Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4491–4493
Tetrahedron Letters

Asymmetric synthesis of 2-alkyl-substituted 2-hydroxyglutaric acid γ-lactones

Anne Paju,[a] Marit Laos,[a] Artur Jõgi,[a] Malle Päri,[a] Raissa Jäälaid,[b] Tõnis Pehk,[c] Tõnis Kanger[a] and Margus Lopp[a,*]

[a]*Department of Chemistry, Faculty of Science, Tallinn University of Technology, Ehitajate tee 5, 19086, Tallinn, Estonia*
[b]*Competence Centre for Cancer Research, Akadeemia tee 15, 12618 Tallinn, Estonia*
[c]*National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia*

Received 6 February 2006; revised 30 March 2006; accepted 6 April 2006
Available online 11 May 2006

Abstract—3-Alkyl-1,2-cyclopentanediones **1** are transformed into 2-alkyl-2-hydroxyglutaric acid γ-lactones **3** in up to 83% isolated yields and up to 96% ee, affording a simple access to many bioactive compounds, including diacylglycerol lactones (DAG-lactones).

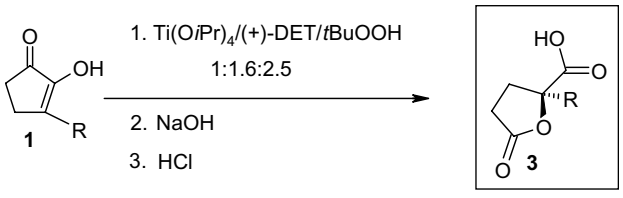
Chiral 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acid (2-alkyl-2-hydroxyglutaric acid γ-lactone) units are present in the structures of various natural compounds with potential pharmacological applications.[1] Additionally, monoprotected 5-bis(hydroxymethyl)tetrahydro-2-furanones are convenient templates for diacylglycerol lactones (DAG-lactones), which are found to be more potent protein kinase C inhibitors than the parent natural compounds, and can be regarded as promising therapeutic agents for treatment of cancer, diabetes, etc.[2]

There are several approaches which describe methods for the synthesis of these chiral tertiary γ-lactone structures, including enzymatic desymmetrization of parent esters[3] and chemical synthesis from natural chiral compounds.[1b,4] However, there are only a few examples of the asymmetric chemical synthesis of related structures, using a chiral auxiliary,[5] chiral reagent[1a] and chiral catalyst.[1d,2a]

We have previously found that 3-alkyl-cyclopentane-1,2-diones **1**, are oxidized with the chiral Ti(O-*i*-Pr)$_4$/tartaric ester/*t*-BuOOH complex resulting in a mixture of different oxidation products, and amongst them 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acids **3** in 28–44% yields.[6] We have now developed a simple and practical method for the synthesis of enantiomerically enriched 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acids **3**, which may serve as a base for various substituted lactones, including templates for DAG-lactones and their analogues (Scheme 1).

While oxidizing 3-substituted cyclopentane-1,2-diones with the Ti(O-*i*-Pr)$_4$/tartaric ester/*t*-BuOOH complex in a 1:1.6:2.5 ratio the main oxidized products appear in a complex mixture (mixture A), containing 3-hydroxyacetals **2**, lactones **3**, mono-esters **4**, dimeric esters **5** (characteristic only for **1d** and **1e**) and keto acid **6**, which required a laborious chromatographic separation (Scheme 2).

The mixture A contained two types of esters, in which **3** and **4** are base sensitive and **5** is acid sensitive. Hence, a base/acid work-up procedure was applied in order to

