Monatshefte für Chemie 123, 741 – 747 (1992)

Monatshefte für Chemie
Chemical Monthly
© Springer-Verlag 1992
Printed in Austria

Preparation of Enantiomerically Pure 5,6-Dihydroxy-isobenzofuranones and 5,6-Dihydroxy-4,7-methano-isobenzofuranones

Anna Edelsbacher, Ernst Urban*, and **Waltraud Weidenauer**

Institut für Pharmazeutische Chemie, Universität Wien, A-1090 Wien, Austria

Summary. Optically pure available lactones **1** and **5** were diastereoselectively oxidised to *cis*-diols **2** and **6** by $KMnO_4$ and to epoxides **3** and **7** by 3-chloroperoxybenzoic acid. Epoxide **3** was cleaved to *trans*-diol **4**, whereas hydrolysis of **7** afforded tricyclic carboxylic acid **8**. Optically pure dihydroxylactones **2**, **4**, and **6** are valuable models for structure determination of the antimicrobial garlic component garlicin.

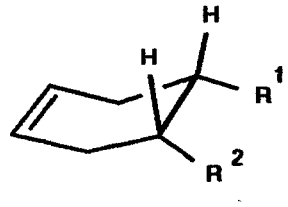
Keywords. Garlicin; Isobenzofuranone; Lactones; Diastereoselective synthesis.

Synthese enantiomerenreiner 5,6-Dihydroxy-isobenzofuranone und 5,6-Dihydroxy-4,7-methano-isobenzofuranone

Zusammenfassung. Die in enatiomerenreiner Form verfügbaren Lactone **1** und **5** wurden durch diastereoselektive Oxidation mit $KMnO_4$ zu den *cis*-Diolen **2** und **6** bzw. mit 3-Chlorperoxybenzoesäure zu den Epoxiden **3** und **7** umgesetzt. Das Epoxid **3** liefert bei der Hydrolyse das *trans*-Diol **4**, während aus **7** die tricyclische Carbonsäure **8** entsteht. Die optisch reinen Dihydroxylactone **2**, **4** und **6** können als Vergleichssubstanzen zur Strukturaufklärung des antimikrobiellen Knoblauchinhaltsstoffes Garlicin dienen.

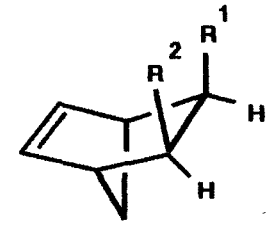
Introduction

Recently we published the preparation of racemic 5,6-dihydroxyisobenzofuranones **2** and **4** [1, 2] and 5,6-dihydroxy-4,7-methanoisobenzofuranone **6** [3] by diastereoselective conversion of unsaturated lactones **1** and **5**, respectively. The relative configurations at the chiral centers of **2**, **4** and **6** were determined by ^{1}H-NMR studies [1, 3] and X-ray analysis [2] of derivatives obtained from **2**, **4** and **6**. Now we want to report on the synthesis of both enantiomers of lactones **2**, **4**, and **6**, using readily available chiral starting compounds **1** and **5** in optically pure form. (−)-**1** and (+)-**5** were first prepared by stereospecific horse liver alcohol dehydrogenase (=*HLADH*) catalyzed oxidation of *meso*-diol **9a** [4] and **11** [5]. Both enantiomers of **1** and **5** were obtained by chemoselective reduction at the esterificated or free carboxylic function of optical pure mono-ester **10** and **12** followed by lactonisation [6, 7]. Monoester (+)-**10** was received by pig liver esterase cat-



