]). One of the few examples of low enantioselectivity was observed in the case of the oxidation of an unprotected hydroxyl substrate 3-hydroxyethyl-1,2-cyclopentanedione (ee 25%; yield 48%).[16,17]

Herein we reveal highly improved enantioselectivity and efficiency of 3-hydroxylation/ring cleavage of 3-hydroxyethyl-1,2-cyclopentanedione substrates, resulting in lactone acids in good yield and stereoselectivity. Also, the results of transforming the obtained lactone acids into new stable spiro-γ-dilactones are presented. The method described allows access to several spiro-compounds that have become of interest recently because of their bioactive potency.[19–21] Several synthetic methods for their synthesis have recently been developed.[22–25]

2. Results and discussion

2.1. Substrates

3-Hydroxyethyl-1,2-cyclopentanedione **1a** was prepared as described in Part 1.[17] Racemic 4-benzyloxy-3-hydroxyethyl-1,2-cyclopentanedione **1b** was synthesized using diol **2** as the main intermediate (from lactone of *cis*-2-hydroxycyclopent-4-ene-1-acetic acid[26]), according to Scheme 1.

Our attempts to benzylate the primary *tert*-butyldimethylsilyl monoether[27] of diol **2** failed because of the intermolecular migration of the silyl group, resulting mainly in a mixture of dibenzylated and disilylated products. For this reason, we were forced to use a longer reaction sequence for the synthesis of **3** (a–d in Scheme 1). The suitably protected diol **3** was oxidized with 4-methylmorpholine *N*-oxide in the presence of osmium tetraoxide affording diol **4** in 83% isolated

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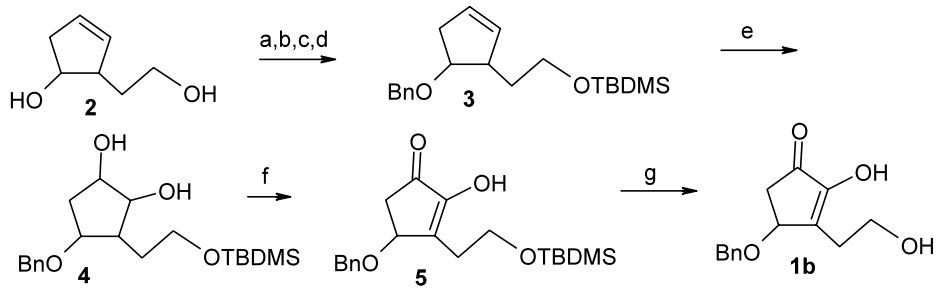
doi:10.1016/S0957-4166(03)00452-X



Scheme 1. Synthesis of the substrate **1b**. *Reagents and conditions*: (a) DHP 1.2 equiv. *p*TsOH, 53%; (b) BnBr, NaH; (c) CH_3CN, H_2SO_4/H_2O, 86% in two steps; (d) TBDMSCl, imidazole, DMF, 84%; (e) NMO, OsO_4, 83%; (f) DMSO, TFAA, TEA, CH_2Cl_2, −60°C, 70%; (g) 1 M HCl, THF, 83%.

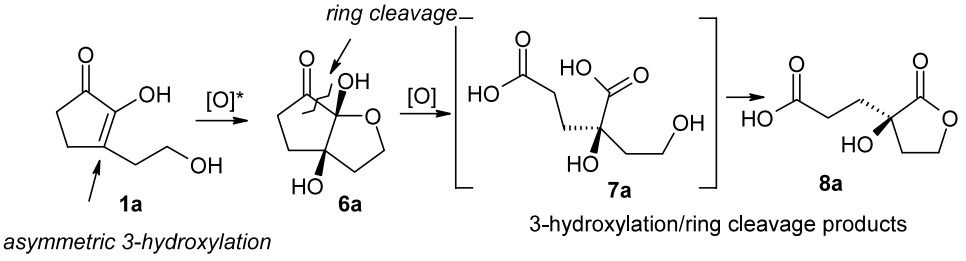
yield after chromatography on silica gel. The diol **4** was oxidized using a modified Swern oxidation procedure,[28] resulting in diketone **5** in 70% yield. The substrate **1b** was obtained in 83% yield after removal of the primary hydroxyl protecting group.

2.2. Hydroxylation/ring cleavage of 3-hydroxyethyl-1,2-cyclopentanedione 1a. Synthesis of spirodilactone 9

The hydroxylation/ring cleavage process consists of two steps: 3-hydroxylation of the substrate and oxidative ring cleavage of the 1,2-dione derivative. The thus formed dihydroxy diacid **7** lactonizes with the primary hydroxy group into lactone acid **8**, different from those formed in the case of alkyl lactone acids, in which the tertiary hydroxyl group is involved; Part 2[18] (Scheme 2).