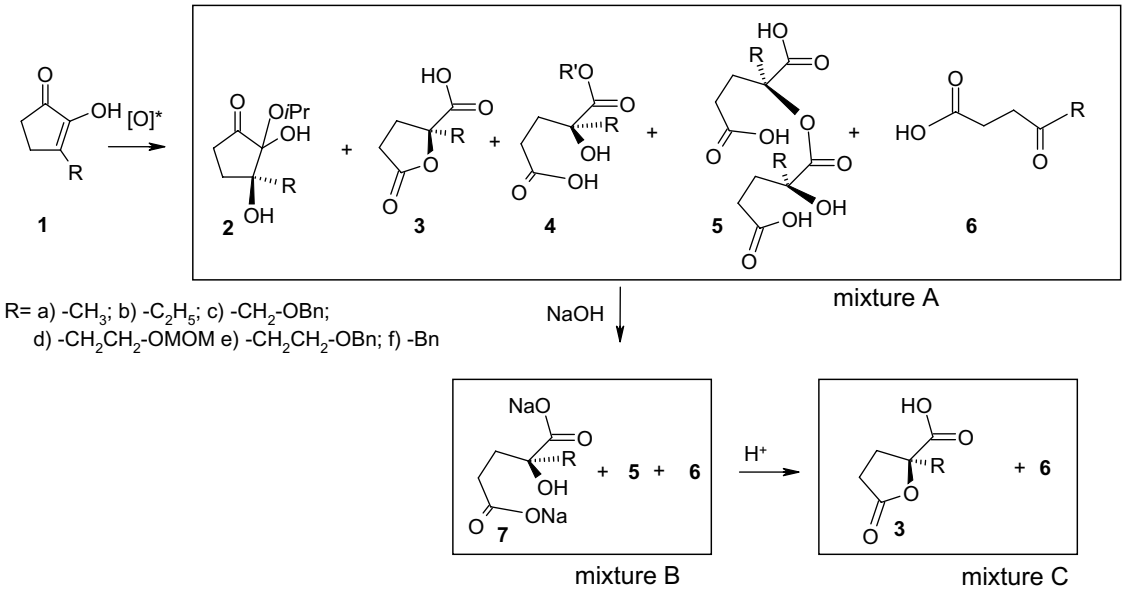


R= a) -CH_3; b) -C_2H_5; c) -CH_2-OBn;
d) -CH_2CH_2-OMOM e) -CH_2CH_2-OBn; f) -Bn

Scheme 1.

Keywords: Asymmetric oxidation; Tetrahydrofuran carboxylic acid; DAG-lactone; 2-Hydroxyglutaric acid lactone.
* Corresponding author. Tel.: +372 620 2802; fax: +372 620 2995; e-mail: lopp@chemnet.ee

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.013



Scheme 2.

simplify it and thus obtain lactone acids **3** by crystallization or by simple chromatography. Thus, basic treatment of the mixture A converted lactones **3** and mono-esters **4** to the same diacid salt **7**. Furthermore, the mono-oxidation product **2**, which is always present after oxidation in mixture A[6b] was also oxidized with the excess *t*-BuOOH in the mixture during basic work-up and also formed salt **7** (this transformation was confirmed in a separate experiment with isolated acetal **2**). As a result, a three component mixture B was formed, which consisted of salt **7**, dimer **5** (in the case of **1d** and **1e**, 17% and 13%, respectively), and keto acid **6** (as a decarboxylation product of lactone acid **3**). When mixture B was treated with acid, lactone **3** was formed as the main product.[7] Dimer **5** was hydrolyzed under the acidic conditions (confirmed in a separate experiment in the case of **5e**, using a mixture of AcOH–*i*-PrOH–H_2O 4:4:1)[8] also resulting in lactone acid **3**. Lactone acid **3** and achiral keto acid **6** which are formed after acidification of mixture B were easily separable by chromatography or crystallization. The results obtained are presented in Table 1.

According to the data obtained, the isolated yield of 2-alkyl lactone acids **3** was in the range of 69–83%. Also, the process is highly enantioselective (ee of the isolated lactone acids **3** is in the range of 93–99%).

Lactone acid **3c** is a convenient precursor of DAG-lactone template **8c**.[2,3b] Thus, benzyloxymethyl lactone acid **3c** was reduced with borane dimethylsulfide complex[4a] yielding the enantiomeric DAG-lactone template in one step and with a good yield (76%)[10] (Scheme 3).

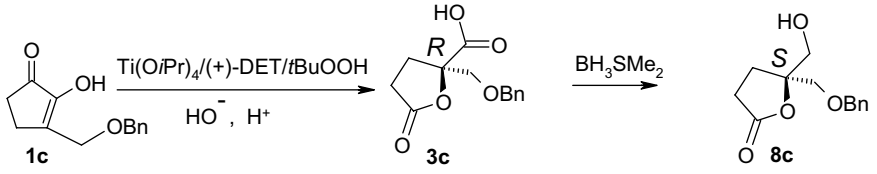
Table 1. Oxidation of 3-alkyl-cyclopentane-1,2-diones **1** with the Ti(O-*i*-Pr)$_4$/(+)-tartaric ester/*t*-BuOOH complex[7]

Entry	Substrate	Isolated lactone acid **3**[9]		Keto acid **6**
		Yield (%)	ee (%)	
1	**1a**[a]	75(60[b])	93(99[b])	6
2	**1b**	72	93	10
3	**1c**	75	96	3
4	**1d**	69[c]	94	—
5	**1e**	71[c]	95	3
6	**1f**[a]	83	96	6

[a] Both enantiomers were synthesized.
[b] From a 50 g scale experiment after recrystallization.
[c] Together with dimer **5**.

