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Tetrahedron 60 (2004) 9081–9084
Tetrahedron

A short enantioselective synthesis of homocitric acid-γ-lactone and 4-hydroxy-homocitric acid-γ-lactones

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Received 27 May 2004; revised 12 July 2004; accepted 28 July 2004

Available online 26 August 2004

Abstract—A simple method for the synthesis of enantiopure homocitric acid γ-lactone and its 4-hydroxy analogues starting from spiro-γ-dilactone, in up to 74% isolated yield is described.

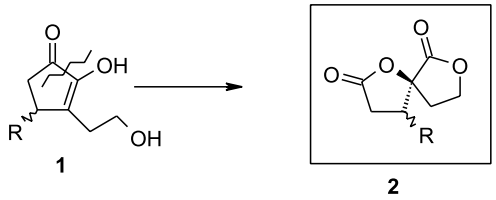
1. Introduction

(−)-*R*-Homocitrate is an intermediate in lysine biosynthesis pathway in yeast and some fungi.[1–4] This pathway is absent in plants and mammalians. That feature makes (−)-*R*-homocitrate and various citric acid derivatives promising candidates for anti-fungi therapy in human medicine, and prospective anti-fungi agents for crop protection in agriculture. The list of new antifungal citrates is far from being exhausted.[5] Additionally, chiral hydroxy acids are known as useful chiral synthons, ligands and auxiliaries in asymmetric organic synthesis.[6]

Maragoudakis and Strassmann accomplished the first synthesis of racemic homocitrate in 1966.[7] In the same year, enantioenriched *S*-homocitric acid was synthesized from (−)-quinic acid.[8] In the late nineties, interest towards homocitric acid increased again and it was synthesized from L-lactic acid and L-serine,[9] citric acid,[10] monoethyl malonate[11] and D-Na-malate.[12]

To the best of our knowledge, the 4-hydroxy derivatives of homocitric acid have not been found from natural sources yet, and have not been synthesized before. However, the corresponding isomers of hydroxycitric acids, (2*S*,3*S*)- and (2*S*,3*R*)-2-hydroxycitric acid and their derivatives are extensively distributed in nature and are present in plants.[13,14] Several reports pertaining to the pharmaceutical applications of these compounds are available.[15–17] All of the above mentioned reasons make the search for new synthetic methods of chiral citrates, their derivatives and analogues an important goal for synthetic chemists.

Asymmetric oxidation of ketones is a challenging option in the synthesis of enantioenriched compounds.[18,19] We have previously found that 3-substituted cyclopentane-1,2-diones can be oxidized with Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate/*tert*-BuOOH complex (Sharpless complex),[20] resulting in enantiopure 2-alkyl-γ-lactone acids in the case of alkyl-substituted diketones[21–23] and spirodilactones **2** in the case of hydroxyethyl substituted diketones **1**.[24] These stable compounds can be used as key intermediates in many transformations. (Scheme 1).



Scheme 1.

In the present paper we demonstrate how the derivatives of hexanetriacid can be obtained starting from spirodilactone **2** according to a simple and efficient scheme (Scheme 2).

2. Results and discussion.

2.1. Preparation of homocitric acid-γ-lactone

Homocitric acid-γ-lactone was synthesized starting from

Keywords: Asymmetric oxidation; Spirodilactone; Homocitric acid; γ-Lactone; 4-Hydroxy-homocitric acid; γ-Lactone.
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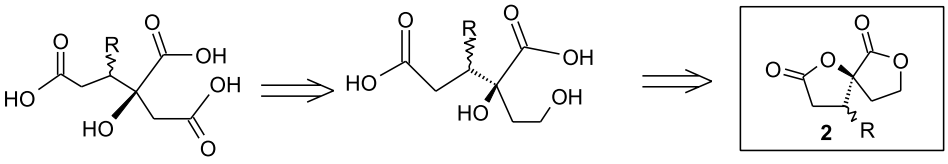
doi:10.1016/j.tet.2004.07.096



Scheme 2.

spirodilactone (*R*)-**2a** (**2a** was obtained from asymmetric oxidation of 3-hydroxyethyl-cyclopentane-1,2-dione according the described procedure[24]). We first made an attempt to convert spirodilactone **2a** into a diester **3a** (path (a), Scheme 3). However, *trans*-esterification of **2a** with methanol under basic conditions ($NaHCO_3$, K_2CO_3 or NaOMe) resulted in a 3:7 ratio of diester **3a** and lactone ester **4a** (in a 94% overall yield). The same mixture was obtained when one of the reaction products—lactone ester **4a**—was treated with methanol. Diester **3a** and lactone ester **4a** are easily separable from each other on silica gel. Jones oxidation of the separated diester **3a** followed by hydrolysis and acidification, resulted in (*R*)-homocitric acid-γ-lactone **5a** in 46% yield for two steps.