We have previously found that the 3-hydroxymethyl-substituted cyclopentane-1,2-dione (with an unprotected hydroxyl group) is oxidized considerably more selectively when 2 equivalents of the Ti-complex are applied ($Ti(OiPr)_4$/substrate ratio 2:1 instead of ~1:1 ratio that is preferable for other substrates). In our preliminary experiment, where this $Ti(OiPr)_4$/substrate ratio was used for the oxidation of hydroxyethyl-substituted substrate **1a**, the enantioselectivity of the 3-hydroxylation/ring cleavage process was low[16,17] (Table 1, no 1, **8a** ee% 25; also, for 3-hydroxylation product **6a**, the ee% was similar—30%). The isolated yield of the target compound was also moderate (48%).

In the case of hydroxyethyl substrate **1a**, in contrast to the hydroxymethyl-substituted substrate, drastically higher enantioselectivity of the hydroxylation/ring cleavage was achieved when only one equivalent of $Ti(OiPr)_4$ was used. (Table 1, no 2, $Ti(OiPr)_4$/substrate ratio 1:1, ee >95%). Also, the isolated yield of lactone acid **8a** was considerably higher in this case (58%). In this experiment, we used substrate/TBHP ratio 1:1.5 that is obviously not sufficient to achieve complete double-oxidation (at least two molecules of TBHP are



Scheme 2. Asymmetric 3-hydroxylation/ring cleavage of 3-hydroxyethyl-1,2-cyclopentanedione.

Table 1. Ring-cleavage products of 3-hydroxyethyl-1,2-cyclopentanedione **1a**

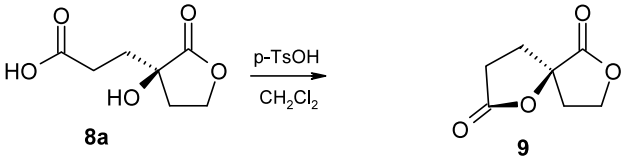
No	Lactone acid **8a**		Spirodilactone **9**	3-Hydroxylation product **6a**		Recovered **1a** (%)
	Yield (%)		Ee (%)	Yield (%)	Ee (%)	
1[a17]	48		25	25	30	16
2[b]	58		>95	25	>95	8
3[c]	75		>95	11	>95	Traces

Conditions: reaction time 68 h; −20°C.
[a] Ratio: substrate/$Ti(OiPr)_4$/DET/TBHP 1:2:2.5:1.5.
[b] Ratio: substrate/$Ti(OiPr)_4$/DET/TBHP 1:1:1.25:1.5.
[c] Ratio: substrate/$Ti(OiPr)_4$/DET/TBHP 1:1:1.25:2.5.

consumed for the complete oxidation of one molecule of the substrate). When we increased the amount of oxidant in the catalyst, with the Ti(O*i*Pr)$_4$/substrate ratio remaining unchanged, an excellent result was obtained: high enantiopurity (ee >95%) with a good yield (isolated yield 75%) of the target lactone acid **8a** (Table 1, no 3). Together with the main oxidation product **8a**, a non-cleaved hydroxylated product **6a** (11%) was isolated from the reaction mixture after chromatography on silica gel. We observed also that in the case of using Ti(O*i*Pr)$_4$/oxidant ratio 1:2.5, only traces of the substrate **1a** remained unreacted.

The asymmetric hydroxylation/ring cleavage of 3-hydroxyethyl-cyclopentane-1,2-dione **1a** gave simple access to the spirodilactone **9**. Thus, lactone acid **8a** was converted into a crystalline stable spirodilactone **9** by a simple treatment with *p*-TsOH in dichloromethane (94% yield) (Scheme 3).

The enantiomeric purity of compound **9** was measured by chiral-HPLC, using separately prepared racemic spirodilactone *rac*-**9** for comparison. The analysis proved the high enantiomeric purity of spirodilactone **9** (ee >95%). In the hydroxylation/ring cleavage process, only the hydroxylation is an asymmetric reaction. This means that the hydroxylation product **6a** has the same enantiomeric purity as the lactone acid **8a** (or spirodilactone **9**). The formation of spirodilactone **9** does not change the configuration of the stereogenic centre. The absolute configuration for the main enantiomer of **9** was suggested to be *R* on the bases of the analogy with the oxidation of the corresponding 3-methyl-cyclopentane-1,2-dione where the absolute configuration was established by chemical correlation.[17] We assumed that the enantioface preference in the case of substrate **1a** is the same as that of 3-methyl-cyclopentane-1,2-dione. We can also state that the free hydroxyl substrate **1a** and the same benzyl protected substrate[18] have an identical face preference, because in both cases, the obtained spirolactone **9** has the same sign of optical rotation.



Scheme 3. Synthesis of spirodilactone **9**.

