Pergamon

Tetrahedron Letters 41 (2000) 6883–6887

TETRAHEDRON LETTERS

Asymmetric oxidation of 1,2-cyclopentanediones

Anne Paju,[a] Tõnis Kanger,[b] Tõnis Pehk[c] and Margus Lopp[a,*]

[a]*Department of Chemistry, Tallinn Technical University, Ehitajate tee 5, 19086 Tallinn, Estonia*
[b]*Institute of Chemistry at Tallinn Technical University, Akadeemia tee 15, 12618 Tallinn, Estonia*
[c]*National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia*

Received 4 May 2000; accepted 29 June 2000

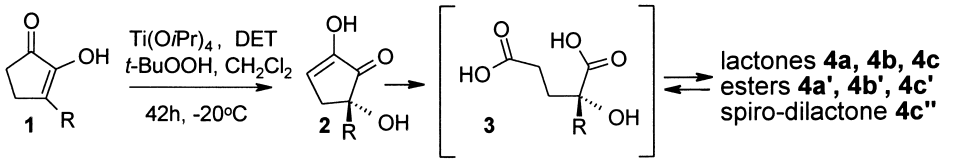
Abstract

Cyclic 3-alkyl-1,2-cyclopentanediones undergo a direct asymmetric oxidation with the DET/Ti(O*i*Pr)$_4$/*t*BuOOH oxidative system, resulting in enantiomeric α-hydroxy compounds and ring-cleaved hydroxylated acids (lactones) up to 95% *ee*.

Keywords: asymmetric reaction; oxidation; hydroxylation; lactones.

The titanium tetraisopropoxide/diethyl tartrate/*tert*-butyl hydroperoxide (Ti(O*i*Pr)$_4$/DET/*t*BuOOH) catalyst system developed by Sharpless et al.[1] has been widely used in the asymmetric oxidation of allylic alcohols[1] and sulfides.[2] Recently, we found that several ketones are also oxidized under the conditions of the Sharpless oxidation: cyclobutanones undergo asymmetric Baeyer–Villiger oxidation,[3] resulting in enantiomerically enriched lactones,[4] and β-hydroxyketones undergo asymmetric α-hydroxylation,[5] resulting in α,β-dihydroxy ketones[6] in high enantiomeric purity. On the basis of these results, it may be assumed that the unique properties of the Ti/DET complex could be used more extensively in asymmetric synthesis.

We investigated the oxidation of different 3-alkyl-cyclopentane-1,2-diones[7] **1** using Sharpless oxidation conditions and found that they undergo a direct asymmetric oxidation, resulting in enantiomerically enriched products (Scheme 1). The results obtained are presented in Table 1.

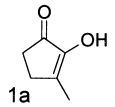
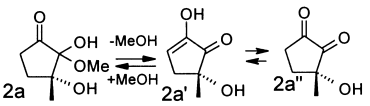
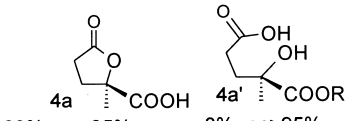
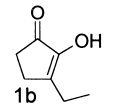
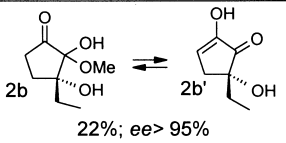
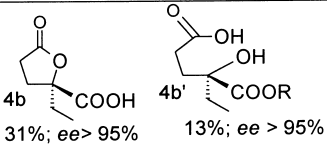
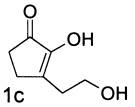
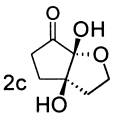
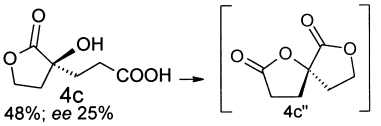
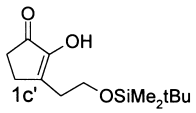
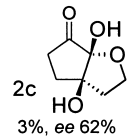
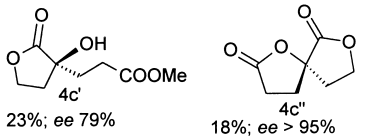


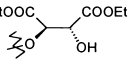
Scheme 1.