9a, 9b, 10

	R^1	R^2
9a	CH_2OH	CH_2OH
9b	$COOCH_3$	$COOCH_3$
(−)-10	COOH	$COOCH_3$
(+)-10	$COOCH_3$	COOH



11, 12

	R^1	R^2
11	CH_2OH	CH_2OH
(−)-12	$COOCH_3$	COOH
(+)-12	COOH	$COOCH_3$

Scheme 1

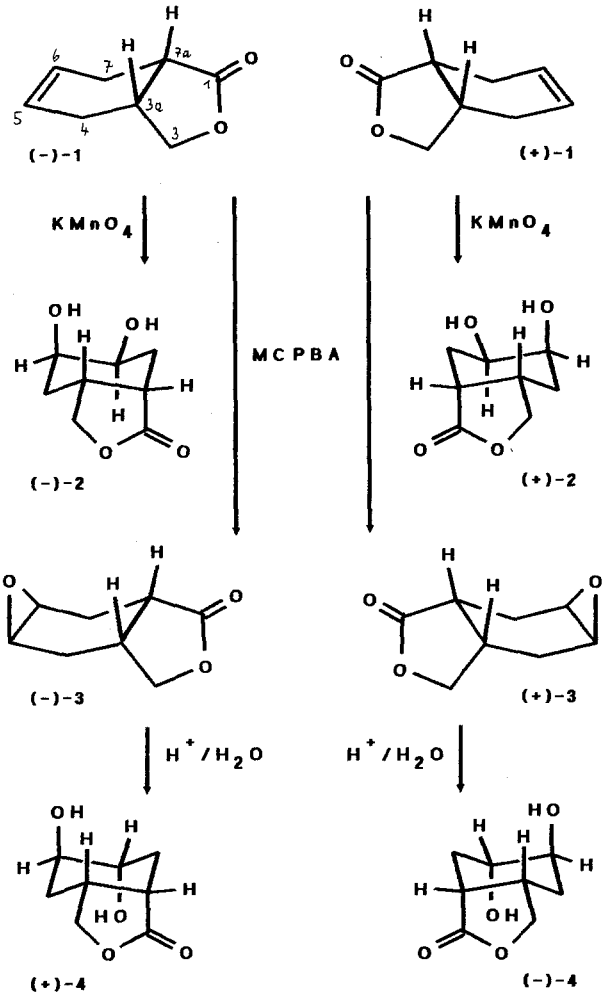
alyzed hydrolysis of diester **9b** [6], whereas both enantiomers of **10** and **12** are available by enantiomeric separation via the ephedrine salts [6, 8].

Results and Discusion

We used optically pure half-esters **10** and **12**, prepared by resolution of racemates via ephedrine salts [6, 8], as starting material to synthesise enantiomerically pure lactones **1** and **5**. Chemoselective reduction of the ester function with lithium-boronhydride in *THF* followed by lactonisation afforded both enantiomers of **1** (66%) and **5** (85%) in preparative useful yields. Optical purity of **1** and **5** was ensured comparing optical rotations with literature values (obtained from lactones synthesised by *HLADH* catalyzed oxidation of **9a** [4] and **11** [5]). As this enzymatic approach to **1** and **5** was regarded as enatioselective (ee > 97% [4, 5]) and differences of optical rotation values to our results were only small ($\leqslant$ 1.2%), we considered **1** and **5** to be useful starting materials for synthesis of optically pure **2**, **4**, **6**, and **8**.

Pure lactones **1** and **5** were transformed to both enantiomers of *cis*-diols **2** and **6**, epoxides **3** and **7**, *trans*-diol **4** and tricyclic carboxylic acid **8**, like previously described racemic lactones. It was possible to establish absolute configurations of **2**−**4** and **6**−**8**, because the absolute configurations of the chiral centers C-3a, C-4, C-7, and C-7a in **1** and **5** were confirmed by Jones [4, 5] and relative configurations of newly introduced asymmetic centers C-5 and C-6 could be determined by ^{1}H-NMR studies [1, 3] and X-ray analysis [2].

Optically pure dihydroxylactones **2**, **4**, and **6** are models with known absolute configuration, which should be valuable in structure determination of the anti-microbial garlic component garlicin [11].