2.3. Oxidation of *rac*-4-benzyloxy-3-hydroxyethyl-1,2-cyclopentanedione 1b. Synthesis of diastereomeric spirodilactones 10 and 11

In order to find a method to obtain substituted spirodilactones for further conversions, we investigated the possibility of an asymmetric oxidation of the racemic substrate, benzyloxysubstituted cyclopentane-1,2-dione **1b**. We expected to clarify which type of selection (enantioselection at the prochiral centre or diastereoselection in respect to the existing stereogenic centre at OBn carbon atom) prevails.

First, we selected the Ti(O*i*Pr)$_4$/substrate ratio close to 1:1. In order to follow the kinetic resolution conditions, the amount of oxidant was selected close to the theoretical amount (Ti(O*i*Pr)$_4$/TBHP ratio ~1:1; Table 2, no 1). As a result of the asymmetric oxidation process, after flash chromatography on silica gel, we obtained a mixture of diastereomeric lactones **8b** and non-cleaved hydroxylated acetals **6b** and **6c** (Fig. 1).

The mixture of lactones was directly converted to spirodilactones **10** and **11** by treatment with *p*-TsOH (88%). Two diastereomeric spirodilactones in the ratio 6:1 were formed (according to mobility on silica gel: a major, the more polar compound **10** and a minor, the less polar compound **11**). The structures of the compounds were established by NMR spectroscopy. The relative configurations of the stereogenic centres were unambiguously assigned by MM conformational analysis and observed NMR effects from the nonbonded interactions. It was found that the more polar compound **10** has a *cis*-configuration and the less polar compound **11** a *trans*-configuration of the OBn groups

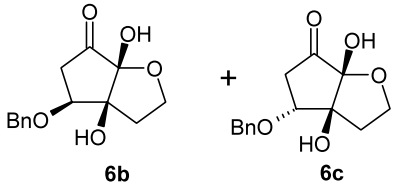


Figure 1. 3-Hydroxylation products of **1b**.

Table 2. Hydroxylation/ring cleavage of *rac*-4-benzyloxy-3-hydroxyethyl-1,2-cyclopentanedione **1b**

No	Ti(O*i*Pr)$_4$/DET/TBHP	Lactone **8b** yield (%)	Sprirodilactones			Acetals **6b**+**6c** yield (%)	Recovered **1b**	
			Ratio **10**/**11**	**10** ee (%)[a]	**11** ee (%)[a]		Yield (%)	Ee (%)[a]
1	1/1.6/1.1	32	~6:1	88	93	9	22	N.d.[b]
2	1/1.6/1.5	43	~6:1	86	93	9	17	71
3	1/1.6/2.5	57	3.7:1	78	93	9	9	N.d.[b]

Conditions: reaction time 45 h; –20°C.
[a] Determined using a HPLC chiral column (see Fig. 2).
[b] Not determined.

in respect to the carbonyl substituent of the other lactone ring. The enantiomeric purity of the compounds was determined by chiral HPLC and was found to be 88% ee for **10** and 93% ee for **11**. We supposed that for substrate **1b**, the enantioselection was the same as in the case of the other 1,2-cyclopentanedione substrates investigated so far corresponding to (*S*′)-configuration for spirodilactones **10** and **11**. Based on the above mentioned data, the configurations of stereoisomeric spirodilactones were proposed as presented in Scheme 4.

The enantiomeric purity of the recovered **1b** was 71% ee. To confirm the configuration of the stereogenic centres, the recovered **1b** was oxidized non-asymmetrically to give lactones **8b**, followed by conversion into spirodilactones **10** and **11**, and analysed by chiral HPLC. As expected, the ratio of the diastereomeric spirodilactones corresponds to the assumptions made above: in the recovered starting compound **1b**, where the (*S*)-enantiomer should prevail, it gave a diastereomeric mixture *S*,*R*′ and *S*,*S*′ in the expected ratio (Fig. 2).

It is worth mentioning that the diastereoselectivity (and the face selection) of the process depends on the initial configuration of the carbon bearing the OBn group (the present case can be well described according to reference[29]). Thus for (*R*)**-1b**, the diastereoselectivity ((*R*,*S*′)**-10** versus (*R*,*R*′)**-11**) is very high (*de* of (*R*,*S*′)**-10** = ~98%) while for (*S*)**-1b**, the diastereoselectivity ((*S*,*S*′)**-11** versus (*S*,*R*′)**-10**) is quite low (*de* = ~46%). The enantiomeric purity for (*R*,*S*′)-diastereomer **10** was found ee = 88% and for (*S*,*S*′)-diastereomer **11** ee = 93% (Table 2, no 1).