The moderate yield of **3a** from the *trans*-esterification procedure forced us to find alternatives. So, we tried a direct oxidation of spirodilactone **2a** in a form a diacid Na—or K-salt. Indeed, using simple reagents like $KMnO_4$ or $K_2S_2O_8$ (with $RuCl_3\times H_2O$ as a catalyst)[25] in basic medium afforded (*R*)-(−)-homocitric acid-γ-lactone *R*-**5a** directly from (*R*)-**2a** in 56 and 74% yield, correspondingly (path (b), Scheme 3).

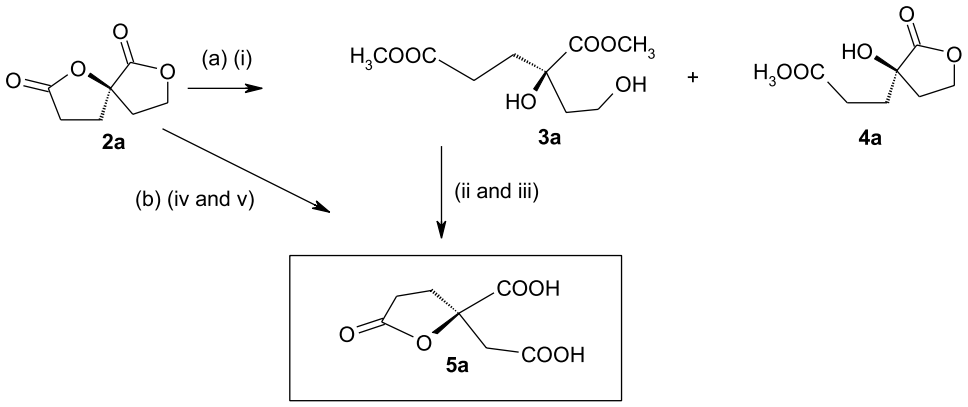
Comparison of the optical rotation of the obtained product ($[\alpha]_D=-49.8$ for **5a**) with that of the natural product[8] confirms the (*R*) absolute configuration of the homocitric acid lactone. This result is in good agreement with our earlier suggestion that the oxidation of the substrate **1a** using Ti(O*i*Pr)$_4$/(+)-diethyl tartrate/*tert*-BuOOH complex results in *R*-configuration of the newly formed stereogenic center in **2a**.[24]

2.2. Preparation of 4-hydroxyhomocitric acid-γ-lactones

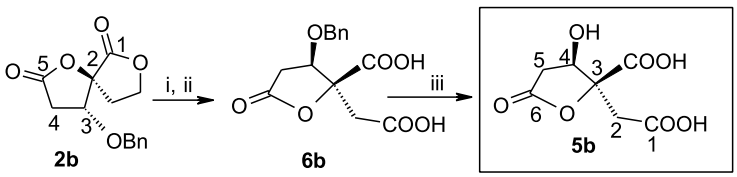
The synthesis of new homocitric acid analogs—4-hydroxy-homocitric acids was accomplished starting from benzyl-oxy-substituted spirodilactones (2*S*,3*R*)-**2b** and (2*S*,3*S*)-**2c**, respectively. Preparation of the initial diketone **1b**, its asymmetric conversion into diastereomeric spirodilactones **2b**:**2c** as a 6:1 mixture, and separation of the diastereomers has been described by us earlier.[24] The major diastereomer **2b** from this procedure (*ee* 86–88%) was recrystallized from CH_2Cl_2–ether mixture affording the necessary substrate **2b** in good yield (73%) and high enantiomeric purity (ee 98.5%). Compound (2*S*,3*R*)-**2b** was subjected to oxidation with $K_2S_2O_8$ (cat. $RuCl_3\times H_2O$) using the same procedure that is described for **2a** (Scheme 4).

Thus, (−)-4-hydroxyhomocitric acid-γ-lactone (3*S*,4*R*) **5b** was obtained from spirodilactone (2*S*,3*R*)-**2b** after oxidation, cyclization and removing the protecting benzyl group in 59% overall yield (Scheme 4).