According to the optical rotation, the absolute configuration of **8c** is in accordance with that from our previous determinations of 2-methyl-5-oxotetrahydrofuran-2-carboxylic acid **3a**[6b] and homocitric acid lactone[11] from the asymmetric oxidation; as expected, from diketone **1c** with (+)-diethyl tartrate, lactone acid **3c** with *R*-configuration and lactone **8c** with *S*-configuration were obtained.[4b]

The method described opens a simple, straightforward and highly efficient procedure for synthesizing enantiomeric 2-alkyl-2-hydroxyglutaric acid γ-lactones, DAG-lactone templates and other compounds of similar



Scheme 3.

structure from 3-alkyl-1,2-cyclopentane diones. The method also has preparative utility.

Acknowledgements

Support from the Estonian Science Foundation (Grant Nos 5628 and 6778), from the Estonian Ministry of Education and Science (Grant 0142725s06) and from the Competence Centre for Cancer Research is acknowledged.

References and notes

1. (a) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 4569–4577; (b) Makino, K.; Shintani, K.; Yamatake, T.; Hara, O.; Hatano, K.; Hamada, Y. *Tetrahedron* **2002**, *58*, 9737–9740; (c) Masaki, H.; Mizozoe, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Tetrahedron Lett.* **2000**, *41*, 4801–4804; (d) Janecki, T.; Błaszcyk, E.; Studzian, K.; Rózalski, M.; Krajewska, U.; Janecka, A. *J. Med. Chem.* **2002**, *45*, 1142–1145.
2. (a) Kang, J.-H.; Siddiqui, M. A.; Sigano, D. M.; Krajewski, K.; Lewin, N. E.; Pu, Y.; Blumberg, P. M.; Lee, J.; Marquez, V. E. *Org. Lett.* **2004**, *6*, 2413–2416; (b) Duan, D.; Lewin, N. E.; Sigano, D. M.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2004**, *47*, 3248–3254; (c) Lee, J.; Sharma, R.; Wang, S.; Milne, G. W. A.; Lewin, N. E.; Szallasi, Z.; Blumberg, P. M.; George, C.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 36–45.
3. (a) Pitacco, G.; Sessanta o Santi, A.; Valentin, E. *Tetrahedron: Asymmetry* **2000**, *11*, 3263–3267; (b) Chênevert, R.; Duguay, D.; Touraille, F.; Caron, D. *Tetrahedron: Asymmetry* **2004**, *15*, 863–866.
4. (a) Ravid, U.; Silverstein, R. M.; Smith, R. L. *Tetrahedron* **1978**, *34*, 1449–1452; (b) Lee, J.; Wang, S.; Milne, G. W. A.; Sharma, R.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 29–35.
5. (a) Dias, L. C.; de Castro, I. B. D.; Steil, L. J.; Augusto, T. *Tetrahedron Lett.* **2006**, *47*, 213–216; (b) Jang, D.-P.; Chang, J.-W.; Uang, B.-J. *Org. Lett.* **2001**, *7*, 983–985; (c) Donohoe, T. J.; Stevenson, C. A.; Helliwell, M.; Irshad, R.; Ladduwahetty, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1315–1322.
6. (a) Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron Lett.* **2000**, *41*, 6883–6887; (b) Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565–1573.
7. A typical synthetic procedure: to a solution of Ti(O-*i*-Pr)$_4$ (0.3 mL, 1 mmol) and 4 Å powdered molecular sieves (100 mg) in CH_2Cl_2 (6 mL) at −20 °C under an argon atmosphere, (+)-DET (0.27 mL, 1.6 mmol) was added and the mixture was stirred for 15 min. Then, 3-alkyl-2-hydroxy-2-cyclopenten-1-one (1 mmol) in CH_2Cl_2 (2.0 mL) was added and the reaction mixture was stirred for 30 min. Next *t*-BuOOH (0.4 mL, 2.5 mmol, 6.25 M solution in decane) was added and the reaction was kept at −20 °C for 68 h. Water (6.0 mL) was added and the mixture was stirred for 1 h at room temperature, then 1.2 mL of 30% NaOH in saturated