Both of the starting compounds (*R*)**-1b** and (*S*)**-1b** gave preferentially (*S*)-hydroxylation (*S*,*S*′):(*R*,*R*′) = ~150:1 and (*R*,*S*′):(*S*′,*R*′) = ~2.7:1). This result enables us to increase the overall oxidation yield in certain limits, by adding more oxidant without a considerable loss in the

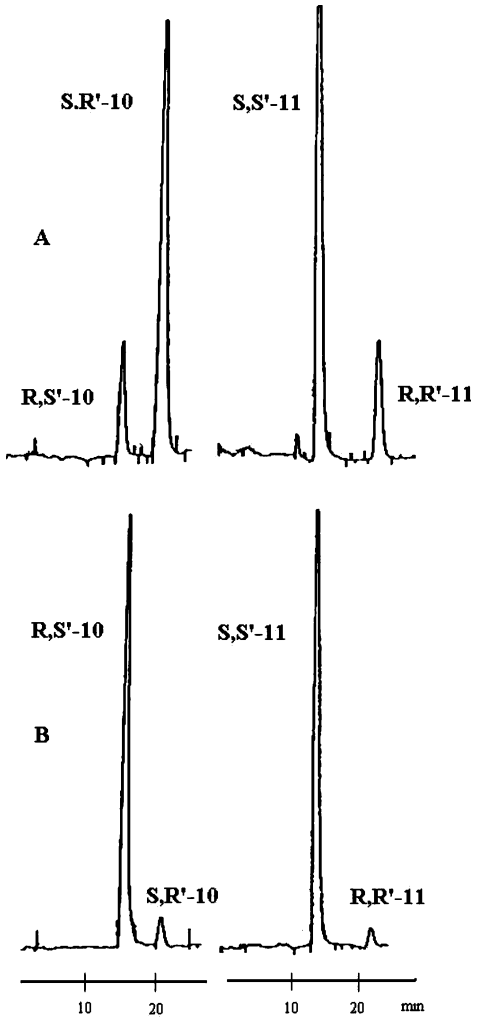
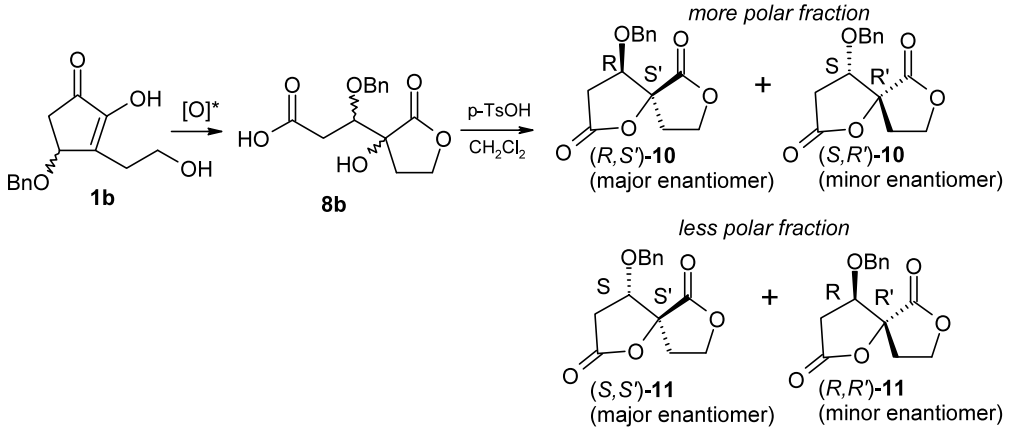


Figure 2. HPLC chromatogram of diastereomeric spirodilactones **10** and **11**. (A) Spirodilactones **10** and **11** made by non-asymmetric oxidation of the recovered **1b** (Table 2, no 2). (B) Spirodilactones **10** and **11** from the asymmetric oxidation product—lactones **8b**.



Scheme 4. Hydroxylation/ring cleavage of 4-benzyloxy-3-hydroxyethylcyclopentane-1,2-dione **1b**: synthesis of spirodilactones **10** and **11**.

purity of spirodilactone **10** and with no loss in the purity of spirodilactone **11**. Thus, the use of $Ti(OiPr)_4$/TBHP ratio 1:1.5 only slightly reduced the purity of the spirodilactone **10** and did not affect the purity of **11** (Table 2, no 2). Only the use of the $Ti(OiPr)_4$/TBHP ratio 1:2.5 reduces, moderately, the purity of **10** (ee 78% versus 88%; Table 2, nos 3 and 1). However, a more complete oxidation of the substrate gives us preparative access to the minor spirodilactone isomer **11**, which can be obtained at high enantiomeric purity (ee 93%).

3. Conclusion

Direct asymmetric oxidation of 1,2-cyclopentanediones described in this series of papers (see also Part 1[17] and Part 2[18]) gives us a direct and simple access to non-racemic substituted five-membered carba-rings (3-hydroxy-3-alkyl cyclopentane-1,2-diones) and oxa-rings (five-membered lactones). Also, a simple method for constructing chiral spirodilactones with high enantiomeric purity is described. The high enantioselectivity and good yield of the asymmetric oxidation of cyclopentanediones makes it attractive for preparative elaborations. The results obtained encourage one to search for other new applications of the $Ti(OiPr)_4$/DET/TBHP complex in asymmetric synthesis.