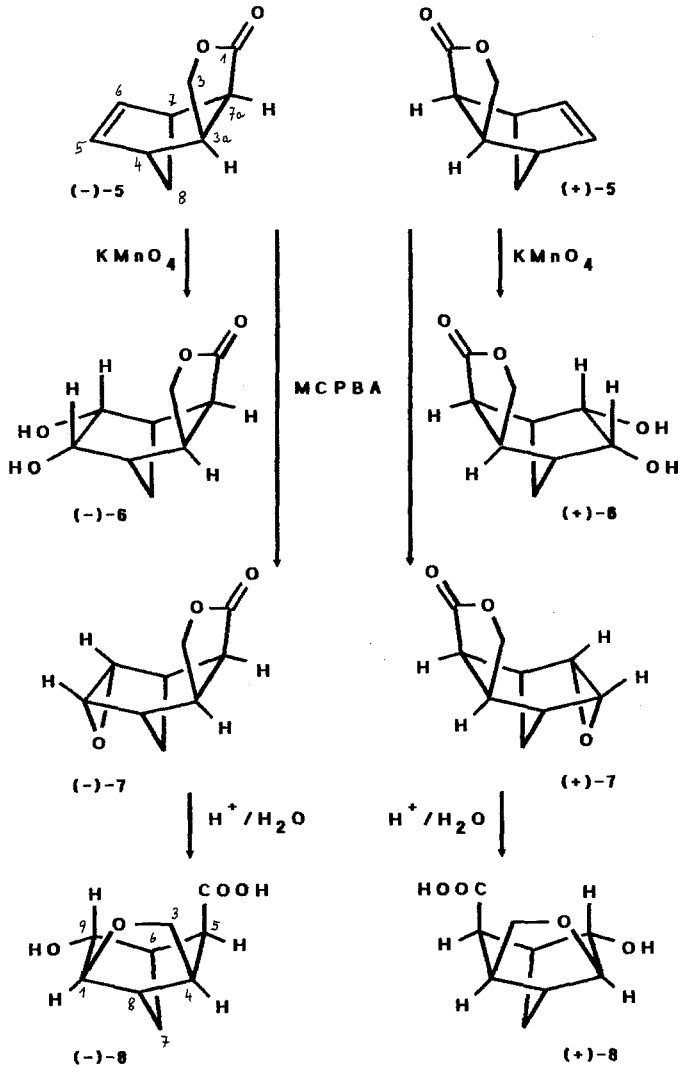
Scheme 2

Experimental Part

^{1}H-NMR-spectra, mass-spectra and main bands of IR-spectra of the pure enantiomers correspond to spectra of earlier published racemic forms [1 – 3]. Melting points (not corrected): Kofler hot stage, optical rotation: Perkin Elmer 241 polarimeter, measuring cell connected with a thermostat (accuracy ±0.02°C).

General Procedure A: Preparation of Lactones **1** *and* **5**

100 mmol of the pure half-ester were dissolved in 100 ml of H_2O containing 100 mmol of LiOH. After standing at room temperature for 30 min, the solvent was evaporated and the residue was dried in vacuo (0.03 Torr). The obtained Li-salt was suspended in 150 ml *THF* under Argon, 100 ml (200 mmol) $LiBH_4$-solution (2 *M* in *THF*) was added and the mixture was refluxed for 2 h. After careful addition of 50 ml methanol, the mixture was again refluxed for 30 min to destroy excess $LiBH_4$. After evaporation of the solvent under reduced pressure, the residue was diluted with 20 ml H_2O, acidified with 250 ml 6 *N* HCl and extracted with 4 × 150 ml dichloromethane. The organic layer was dried over Na_2SO_4, the solvent was distilled off in vacuo and the residue was purified by distillation or crystallisation.



Scheme 3

General Procedure B: Preparation of cis-Diols **2** *and* **6**

30 mmol of the unsaturated lactone were dissolved in 100 ml ethanol and a solution of 4.74 g (30 mmol) $KMnO_4$ and 3.61 g (30 mmol) $MgSO_4$ in 150 ml H_2O was added at $-40°C$. The suspension was mixed with a mechanical stirrer, allowed to warm up to room temperature and stirred without cooling for 1 h. The brown slurry was filtered off and washed with hot water. The filtate was concentrated in vacuo and extracted in a liquid-liquid extractor with ethyl acetate. After evaporation of the solvent the *cis*-diols were purified by crystallisation.