NaCl solution[12] was added and the mixture was again stirred at room temperature for an additional 1 h. The CH_2Cl_2 layer was removed and the mixture was acidified with 1 M HCl solution (pH = 1) and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and concentrated HCl solution (0.2 mL) was added (in the case of **3d** a catalytic amount of *p*TsOH was used as the acid) and the mixture was stirred for 2 h at room temperature. Then, 10 mL of water was added and the CH_2Cl_2 layer was separated. The water layer was extracted with EtOAc and the combined extracts were dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by flash chromatography to give the corresponding γ-lactone acids **3**.
8. Kocieński, P. J. In *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, NY, 2004; pp 404–405.
9. The synthesized lactone acids have the following physical characteristics: Compounds **3a, 3b, 3e** are identical to those from Ref. 6b; Compound **3c**, 2-[(benzyloxy)methyl]-5-oxotetrahydrofuran-2-carboxylic acid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (br s, 1H, OH); 7.35 (m, 2H, *m*); 7.28–7.32 (m, 3H, *o*,*p*); 4.62 (s, 2H, Bn CH_2); 3.89 and 3.78 (dd, 2H, $J = 10.9$ Hz, CH_2O), 2.59–2.67 (m, 2H, H-4), 2.35–2.46 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.14 (C-5), 174.03 (COOH), 136.97 (*s*), 128.48 (*m*), 127.98 (*p*), 127.73 (*o*), 85.60 (C-2), 73.86 (Bn *C*H$_2$), 71.85 (*C*H$_2$O), 27.91 (C-4), 27.85 (C-3). $[\alpha]_D^{20}$ −10.3 (*c* 3.34, $CHCl_3$). Compound **3d**, 2-[2-(methoxymethoxy)ethyl]-5-oxotetrahydrofuran-2-carboxylic acid: ^{1}H NMR (500 MHz, $CHCl_3$): δ 8.70 (br s, 1H, OH); 4.57 (s, 2H, OCH$_2$O); 3.68–3.69 (m, 2H, OCH_2CH$_2$); 3.34 (s, 3H, OCH$_3$); 2.52 and 2.36 (m, 2H, H-4); 2.18 and 1.98 (m, 2H, OCH$_2$CH_2); 2.16 and 2.02 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.86 (C-1), 178.47 (C-5), 96.24 (OCH$_2$O), 75.57 (C-2), 63.58 (*C*H$_2$O), 55.34 (OCH$_3$), 37.88 (OCH$_2$*C*H$_2$), 33.98 (C-3), 28.39 (C-4). $[\alpha]_D^{24}$ −30 (*c* 3.05, $CHCl_3$). Compound **3f**, 2-benzyl-5-oxotetrahydrofuran-2-carboxylic acid: ^{1}H NMR (500 MHz, $CDCl_3 + \Delta CD_3OD$): δ 7.11–7.20 (m, 5H, *o*,*m*,*p*); 3.26 and 3.03 (2d, 2H, $J = 14.6$ Hz, Bn CH_2); 2.37 and 2.13 (m, 2H, H-3), 2.35 and 1.98 (m, 2H, H-4). ^{13}C NMR (125 MHz, $CDCl_3 + \Delta CD_3OD$): δ 176.60 (C-5), 172.95 (COOH), 133.87 (*s*), 130.25 (*o*), 128.13 (*m*), 127.01 (*p*), 86.27 (C-2), 41.81 (Bn *C*H$_2$), 29.71 (C-3), 27.84 (C-4). $[\alpha]_D^{20}$ −5.3 (*c* 1.97, acetone) and +5.4 (*c* 2.01, acetone). The enantiomeric purity of **3c**, **3f** (directly) and **3d** (as the spirodilactone[6b]) was determined by chiral HPLC (Diecel Chiralcel ODH).
10. The NMR and IR spectra are identical to those from Ref. 4b, however, the chemical shifts for the two proton AB systems of the α-methylene carbons to the ring should be exchanged on the basis of *J*-based selective ^{1}H–^{13}C polarization transfer experiments. Assignment of ^{13}C NMR shifts follows: 177.55 (C-2), 137.45 (*s*), 128.40 (*m*), 127.78 (*p*), 127.53 (*o*), 87.68 (C-5), 73.57 (Bn), 72.35 (*C*H$_2$OCH$_2$), 65.26 (CH$_2$OH), 29.16 (C-5), 25.57 (C-4). $[\alpha]_D^{21}$ +9.67 (*c* 2.4, $CHCl_3$) (lit.[4b] $[\alpha]_D^{21}$ +7.73 (*c* 4.4, $CHCl_3$)).
11. Paju, A.; Kanger, T.; Pehk, T.; Eek, M.; Lopp, M. *Tetrahedron* **2004**, *60*, 9081–9084.
12. Cao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.