4. Experimental

^1H 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) for ^1H and $CDCl_3$ (δ 77.0 ppm), CD_3OD (δ 49.0 ppm) for ^{13}C were used as internal references. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrometer. Mass spectra were measured on a Hitachi M80B spectrometer using the EI (70 eV) and CI (isobutane) mode. Elemental analyses were performed on a Perkin–Elmer C,H,N,S-Analyzer 2400. 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. DMF and Et_3N were distilled from CaH_2 before use.

The enantiomeric purities of the spirodilactones were determined on a LKB liquid chromatograph with Uvicord UV detector, using a Daicel Chiracel ODH chiral column.

4.1. 4-Benzyloxy-2-hydroxy-3-(2-hydroxyethyl)-2-cyclopenten-1-one, 1b

To a solution of diol **2** (512 mg, 4 mmol) in dry CH_2Cl_2 (15 mL) dihydropyran (0.47 mL, 5.2 mmol), a crystal of *p*TsOH was added. The mixture was stirred for 2.5 h at rt and then the reaction quenched by the addition of Et_3N (20 μL). The solvent was removed and the residue subjected to flash chromatography (silica gel hexanes/acetone 50:1 to 20:1) to give primary mono-tetrahydropyranyl protected alcohol (447 mg, 53%).

To a solution of mono-tetrahydropyranyl protected alcohol (0.848 g, 4 mmol) in DMF (6 mL), NaH (230 mg, 6 mmol, 60–65% in mineral oil) was added at 0°C. After the reaction subsided, benzyl bromide (0.86 mL, 7.2 mmol) was added. The reaction was stirred overnight at rt, then quenched with water (10 mL) and extracted three times with ether. The combined extracts were washed with water and then brine, dried over $MgSO_4$ and the solvents evaporated. The residue was dissolved in CH_3CN (25 mL) and 0.2 M H_2SO_4 solution (15 mL) added. After stirring at rt for 27 h, 1 M $NaHCO_3$ solution (3 mL) was added and CH_3CN removed under vacuum. The water phase was extracted three times with EtOAc, washed with saturated $NaHCO_3$ and then brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc, 10:2) affording 750 mg (86%) of the secondary monobenzyl protected alcohol.

A solution of the above mentioned alcohol (876 mg, 4 mmol), TBDMSCl (904 mg, 6 mmol) and imidazole (545 mg, 8 mmol) in dry DMF (16 mL) was stirred at rt for 20 h. Ether (150 mL) was then added, the mixture washed water, 5% $NaHCO_3$ solution, water and then brine, dried over $MgSO_4$ and then the ether evaporated. The residue was purified by flash chromatography (silica gel, hexanes/acetone 100:1) to give alcohol **3** (1.121 g, 84%).

To a stirred solution of compound **3** (1.27 g, 3.83 mmol) and NMO (449 mg, 383 mmol) in THF (40 mL), *t*-BuOH (20 mL) and water (9.6 mL) were added, followed by the addition of OsO_4 (0.98 mL, 0.077 mmol, 2.5 weight% solution in *t*-BuOH). The formed pale yellow solution was stirred at rt for 24 h and then quenched with 10% $Na_2S_2O_3$ solution (40 mL). The mixture was diluted with brine (40 mL) and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and the solvents evaporated. Flash chromatography (silica gel, hexanes/acetone 10:1 to 10:1.5) yielded the diol **4** (1.15 g, 83%).

To a solution of DMSO (0.71 mL, 10 mmol) in CH_2Cl_2 (43 mL), TFAA (1.29 mL, 9.1 mmol) was added dropwise at −60°C. The mixture was stirred for 10 min, followed by the addition of the above diol **4** (1.114 g, 3.04 mmol) in CH_2Cl_2 (4 mL). After stirring at −60°C for 1.5 h, Et_3N (2.8 mL, 20.2 mmol) was added at −60°C and the mixture stirred for 1.5 h at that temperature. The reaction mixture was allowed to warm up to ca. 5°C, then poured into a cold 1N HCl solution (120 mL) and extracted twice with CH_2Cl_2. The extract was washed with water, brine, and then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 15:1) to give 768 mg (70%) of diketone **5**.