General Procedure C: Preparation of Epoxides **3** *and* **7**

To 30 mmol of unsaturated lactone dissolved in 100 ml CH_2Cl_2 was added a solution of 11.3 g *MCPBA* (purity 55%, 36 mmol) in 200 ml CH_2Cl_2. The mixture was refluxed for 3 h and washed with aqueous $NaHSO_3$-solution (10%, 2×100 ml) and Na_2CO_3-solution (2 *N*, 2×100 ml). The organic layer was dried (Na_2SO_4) and the solvent distilled off in vacuo. The epoxides were purified by distillation or crystallisation.

General Procedure D: Ppreparation of trans-Diol **4**

To 30 mmol of the epoxy-lactone dissolved in 50 ml acetonitrile was added 5 ml H_2O and 3 g DOWEX 50 WX8 (H^+-form) and the mixture was stirred at room temperature for 20 h. After removal of the ion-exchange-resin by filtration, acetonitrile was distilled off and the aqueous layer was extracted in a liquid-liquid-extractor with ethyl acetate. After evaporation of the solvent the *trans*-diols were purified by crystallisation.

General Procedure E: Preparation of Tricyclic Ether **8**

To 50 mmol of the epoxy-lactone in 20 ml of acetonitrile was added 20 ml 6 *N* H_2SO_4 and the mixture was stirred at room temperature for 20 h. After evaporation of acetonitrile the aqueous layer was extracted with ethyl acetate (4 × 50 ml). The combined organic layers were dried (Na_2SO_4), the solvent was distilled off in vacuo and the residue was purified by crystallisation.

(3 aR,7 aS)-3 a,4,7,7 a-Tetrahydro-isobenzofuranone (−)-**1**

Starting material 18.42 g (−)-**10**, method A, kugelrohr distillation, b. p. 80°C/0.003 Torr, (9.26 g, 67%). $[\alpha]^{25}_D = -67.5°$ ($c = 1.038$ in $CHCl_3$), $[\alpha]^{25}_D = -67.1°$ ($c = 1.000$ in $CHCl_3$) [4]; $[\alpha]^{20}_D = -87.6°$ ($c = 2.649$ in acetone), $[\alpha]^{20}_D = -85.4°$ ($c = 2.630$ in acetone) [6].

(3 aS,7 aR)-3 a,4,7,7 a-Tetrahydro-isobenzofuranone (+)-**1**

Starting material 18.42 g (+)-**10**, method A, kugelrohr distillation, b. p. 80°C/0.003 Torr, (9.12 g, 66%). $[\alpha]^{25}_D = +67.3°$ ($c = 1.022$ in $CHCl_3$), $[\alpha]^{20}_D = +87.8°$ ($c = 2.672$ in acetone); $[\alpha]^{20}_D = +85.2°$ ($c = 2.640$ in acetone) [6].

(3 aR,5 R,6 S,7 aS)-5,6-Dihydroxy-perhydro-isobenzofuranone (−)-**2**

Starting material 4.15 g (−)-**1**, method B, colourless crystals (2.48 g, 48%), m. p. 152°C (ethyl acetate). $C_8H_{12}O_4$ (172.20); calcd. C 55.80, H 7.09; found C 55.89, H 7.04. $[\alpha]^{25}_D = -15.9°$ ($c = 1.002$ in *DMSO*).

(3 aS,5 S,6 R,7 aR)-5,6-Dihydroxy-perhydro-isobenzofuranone (+)-**2**

Starting material 4.15 g (+)-**1**, method B, colourless crystals (2.11 g, 41%), m. p. 152°C (ethyl acetate). $C_8H_{12}O_4$ (172.20); calcd. C 55.80, H 7.09; found C 55.90, H 6.97. $[\alpha]^{25}_D = +15.8°$ ($c = 1.001$ in *DMSO*).