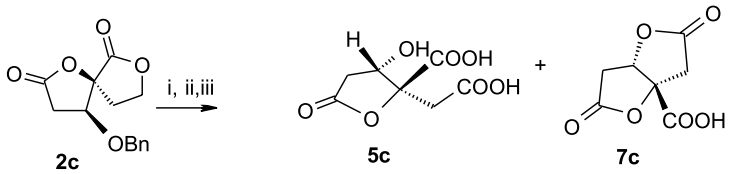
An analogous process, starting from the minor isomer (2*S*,3*S*)-**2c**, resulted in a mixture of two compounds: **5c** and **7c** (identified only by ^1H and ^{13}C NMR spectra) (Scheme 5). The *cis*-orientation of the –OH and –CH_2COOH groups in



Scheme 3. Reagents and conditions: (a) (i) $NaHCO_3$, MeOH, rt. (ii) Jones' reagent, 71%. (iii) LiOH, THF 6 h, then 1 M HCl, 65%. (b) (iv) $KMnO_4$, 1 M NaOH, 16 h, rt, (56%). (v) 1 M HCl, (74%) or (iv) $K_2S_2O_8$, $RuCl_3\times H_2O$, 0.2 N KOH. (v) 1 M HCl, (74%).



Scheme 4. Reagents and conditions: (i) $K_2S_2O_8$, $RuCl_3\times H_2O$, 0.2 M KOH. (ii) conc. HCl, CH_2Cl_2 (61% for two steps). (iii) Pd/C, H_2 (96%).



Scheme 5. Reagents and conditions: (i) $K_2S_2O_8$, $RuCl_3\times H_2O$, 0.2 M KOH. (ii) conc. HCl, CH_2Cl_2. (iii) Pd/C, H_2.

5c was also established by ^1H and ^{13}C NMR spectra confirming the structure of **7c**.

3. Conclusions

The described method affords a simple and short access to homocitric acid and its derivatives. The method enables synthesis of homocitric acid γ-lactones in both enantiomeric forms starting from 3-hydroxymethyl-1,2-cyclopentanedione via spirodilactone **2a** with the overall isolated yield of the target compounds more than 50%. The (−)-4-hydroxy-homocitric acid-γ-lactones **5b**, **5c** and bilactone acid **7c** can be obtained from 4-hydroxy-3-hydroxyethyl-cyclopentane-1,2-diones in a similar way. These are new compounds with a furanone skeleton, and biological activity is currently under study.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker AMX-500 spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from TMS. Deuterated solvent peaks were used as internal references: deutero-methanol at 3.30 and 49.00 ppm, deutero-acetone at 2.05 and 29.80 ppm. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrometer. Elemental analyses were performed on a Perkin–Elmer C,H,N,S-Analyzer 2400. Optical rotations were obtained using an 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. The enantiomeric purity of the spirodilactones **2a–c** was determined on a LKB liquid, chromatograph with Uvicord UV detector, using a Daicel Chiracel ODH chiral column.

4.2. (−)-Homocitric acid lactone (5a)

Method A. To a solution of spirodilactone **2a** (64 mg, 0.41 mmol) in a mixture of 1 M NaOH/CH_2Cl_2 1:1 (4 mL), $KMnO_4$ (97 mg, 0.62 mmol) was added at 0 °C and the mixture was stirred for 16 h at room temperature. Then EtOH (4 mL) was added and the solution was filtered through Celite. EtOH was removed under reduced pressure, the remaining water was acidified to pH 1 with 6 M HCl solution and the mixture was evaporated. The residue was dissolved in acetone (10 mL) and the solid material was filtered off. Removal of the acetone, followed by flash chromatography (silica gel, petroleum ether–acetone 10:5 to 10:6) gave **5a** as white solid (43 mg, 56%); $[\alpha]_D^{20}=-49.8$ (*c* 0.36, water); ^1H NMR ($(CD_3)_2CO$): δ 3.00 and 3.20 (both d, 2H, $J=17.1$ Hz, H-2), 2.47 and 2.54 (both m, 2H, H-4), 2.60 and 2.62 (both m, 2H, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ 176.33 (C-6), 172.43 (3-COOH), 170.47 (C-1), 83.42 (C-3), 41.64 (C-2), 31.83 (C-5), 28.26 (C-4); IR (KBr, cm^{-1}): 3121, 2983, 2934, 1755, 1723, 1674, 1386, 1244, 1186, 1062. Anal. calcd for $C_7H_8O_6$: C, 44.69; H, 4.29. Found: C, 44.65; H, 4.26.