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

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01106-0

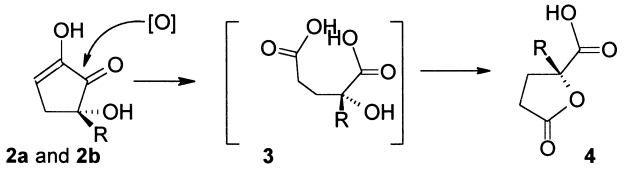
Table 1
Oxidation of cyclopentanediones under Sharpless oxidation conditions[a]

Entry	Cyclic dione	Hydroxylation products yield% / *ee*%	Ring cleavage oxidation products yield% / *ee*%
1[b]	 1a	 2a, 2a', 2a'' 40%; *ee* >95%	 4a 23%, *ee*>95%; 4a' 8%, *ee*>95%
2[b]	 1b	 2b, 2b' 22%; *ee*> 95%	 4b 31%; *ee*> 95%; 4b' 13%; *ee* > 95%
3[c]	 1c	 2c 25%; *ee* 30%	 4c 48%; *ee* 25%; 4c''
4[b]	 1c'	 2c 3%, *ee* 62%	 4c' 23%; *ee* 79%; 4c'' 18%; *ee* > 95%

[a] Isolated yields after chromatography on silica gel; *ee* of compounds was determined as follows: **2** and **4c**, **4c'**, **4c''** by HPLC using a chiral column (Daicel Chiralcel ODH); **4a** and **4b** by NMR from the (-) menthol esters of the compounds; **4a'** and **4b'** by NMR, in the cases of **4a**, **4b**, **4a'** and **4b'** no traces of diastereomeric compounds were observed.
[b] Conditions: Ti(O*i*Pr)$_4$/(+)DET/*t*BuOOH ratio 1:1.6:1.5; -20°C, 42h; reaction was quenched by adding citric acid (CH_2Cl_2 with 10% of methanol); R= 
[c] Conditions: Ti(O*i*Pr)$_4$/(+)DET/*t*BuOOH ratio 2:2.5:1.5; -20°C, 42h; reaction was quenched by adding citric acid (ether with 10% of acetone); acid **4c** was separately converted into spiro-lactone **4c''** using p-TsOH as a catalyst in CH_2Cl_2

The formation of two major types of oxidation product was observed: primary hydroxylation products **2** and derivatives of more oxygenated, ring-cleaved, hydroxylation products **3** (isolated as lactones **4**). The enantiomeric purity of both types of the products is high in the case of 3-alkylsubstituted substrates **1a** and **1b**, while in the case of the hydroxyethyl substrates **1c** and **1c′** the enantiomeric purity of the products is moderate. In the case of the silyl protected substrate **1c′**, the *ee* is considerably higher than in the case of the unprotected OH compound **1c**. The latter may result in a complex where two chiral ligands are attached. This may cause opposite face selection and reduce the total enantioselectivity. Also, the deprotection of **1c′** that occurs during the course of the oxidation may reduce the enantioselectivity.

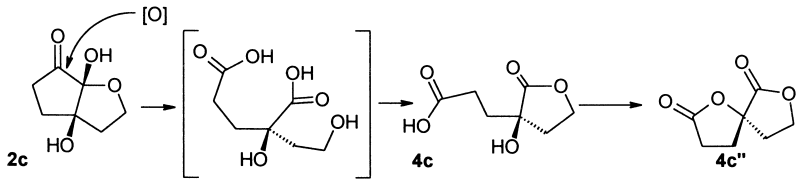
We assume that at first the α-hydroxylation reaction results in hemiacetals **2a**, **2b** and **2c**, or enols **2a′** and **2b′**, correspondingly.[8] In the case of the hydroxyethyl substrates (**1c** and **1c′**), the primary oxidation products form bicylic intramolecular acetals **2c**. All these hydroxylated diketones **2a** and **2b** may be oxidized further, resulting in the ring cleavage products, i.e. the derivatives of the aliphatic diacids **3** (isolated as lactones and esters **4a** and **4b**, respectively) (Scheme 2). In the same way, the bicyclic acetal **2c** oxidizes further, resulting in the lactones **4c** and spiro-