To a solution of the above diketone **5** (768 mg, 2.12 mmol) in THF (21 mL), 1 M HCl solution (8.5 mL) was added. After stirring at rt for 1.5 h the mixture was diluted with water (25 mL). The mixture was extracted three times with EtOAc and the combined extracts washed with brine, dried over $MgSO_4$ and then concentrated. The residue was purified by flash chromatography (silica gel, hexanes/acetone, 10:3), yielding 438 mg (83%) of 4-benzyloxy-2-hydroxy-3-(2-hydroxyethyl)-2-cyclopenten-1-one **1b** as a white solid; ^{1}H NMR (500 MHz $CDCl_3$): δ 2.38 (dd, 1H, $J=1.0$ and 18.3 Hz, H-5), 2.65 (m, 2H, H-3′), 2.68 (dd, 1H, $J=5.5$ and 18.3 Hz, H-5), 3.70 (bs, 1H, OH), 3.85 (ddd, 1H, $J=4.3$, 7.0 and 11.0 Hz, H-3″), 3.89 (ddd, 1H, $J=4.5$, 6.4 and 11.0 Hz, H-3″), 4.52 and 4.63 (both d, 2H, $J=11.6$ Hz, Bn CH_2), 4.53 (dd, 1H, $J=1.0$ and 5.5 Hz, H-4), 7.30–7.38 (m, 5H, Bn), 7.90 (bs, 1H, OH); ^{13}C NMR (125 MHz $CDCl_3$): δ 30.17 (C-3′), 39.50 (C-5), 60.36 (C-3″), 71.72 (Bn CH_2), 74.57 (C-4), 127.96 (*o*-Bn), 128.08 (*p*-Bn), 128.55 (*m*-Bn); 137.22 (*s*-Bn), 141.10 (C-3), 151.34 (C-2), 199.54 (C-1); IR (KBr, cm^{-1}): 3448, 3091, 2875, 1707, 1666, 1498, 1432, 1391, 1119, 1092, 1071; EI (*m*/*z*, %): 218 (1.3), 157 (9.1), 142 (13.2), 112 (23.1), 108 (52.3), 107 (36.3), 91 (100).

4.2. Typical procedure for the synthesis of lactone-acids by asymmetric oxidation of 3-hydroxyethyl-1,2-cyclopentanediones

To a solution of Ti(O*i*Pr)$_4$ (0.3 mL, 1 mmol) and 4Å powdered molecular sieves (100 mg) in CH_2Cl_2 (6 mL), (+)-DET (0.21 mL, 1.25 mmol for **1a** and 0.27 mL, 1.6 mmol for **1b**) was added and the mixture stirred for 15 min at −20°C. After the 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 kept at −20°C for a requisite time (**1a**: 68 h; **1b**: 45h). The reaction was quenched by stirring with a solution of citric acid (192 mg, 1 mmol in a mixture of 10% acetone in ether, 30 mL) 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).

4.2.1. (*R*)-3-(3-Hydroxy-2-oxotetrahydrofuran-3-yl)propanoic acid, 8a. Diketone **1a** was oxidized according to the typical procedure and purified by column chromatography (petroleum ether/acetone 10:3 to 10:6) to afford lactone acid **8a** as a white solid (130 mg, 75%); ee >95%; $[\alpha]_D^{20}=+13$ (*c* 2.04, MeOH); ^{1}H NMR (500 MHz $CDCl_3$+CD_3OD): δ 1.75 (ddd, 1H, $J=6.2$, 9.2 and 15.0 Hz, H-3), 1.91 (ddd, 1H, $J=6.2$, 9.2 and 15.0 Hz, H-3), 2.07 (ddd; 1H, $J=6.0$, 7.0 and 13.5 Hz, H-4′), 2.10 (ddd, 1H, $J=7.0$, 8.0 and 13.5 Hz, H-4′), 2.10 (ddd, 1H, $J=7.0$, 8.0 and 13.5 Hz, H-4′), 2.29 (ddd, 1H, $J=6.2$, 9.2 and 16.6 Hz, H-2), 2.34 (ddd, 1H, $J=6.2$, 9.2 and 16.6 Hz, H-2), 4.06 (ddd, 1H, $J=7.0$, 8.0 and 9.0 Hz, H-5′), 4.19 (ddd, 1H, $J=6.0$, 7.0 and 9.0 Hz, H-5′); ^{13}C NMR (125 MHz $CDCl_3$+CD_3OD): δ 27.57 (C-2), 30.35 (C-3), 34.71 (C-4′), 65.06 (C-5′), 73.13 (C-3′), 175.52 (C-1), 178.44 (C-2′).