(3 aR,5 R,6 S,7 aS)-5,6-Epoxy-perhydro-isobenzofuranone (−)-**3**

Starting material 4.15 g (−)-**1**, method C, kugelrohr distillation, b. p. 110−120°C/0.003 Torr, colourless crystals (4.12 g, 89%), m. p. 86°C. $C_8H_{10}O_3$ (154.16); calcd. C 62.33, H 6.54; found C 62.44, H 6.56. $[\alpha]^{25}_D = -12.9°$ ($c = 1.003$ in $CHCl_3$).

(3 aS,5 S,6 R,7 aR)-5,6-Epoxy-perhydro-isobenzofuranone (+)-**3**

Starting material 4.15 g (+)-**1**, method C, kugelrohr distillation, b. p. 110−120°C/0.003 Torr, colourless crystals (3.88 g, 84%), m. p. 85°C. $C_8H_{10}O_3$ (154.16); calcd. C 62.33, H 6.54; found C 62.51, H 6.63. $[\alpha]^{25}_D = +12.7°$ ($c = 1.006$ in $CHCl_3$).

(3 aS,5 S,6 S,7 aR)-5,6-Dihydroxy-perhydro-isobenzofuranone (−)-**4**

Starting material 4.63 g (−)-**3**, method D, colourless crystals (2.32 g, 45%), m. p. 150°C (ethyl acetate). $C_8H_{12}O_4$ (172.20); calcd. C 55.80, H 7.09; found C 55.98, H 6.92. $[\alpha]^{25}_D = -29.4°$ ($c = 1.003$ in *DMSO*).

(3 aR,5 R,6 R,7 aS)-5,6-Dihydroxy-perhydro-isobenzofuranone (+)-**4**

Starting material 4.63 g (−)-**3**, method D, colourless crystals (2.79 g, 54%), m. p. 148°C (ethyl acetate). $C_8H_{12}O_4$ (172.20); calcd. C 55.80, H 7.09; found C 55.87, H 7.07. $[\alpha]^{25}_D = +28.9°$ ($c = 1.001$ in *DMSO*).

(3 aS,4 R,7 S,7 aR)-4,7-Methano-3 a,4,7,7 a-tetrahydro-isobenzofuranone (−)-**5**

Starting material 19.62 (−)-**11**, method A, colourless crystals (13.22 g, 88%), m. p. 99°C (methanol). $C_9H_{10}O_2$ (150.19); calcd. C 71.97, H 6.72; found C 71.73, H 6.67. $[\alpha]^{25}_D = -144.15°$ ($c = 5.182$ in $CHCl_3$); $[\alpha]^{26}_D = -148.20°$ ($c = 0.52$ in $CHCl_3$) [10].

(3 aR,4 S,7 R,7 aS)-4,7-Methano-3 a,4,7,7 a-tetrahydro-isobenzofuranone (+)-**5**

Starting material 19.62 g (+)-**11**, method A, colourless crystals (12.77 g, 85%), m. p. 100°C (methanol). $C_9H_{10}O_2$ (150.19); calcd. C 71.97, H 6.72; found C 71.72, H 6.71. $[\alpha]^{25}_D = +144.97°$ ($c = 5.095$ in $CHCl_3$); $[\alpha]^{25}_D = +143.20°$ ($c = 5.200$ in $CHCl_3$) [5], $[\alpha]^{20}_D = +145.00°$ ($c = 5.200$ in $CHCl_3$) [7], $[\alpha]^{26}_D = +147.52°$ ($c = 0.52$ in $CHCl_3$) [10].

(3 aS,4 S,5 S,6 R,7 R,7 aS)-5,6-Dihydroxy-4,7-methano-perhydro-isobenzofuranone (−)-**6**

Starting material 4.51 g (−)-**5**, method B, colourless crystals (3.04 g, 55%), m. p. 145°C (ethanol). $C_9H_{12}O_4$ (184.21); calcd. C 58.68, H 6.58; found C 58.59, H 6.46. $[\alpha]^{20}_D = -100.73°$ ($c = 1.026$ in *DMSO*).