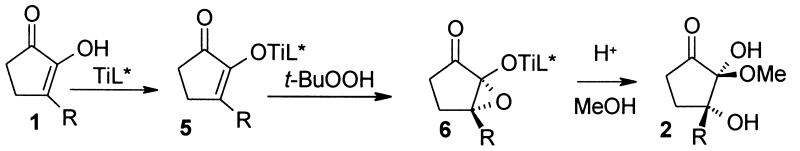
Scheme 2.

dilactone **4c**″. In the case of the substrate **1c**′, the hydrolysis was performed in a methanolic mixture and a methyl ester **4c**′ was also formed, together with the spiro-dilactone **4c**″ (Scheme 3).

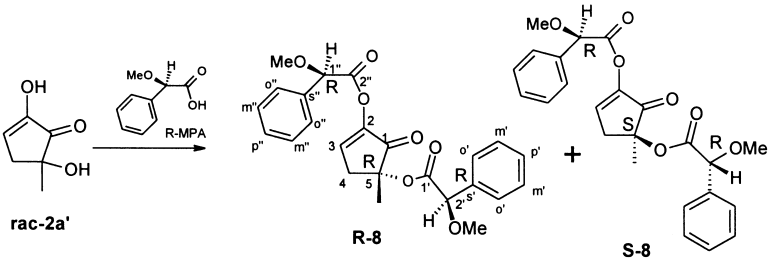
We assume that the Ti catalyst forms, at first, in enolate complex **5** with substrate **1**. This complex is responsible for the asymmetric induction and directs the facial selection. Then, the intermediate epoxide **6** undergoes methanolysis, resulting in formation of the acetal **2** (Scheme 4). The structures of all the reaction products obtained were established on the basis of NMR studies (2D ^{1}H–^{1}H and ^{1}H–^{13}C COSY correlation was applied when necessary).[9] To determine the absolute configuration of compound **2a**′, the di-(*R*)-MPA ester **8** from compound **2a**′ and the corresponding diastereomeric ester mixtures from racemic **2a**′ were made. The ^{13}C NMR spectra of the diastereomeric mixture *rac*-**8** and **8** (Scheme 5) gave regular and well-defined effects derived from the second aromatic nucleus (the ester of the tertiary alcohol), shifting the C-1 (0.30 ppm), C-4 (0.32 ppm) and H-4 (0.18 and 0.17 ppm) signals in opposite directions. On the basis of these values, the absolute configuration of **2a**′ was determined assuming that the same regularities are observed as are known for secondary alcohols[10] (in the present case the position of the carbinol proton is replaced by the methyl group). Thus, the *R* configuration is proposed for **2a**′ on the basis of all ^{1}H and ^{13}C chemical shifts[11] and their analysis, as described in the literature.[10]



Scheme 3.



Scheme 4.



Scheme 5.

Acknowledgements

Support from the Estonian Science Foundation (Grant Nos. 3834, 3781 and 3164) is acknowledged.