4.2.2. 3-(Benzyloxy)-3-(3-hydroxy-2-oxotetrahydrofuran-3-yl)propanoic acids, 8b. Diketone **1b** (192 mg, 0.77 mmol) was oxidized according to the typical procedure and purified by column chromatography (petroleum ether/acetone 10:2 to 10:5) to afford a mixture of lactone acids **8b** (123 mg, 57%) and acetals **6b** and **6c** (18 mg, 9%, as a sum). **8b**: ^{1}H NMR (500 MHz $CDCl_3$), δ 2.35 (t, 2H, $J=7.1$ Hz, H-4′), 2.71 (dd, 1H, $J=6.8$ and 16.6 Hz, H-2), 3.02 (dd, 1H, $J=4.9$ and 16.6 Hz, H-2), 4.21 (m, 2H, H-3 and H-5′), 4.30 (m, 1H, H-5′), 4.60 and 4.71 (both d, 2H, $J=11.2$ Hz, Bn CH_2), 7.23–7.23 (m, 5H,Bn); ^{13}C NMR (125 MHz $CDCl_3$): δ 34.33 (C-4′), 35.07 (C-2), 65.86 (C-5′), 73.44 (Bn CH_2), 75.90 (C-3′), 78.99 (C-3), 127.95 (*o*-Bn), 127.96 (*p*-Bn), 128.38 (*m*-Bn), 137.08 (*s*-Bn), 176.45 (C-1). **6b**: (atom numbering according to **8b**), ^{1}H NMR (500 MHz $CDCl_3$), δ 2.15 (ddd, 1H, $J=8.0$, 8.7 and 13.2 Hz, H-4′), 2.35 (ddd, 1H, $J=4.0$, 6.7 and 13.2 Hz, H-4′), 2.59 (dd, 1H, $J=3.6$ and 18.1 Hz, H-2), 2.84 (dd, $J=5.5$ and 18.1 Hz, H-2), 3.50 (bs, 1H, OH), 3.96 (bs, 1H, OH), 3.97 (ddd, 1H, $J=4.0$, 8.0 and 8.7 Hz, H-5′), 4.05 (dd, 1H, $J=3.6$ and 5.5 Hz, H-3), 4.23 (dt, 1H, $J=6.7$ and 2*8.7 Hz, H-5′), 4.60 and 4.71 (both d, 2H, $J=11.9$ Hz, Bn CH_2O), 7.30–7.40 (m, 5H, Bn); ^{13}C NMR (125 MHz $CDCl_3$): δ 37.87 (C-4′), 39.57 (C-2), 67.82 (C-5′), 72.21 (Bn CH_2), 75.62 (C-3), 83.72 (C-3′), 101.30 (C-2′), 127.91 (*o*-Bn), 128.34 (*p*-Bn), 128.68 (*m*-Bn), 136.62 (*s*-Bn), 205.77 (C-1). **6c**: (atom numbering according to **8b**), ^{1}H NMR (500 MHz $CDCl_3$), δ 2.18 (ddd, 1H, $J=4.6$, 6.7 and 13.3 Hz, H-4′), 2.69 (td, 1H, $J=2$*8.0, and 13.3 Hz, H-4′), 2.72 (dd, 1H, $J=8.0$ and 18.0 Hz, H-2), 2.73 (dd, $J=8.0$ and 18.0 Hz, H-2), 3.09 (bs, 1H, OH), 4.04 (t, $J=2$*8.0 Hz, H-3), 4.08 (dt, 1H, $J=4.6$ and 2* 8.0 Hz, H-5′), 4.24 (dt, 1H, $J=6.7$ and 2*8.0 Hz, H-5′), 4.46 (bs, 1H, OH), 4.65 and 4.72 (both d, 2H, $J=11.9$ Hz, Bn CH_2O), 7.30–7.40 (m, 5H, Bn); ^{13}C NMR (125 MHz $CDCl_3$): δ 35.35 (C-4′), 40.72 (C-2), 68.94 (C-5′), 72.33 (Bn CH_2), 78.93 (C-3), 86.31 (C-3′), 102.62 (C-2′), 127.66 (*o*-Bn), 127.93 (*p*-Bn), 128.50 (*m*-Bn), 137.49 (*s*-Bn), 206.17 (C-1).

4.3. Synthesis of 1,7-dioxaspiro[4.4]nonane-2,6-diones

4.3.1. (5*R*)-1,7-Dioxaspiro[4.4]nonane-2,6-dione, 9. To a solution of lactone-acid **8a** (56 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) 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 over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, petroleum ether/acetone, 10:3) giving spirodilactone **9** as white crystals (47 mg, 94%); mp 78–79°C; ee>95%; $[\alpha]_D^{20}=+72$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 2.30 (m, 1H, H-4), 2.42 (ddd, 1H, $J=7.0$, 7.7 and 13.9 Hz, H-9), 2.59 (m, 1H, H-4), 2.63 (m, 1H, H-3), 2.69 (ddd, 1H, $J=5.2$, 7.3 and 13.9 Hz, H-9), 2.93 (m, 1H, H-3), 4.39 (ddd, 1H, $J=5.2$, 7.7 and 9.3 Hz, H-8), 4.47 (td, 1H, $J=2$*7.1 and 9.3 Hz, H-8); ^{13}C NMR (125 MHz $CDCl_3$): δ 27.86 (C-3), 29.25 (C-4), 34.15 (C-9), 65.45 (C-8), 82.05 (C-5), 174.04 (C-2), 174.83 (C-6); IR (KBr, cm^{-1}): 2947, 2922, 1786, 1248, 1224, 1069, 1007; EI (*m*/*z*, %): 156 (M^+, 1.0), 112 (80.3), 98 (37.1), 84 (12.8), 70 (11.9), 56 (100); CI (*m*/*z*, %): 157 ($M+H^+$, 76). Anal. calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.92; H, 5.17%.