Method B. To a solution of spirodilactone **2a** (29 mg, 0.19 mmol) in 0.2 M KOH (10 mL), potassium persulfate (251 mg, 0.93 mmol) followed by $RuCl_3\times H_2O$ (1 mg, 0.0044 mmol) was added with vigorous stirring. The mixture was stirred for 24 h at room temperature. Then Na_2SO_3 (94 mg, 0.74 mmol) was added at 0 °C followed by 6 M HCl (2.5 mL) after 0.5 h and stirring was continued for 1 h at room temperature. The reaction mixture was extracted with several portions of dry EtOAc. The combined extracts were dried (Na_2SO_4) and the solvents were removed. The residue was purified by flash chromatography (silica gel, petroleum ether–acetone 10:5 to 10:6) to yield **5a** as white solid (26 mg, 74%); $[\alpha]_D^{20}=-48.9$ (*c* 0.38, water). Anal. calcd for $C_7H_8O_6$: C, 44.69; H, 4.29. Found: C, 44.58; H, 4.33.

4.3. (−)-4-Benzyloxyhomocitric acid lactone (6b)

To a stirred solution of spirodilactone **2b** (48 mg, 0.18 mmol) in a mixture of 0.2 M KOH/CH_2Cl_2 8:1 (10 ml), potassium persulfate (247 mg, 0.92 mmol) and $RuCl_3\times H_2O$ (1 mg, 0.0044 mmol) were added. After stirring for 23 h at room temperature the reaction mixture was extracted with CH_2Cl_2 (10 mL), the aqueous phase was acidified to pH 1 with 1 M HCl and extracted with EtOAc (5×10 mL). The combined extracts were dried (Na_2SO_4) and the solvents were removed. To this crude triacid dry CH_2Cl_2 (10 mL) and concentrated HCl (100 μL) were added. The mixture was vigorously stirred for 2 h at room temperature. Then water (12 mL) was added and the reaction was extracted with EtOAc (3×10 mL). The combined extracts were dried (Na_2SO_4) and the solvents were removed. The residue was purified by flash chromatography (silica gel, petroleum ether–acetone 10:4 to 10:6) to yield **6b** as white solid (33 mg, 61%); $[\alpha]_D^{20}=-21$ (*c* 1.04, acetone); ^1H NMR ($CD_3OD+CDCl_3$): δ_H 7.2–7.4 (m, 5H, Ph), 4.55 and 4.58 (both d, 2H, $J=11.8$ Hz, $PhCH_2$), 4.45 (dd, 1H, $J=6.1$, 7.6 Hz, H-4), 3.24 and 2.85 (both d, 2H, $J=17.2$ Hz, H-2), 2.87 (dd, 1H, $J=7.6$, 17.8 Hz, H-5),

2.71 (dd, 1H, $J=6.1$, 17.8 Hz, H-5); ^{13}C NMR ($CD_3OD+CDCl_3$): δ_C 175.01 (C-6), 171.31 (C-1), 170.64 (C-3COOH), 137.38 (*s*-Ph), 128.96 (*m*-Ph), 128.58 (*p*-Ph), 128.27 (*o*-Ph), 87.36 (C-3), 79.11 (C-4), 73.41 (Bn CH_2), 40.29 (C-2), 35.35(C-5); IR (KBr, cm^{-1}): 2948, 1787, 1725, 1433, 1232, 1095, 1077, 741, 696. Anal. calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 56.81; H, 4.82.

4.4. (−)-4-Hydroxyhomocitric acid lactone (5b)

To a stirred solution of lactone **6b** (30 mg, 0.10 mmol) in MeOH (3 mL) 10% Pd/C (14 mg) was added and the mixture was stirred for 22 h at room temperature. The catalyst was removed by filtration through a pad of Silica gel and the filtrate was evaporated to give **5b** as white solid (20 mg, 96%); $[\alpha]_D^{20}=-17$ (*c* 1.20, acetone); ^{1}H NMR ($(CD_3)_2CO$): δ_H 4.73 (dd, 1H, $J=6.5$, 7.6 Hz, H-4), 3.30 and 2.92 (2H, both d, $J=17.1$ Hz, H-2), 2.97 (1H, dd, $J=7.6$, 17.6 Hz, H-5), 2.60 (1H, dd, $J=6.5$, 17.6 Hz, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ_C 174.20 (C-6), 170.67 (C-3COOH), 170.04 (C-1), 87.97 (C-3), 73.07 (C-4), 39.98 (C-2), 36.72 (C-5); IR (KBr, cm^{-1}): 3416, 2944, 1789, 1737, 1408, 1202, 1176, 1068. Anal. calcd for $C_7H_8O_7$: C, 41.19; H, 3.95. Found: C, 41.55; H, 4.00.