References

1. Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: NewYork, 1991; Vol. 7, Chapter 3.2, pp. 389–436. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
2. Pitchen, P.; Dunach, E.; Desmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193. Furia, F. D.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325–326.
3. For some other possibilities for asymmetric Baeyer–Villiger oxidation of cycloalkanones, see: Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848–1849. Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1247–1248. Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *38*, 6019–6022. Bolm, C.; Schlingloff, G.; Bienewald, F. *J. Mol. Catal. A: Chemical* **1997**, *117*, 347–350. Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151–1152. Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737–750.
4. Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583–7586. Kanger, T.; Kriis, K.; Paju, A.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **1998**, *9*, 4475–4482.
5. For enantiomeric α-hydroxyketones, see: Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919–934 and references cited therein. Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067–5068. Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4389–4392. Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708–714.
6. Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1997**, *38*, 5051–5054.
7. Compounds **1a** and **1b** were obtained from Aldrich; **1c** and **1c′** were prepared from 2-cyclopentene-1-acetic acid.
8. Diketone **2a″** was also seen in ^{13}C NMR spectra (depending on the solvent used).
9. The structures of obtained compounds were confirmed by their fully assigned 500.17 MHz ^{1}H and 125.7 MHz ^{13}C NMR spectra. Compound **2a**: ^{1}H NMR ($CDCl_3$) δ 1.95 and 2.02 (H-4, m), 2.38 (H-5, m), 3.19 (2-OMe, s), 1.32 (3-Me, s), 2.43 and 4.31 (OH at C-2 and C-3); ^{13}C NMR δ 213.12 (C-1), 98.37 (C-2), 76.67 (C-3), 30.30 (C-4), 31.20 (C-5), 50.36 (2-OMe), 19.73 (3-Me). Compound **2a′** (DMSO-d_6), enol form: 6.32 (H-3, t, 3.2 Hz), 2.37 and 2.42 (H-4, dd, $J_{gem} = 17.3$ Hz), 1.16 (5-Me, s); ^{13}C NMR 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). Compound **2a″** (DMSO-d_6), keto form: ^{1}H NMR δ 2.10 (H-4, m), 2.41 and 2.45 (H-5, m), 1.27 (3-Me, s); ^{13}C NMR 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), different from the starting compound **1**, which exists predominantly (>97%) in the enol form in chloroform or in DMSO solution; both forms of **2a′** and **2a″** are seen without any indication of exchange in room temperature NMR spectra. Compound **2b** (*as 3-ethyl-2,3-dihydroxy-2-methoxycyclopentanone*): ^{1}H NMR ($CDCl_3$) δ 1.94 (H-4, m), 2.41 (H-5, m), 3.18 (2-OMe, s), 1.68 (3-Et CH_2, m), 0.98 (3-Et Me, t 7.5); ^{13}C NMR 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), 6.73 and 25.75 (3-Et). Compound **2b′** (*as 5-ethyl-2,5-*