4.3.2. 4-Benzyloxy-1,7-dioxaspiro[4.4]nonane-2,6-diones, (4*R*,5*S*)-10 and (4*S*,5*S*)-11. A mixture of lactone-acids **8b** (89 mg, 0.32 mmol) was cyclisized according to the procedure above for **8a**. Flash chromatography (silica gel, petroleum ether/acetone 10:1.5 to 10:2.5) afforded spirodilactones **10** and **11**. Compound **10**: white crystals (63 mg, 75%); mp 148–150°C; ee 86%; $[\alpha]_D^{21} = -42$ (*c* 4.09, CH_2Cl_2); ^1H NMR (500 MHz $CDCl_3$+CD_3OD): δ 2.33 (ddd, 1H, $J = 2.1$, 6.5 and 13.7 Hz, H-9), 2.65 (ddd, 1H, $J = 9.0$, 10.0 and 13.7 Hz, H-9), 2.69 (dd, 1H, $J = 7.7$ and 17.1 Hz, H-3), 2.82 (dd, 1H, $J = 9.4$ and 17.1 Hz, H-3), 4.20 (ddd, 1H, $J = 6.5$, 9.0 and 10.0 Hz, H-8), 4.32 (dd, 1H, $J = 7.7$ and 9.4 Hz, H-4), 4.33 (dt, 1H, $J = 2.1$ and 2*9.0 Hz, H-8); 4.43 and 4.56 (both d, 2H, $J = 12.0$ Hz, Bn CH_2O), 7.19 (m, 2H, *o*-Bn), 7.23 (m, 1H, *p*-Bn), 7.26 (m, 2H, *m*-Bn); ^{13}C NMR (125 MHz $CDCl_3$+CD_3OD): δ 32.17 (C-9), 33.87 (C-3), 64.84 (C-8), 72.59 (Bn CH_2), 79.27 (C-4), 83.58 (C-5), 127.59 (*o*-Bn), 128.23 (*p*-Bn), 128.47 (*m*-Bn), 135.99 (*s*-Bn), 172.16 (C-2), 172.69 (C-6); IR (KBr, cm^{-1}): 3043, 2918, 2889, 1821, 1787, 1604, 1497, 1456, 1380, 1362, 1212, 1118, 1075, 1010; EI (*m*/*z*, %): 174 (0.4), 157 (4.3), 138 (7.1), 112 (14.3), 107 (59.8), 91 (100); CI (*m*/*z*, %): 263 ($M+H^+$, 28). Anal. calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.20; H, 5.30%.

Compound **11**: colourless oil (11 mg, 13%); ee 93%; $[\alpha]_D^{21} = +153$ (*c* 0.89, $CHCl_3$); ^1H NMR (500 MHz $CDCl_3$): δ 2.55 (ddd, 1H, $J = 5.8$, 7.6 and 14.2 Hz, H-9), 2.72 (dd, 1H, $J = 2.3$ and 17.8 Hz, H-3), 2.85 (ddd, 1H, $J = 6.5$, 7.7 and 14.2 Hz, H-9), 3.07 (dd, 1H, $J = 6.1$ and 17.8 Hz, H-3), 4.28 (ddd, 1H, $J = 5.8$, 7.7 and 9.2 Hz, H-8), 4.30 (dd, 1H, $J = 2.3$ and 6.1 Hz, H-4), 4.46 (ddd, 1H, $J = 6.5$, 7.6 and 9.2 Hz, H-8); 4.46 and 4.67 (both d, 2H, $J = 11.8$ Hz, Bn CH_2O), 7.30 (m, 2H, *o*-Bn), 7.37 (m, 1H, *p*-Bn), 7.38 (m, 2H, *m*-Bn); ^{13}C NMR (125 MHz $CDCl_3$): δ 28.86 (C-9), 34.47 (C-3), 66.01 (C-8), 71.88 (Bn CH_2), 75.32 (C-4), 85.82 (C-5), 127.93 (*o*-Bn), 128.55 (*p*-Bn), 128.78 (*m*-Bn), 136.18 (*s*-Bn), 172.72 (C-2), 173.03 (C-6); IR (film, cm^{-1}): 3065, 2924, 2874, 1792, 1498, 1456, 1383, 1220, 1135, 1095, 1019; EI (*m*/*z*, %): 262 (M^+, 3.8), 174 (6.1), 118 (2.0), 107 (4.2), 91 (100); CI (*m*/*z*, %): 263 ($M+H^+$, 13). Anal. calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.37; H, 5.48%.

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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