(3 aR,4 R,5 R,6 S,7 S,7 aR)-5,6-Dihydroxy-4,7-methano-perhydro-isobenzofuranone (+)-**6**

Starting material 4.51 g (+)-**5**, method B, colourless crystals (3.15 g, 57%), m. p. 146°C (ethanol). $C_9H_{12}O_4$ (184.21); calcd. C 58.68, H 6.58; found C 58.59, H 6.38. $[\alpha]^{20}_D = +100.66°$ ($c = 1.068$ in *DMSO*).

(3 aS,4 S,5 S,6 R,7 R,7 aS)-5,6-Epoxy-4,7-methano-perhydro-isobenzofuranone (−)-**7**

Starting material 4.51 g (−)-**5**, method C, colourless crystals (4.34 g, 87%), m. p. 149°C (ethyl acetate). $C_9H_{10}O_3$ (166.19); calcd. C 65.04, H 6.08; found C 64.82, H 5.83. $[a]^{20}_D = -141.8°$ ($c = 1.190$ in $CHCl_3$).

(3 aR,4 R,5 R,6 S,7 S,7 aR)-5,6-Epoxy-4,7-methano-perhydro-isobenzofuranone (+)-**7**

Starting material 4.51 g (+)-**5**, method C, colourless crystals (4.44 g, 89%), m. p. 149°C (ethyl acetate). $C_9H_{10}O_3$ (166.19); calcd. C 65.04, H 6.08; found C 64.87, H 5.97. $[a]^{20}_D = +139.2°$ ($c = 1.201$ in $CHCl_3$).

*(1 R,4 S,5 S,6 R,8 S,9 R)-9-Hydroxy-2-oxa-tricyclo[4,2,1,0^{4,8}]*nonane-5-carboxylic acid (−)-**8**

Starting material 831 mg (−)-**7**, method E, colourless crystals (676 mg, 73%), m. p. 141°C (ethyl ether). $C_9H_{12}O_4$ (184.21); calcd. C 58.68, H 6.58; found C 58.38, H 6.43. $[\alpha]^{20}_D = -26.52°$ ($c = 1.018$ in acetone).

*(1 S,4 R,5 R,6 S,8 R,9 S)-9-Hydroxy-2-oxa-tricyclo[4,2,1,0^{4,8}]*nonane-5-carboxylic acid (+)-**8**

Starting material 831 mg (+)-**7**, method E, colourless crystals (639 mg, 69%), m. p. 140°C (ethyl ether). $C_9H_{12}O_4$ (184.21); calcd. C 58.68, H 6.58; found C 58.46, H 6.53. $[\alpha]^{20}_D = +25.82°$ ($c = 1.003$ in acetone).

Acknowledgement

We thank Mag. J. Theiner (Institut für Physikalische Chemie) for the elementary analyses.

References

[1] Mostler U., Urban E. (1989) Monatsh. Chem. **120**: 349
[2] Stejskal R., Urban E., Völlenkle H. (1991) Monatsh. Chem. **122**: 145
[3] Aufreiter U., Fuchs M., Urban E. (1992) Arch. Pharm. (Weinheim) **325**: [Ph 980]
[4] Jakovac I. J., Goodbrand H. B., Lok K. P., Jones J. B. (1982) J. Am. Chem. Soc. **104**: 4659
[5] Lok K. P., Jakovac I. J., Jones J. B. (1985) J. Am. Chem. Soc. **107**: 2521
[6] Gais H. J., Lukas K. L. (1984) Angew. Chem. **96**: 140
[7] Metz P. (1989) Tetrahedron **45**: 7311
[8] Storme P., Quaeghebeur L., Vandewalle M. (1984) Bull. Soc. Chim. Belg. **93**: 999; CA **103**: 22341
[9] Mohr P., Waespe-Sarcevic N., Tamm C. (1983) Helv. Chim. Acta **66**: 2501
[10] Takano S., Kurotraki A., Ogasawara K. (1987) Synthesis 1075
[11] Zwergal A. (1952) Pharmazie **7**: 245

Received August 5, 1991. Accepted September 23, 1991