4.5. (+)-4-Hydroxyhomocitric acid lactone (5c) and 4-hydroxyhomocitric acid dilactone (7c)

Analogously to that of **5b** from lactone **2c**, a mixture of (+)-4-hydroxyhomocitric acid lactone (**5c**), (minor component) and 4-hydroxyhomocitric acid dilactone (**7c**) (major component) were obtained. (+)-4-Hydroxyhomocitric acid lactone (**5c**). ^{1}H NMR ($(CD_3)_2CO$): δ_H 4.65 (d, 1H, $J=5.6$ Hz, H-4), 3.20 and 3.06 (2H, both d, $J=17.0$ Hz, H-2), 2.96 (1H, dd, $J=5.6$, 17.8 Hz, H-5), 2.39 (1H, d, $J=17.8$ Hz, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ_C 175.20 (C-6), 168.9 (C-1 and C-3COOH), 88.40 (C-3), 72.05 (C-4), 38.32 (C-2), 37.15 (C-5). 4-Hydroxyhomocitric acid dilactone (**7c**). ^{1}H NMR ($(CD_3)_2CO$): δ_H 5.39 (d, 1H, $J=5.8$ Hz, H-4), 3.56 and 3.00 (2H, both d, $J=18.8$ Hz, H-2), 3.18 (1H, dd, $J=5.8$, 19.0 Hz, H-5), 2.86 (1H, d, $J=19.0$ Hz, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ_C 173.92, 173.06 and 168.86 (C-1, C-6 and C-3COOH), 88.67 (C-3), 81.33 (C-4), 37.93 (C-2), 35.12 (C-5).

Acknowledgements

We would like to thank Mrs. Tiiu Kailas for performing FT IR spectra and elemental analysis, Estonian Science Foundation (Grants nos 4976, 5133, 5628 and Estonian Ministry of Education (Grant 0350312s01).

References and notes

1. Strassman, M.; Ceci, L. N. *Biochem. Biophys. Res. Commun.* **1964**, *14*, 262–267.
2. Strassman, M.; Ceci, L. N. *J. Biol. Chem.* **1965**, *240*, 4357–4361.
3. Hogg, R. W.; Broquist, H. P. *J. Biol. Chem.* **1968**, *243*, 1839–1845.
4. Andi, B.; West, A. H.; Cook, P. F. *Arch. Biochem. Biophys.* **2004**, *421*, 243–254.
5. Recently, new natural alkyl citrates that exhibit high antifungal potention were discovered: Singh, S. B.; Zink, D. L.; Doss, G. A.; Polishook, J. D.; Ruby, C.; Register, E.; Kelly, T. M.; Bonfiglio, C.; Williamson, J. M.; Kelly, R. *Org. Lett.* **2004**, *6*, 337–340.
6. Coppola, G. M.; Schuster, H. F. *Chiral α-Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, 1997.
7. Maragoudakis, M.; Strassmann, M. *J. Biol. Chem.* **1966**, *241*, 695–699.
8. Thomas, U.; Kalayanpur, M. G.; Stevens, C. M. *Biochemistry* **1966**, *5*, 2513–2516.
9. Rodríguez, G. H. R.; Biellmann, J.-F. *J. Org. Chem.* **1996**, *61*, 1822–1824.
10. Ancliff, R. A.; Russell, A. T.; Sanderson, A. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3379–3382.
11. Li, Z.-C.; Xu, J.-Q. *Molecules* **1998**, *3*, 31–34.
12. Ma, G.; Palmer, D. R. J. *Tetrahedron Lett.* **2000**, *41*, 9209–9212.
13. Lewis, Y. S.; Neelakantan, S. *Phytochemistry* **1965**, *4*, 619–625.
14. Ibnusaud, I.; Thomas, P. T.; Rani, R. N.; Sasi, P. V.; Beena, T.; Hisham, A. *Tetrahedron* **2002**, *58*, 4887–4892.
15. Lowenstein, J. M. *J. Biol.Chem.* **1971**, *246*, 629–632.
16. Triscari, J.; Sullivan, A. C. *Lipids* **1977**, *12*, 357–363.
17. Mackeen, M. M.; Ali, A. M.; Lajis, N. H.; Kawazu, K.; Kikuzaki, H.; Nakatani, N. *Zaitschrift für Naturforschung* **2002**, *57c*, 291–295.
18. Bolm, C.; Luong, T. K. K.; Beckmann, O. *Asymmetric Oxidation Reactions*; Oxford University Press: Oxford, 2001 pp 147–152.
19. Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583–7586.
20. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
21. Paju, A.; Kanger, T.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2439–2448.
22. Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron Lett.* **2000**, *41*, 6883–6887.
23. Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565–1573.
24. Paju, A.; Kanger, T.; Niitsoo, O.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2393–2399.
25. Green, G.; Griffith, W. P.; Hollinshead, D. M.; Ley, S. V.; Schröder, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 681–686.