dihydroxy-cyclopent-2-en-1-one): ^{1}H NMR ($CDCl_3$) δ 6.57 (H-3, t, 3.2 Hz), 2.53 and 2,63 (H-4, both dd, J_{gem} = 17.6 Hz), 0.91 (5-Et methyl, t, 7.5 Hz), 1.65 and 1.70 (CH_2 of Et, q 7.5, d 13.7), 6.2 and 2.8 (2- and 5-OH, bs); ^{13}C NMR δ 205.27 (C-1), 150.42 (C-2), 129.63 (C-3), 36.29 (C-4), 75.95 (C-5), 31.15 and 7.66 (5-Et). Compound **2c** (*as 1,5-dihydroxy-2-oxabicyclo[3.3.0]octan-8-one*): ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.80 and 4.05 (H-3, m), 2.05 (H-4, m), 1.87 and 1.92 (H-6, m), 2.34 and 2.36 (H-7, m); ^{13}C NMR 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). Compound **4a** (*as 2-methyl-5-oxotetrahydrofuran-2-carboxylic acid*): ^{1}H NMR ($CDCl_3$) δ 1.70 (CH_3, s), 2.20 (H-3, t 9.9, d 13.4), 2.60 (H-3, d 3.8, d 9.8, d 13.4), 2.63 and 2.72 (H-4, m), 10.4 (COOH); ^{13}C NMR δ 83.50 (C-2), 32.87 (C-3), 28.29 (C-4), 176.71 (C-5), 23.37 (2-Me), 176.31 (2-COOH). Compound **4b** (*as 2-ethyl-5-oxotetrahydrofuran-2-carboxylic acid*): ^{1}H NMR ($CDCl_3$) δ 1.02 (CH_3, t 7.5), 1.89 and 2.12 (CH_2 of Et, q 7.5, d 14.3), 2.23 (H-3, t 9.8, d 13.5), 2.53 (H-3, d 3.9, d 9.8, d 13.5), 2.57 and 2.63 (H-4, m), 9.90 (COOH); ^{13}C NMR δ 86.97 (C-2), 30.97 (C-3), 28.08 (C-4), 176.39 (C-5), 8.03 and 30.33 (2-Et), 176.11 (2-COOH). Compound **4c** (*as 3-(3-hydroxy-2-oxotetrahydrofuran-3-yl)propanoic acid*): ^{1}H NMR ($CDCl_3$) δ 2.30 and 2.34 (H-2, m), 1.75 and 1.91 (H-3, m), 2.09 and 2.11 (H-4′, m), 4.06 and 4.19 (H-5′, m); ^{13}C NMR δ 175.52 (C-1), 27.57 (C-2), 30.35 (C-3), 178.44 (C-2′), 73.13 (C-3′), 34.74 (C-4′), 65.06 (C-5′). Compound **4c′** (*as methyl-3-(3-hydroxy-2-oxotetrahydrofuran-3-yl)propanoate*): ^{1}H NMR ($CDCl_3$) δ 2.59 and 2.61 (H-2, m), 2.03 and 2.15 (H-3, m), 2.26 and 2.38 (H-4′, m), 4.25 and 4.41 (H-5′, m), 3.70 (OMe, s); ^{13}C NMR δ 174.25 (C-1), 28.13 (C-2), 30.85 (C-3), 178.09 (C-2′), 73.82 (C-3′), 35.27 (C-4′), 65.15 (C-5′), 52.08 (OMe). Compound **4c″** (*as 1,7-dioxaspiro[4.4]nonane-2,6-dione*): ^{1}H NMR ($CDCl_3$) δ 2.64 and 2.93 (H-3, m), 2.29 and 2.59 (H-4, m), 4.39 and 4.47 (H-8, m), 2.42 and 2.69 (H-9, m); ^{13}C NMR δ 174.04 (C-2), 27.86 (C-3), 29.25 (C-4), 82.05 (C-5), 174.83 (C-6), 65.45 (C-8), 34.15 (C-9).

10. Pehk, T.; Lippmaa, E.; Lopp, M.; Paju, A.; Borer, B. C.; Taylor, R. J. K. *Tetrahedron: Asymmetry* **1993**, *4*, 1527–1532.
11. 500.17 MHz ^{1}H and 125.7 MHz ^{13}C NMR spectra ($CDCl_3$). Compound *R*-**8**: ^{1}H NMR δ 7.24 (H-3, t 3.2), 2.65 and 2.89 (H-4, dd, J_{gem} = 18.1), 4.78 and 4.97 (H-1″ and H-2′, s), 3.45 and 3.49 (OMe, s), 7.35–7.50 (*o*, *m*, *p*); ^{13}C NMR δ 195.67 (C-1), 146.21 (C-2), 139.71 (C-3), 37.57 (C-4), 78.59 (C-5), 167.64 and 169.73 (C-1′ and C-2″), 82.12 and 82.26 (C-1″ and C-2′), 57.54 and 57.70 (C-OMe), 135.19 and 135.54 (s′ and s″), 127.15 and 127.38 (*o*′ and *o*″), 128.65 and 128.78 (*m* and *m*′), 128.83 and 129.06 (*p* and *p*′). Compound *S*-**8**: ^{1}H NMR δ 7.07 (H-3, t 3.2), 2.54 and 2.71 (H-4, dd, J_{gem} = 18.1), 4.49 and 5.00 (H-1″ and H-2′, s), 3.41 and 3.49 (OMe, s), 7.35–7.50 (*o*, *m*, *p*); ^{13}C NMR 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 (C-1′ and C-2″), 81.82 and 81.98 (C-1″ and C-2′), 57.50 and 57.67 (C-OMe), 135.21 and 135.70 (s′ and s″), 127.22 and 127.40 (*o*′ and *o*″), 128.72 and 128.82 (*m* and *m*′), 128.90 and 129.11 (*p* and *p*′).