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# Synthesis of Potential Antimicrobial Oxiranylisobenzofuranones

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**Summary.** Five epoxylactones of structural similarity to the antimicrobial sesquiterpene lactone heptelidic acid were synthesized. Starting from perhydroisobenzofuranone, 7a-vinyl- and 7a-allyl-perhydroisobenzofuranone were prepared and oxidized to yield epimeric mixtures of 7a-oxiranyl- and 7a-oxiranylmethylperhydroisobenzofuranones which were separated by chromatography. In a four step synthesis perhydroisobenzofurane-1,7-dione was prepared, transformed to 7-methylene-perhydroisobenzofuranone, and reacted with *mCPBA* to give the (3a*RS*, 7*RS*, 7a*RS*)-configurated spirocyclic epoxylactone as a single diastereomer. In a preliminary screening model, epoxylactones proved to be of low toxicity.

**Keywords.** Isobenzofuranones; Epoxylactones; Spiroepoxides; Iodolactonization; Heptelidic acid.

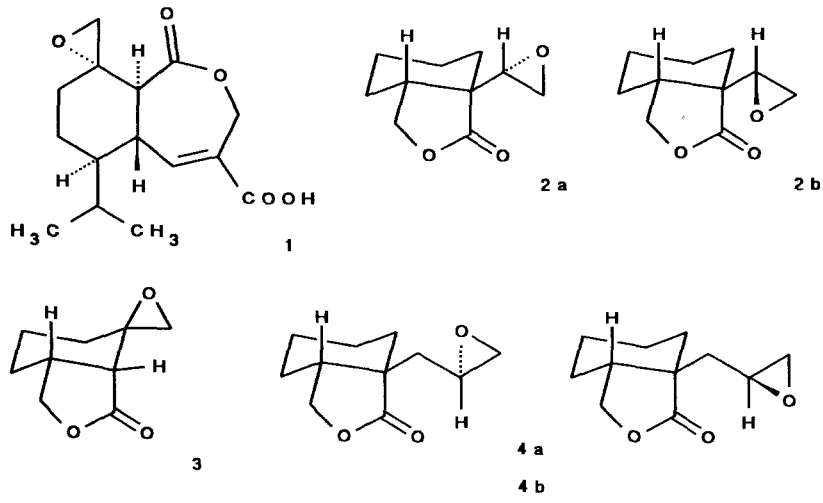
**Synthese von potentiell antimikrobiellen Oxiranylisobenzofuranonen**

**Zusammenfassung.** Fünf Epoxylactonen, die strukturelle Ähnlichkeiten mit dem antimikrobiellen Sesquiterpenlacton Heptelidsäure aufweisen, wurden synthetisiert. Aus Perhydroisobenzofuranon wurden 7a-Vinyl- und 7a-Allyl-perhydroisobenzofuranon dargestellt und durch Oxidation Mischungen der epimeren 7a-Oxiranyl- bzw. 7a-Oxiranylmethyl-perhydroisobenzofuranone erhalten, die chromatographisch getrennt wurden. Aus Perhydroisobenzofuran-1,7-dion, das in vier Stufen zugänglich ist, wurde 7-Methylen-perhydroisobenzofuranon hergestellt und anschließend mit *mCPBS* oxidiert, wobei das (3a*RS*, 7*RS*, 7a*RS*)-konfigurierte, spirocyclische Epoxylacton diastereomerenrein entstand. In einem einfachen Testmodell wiesen die Epoxylactone nur geringe Toxizität auf.

## Introduction

Some time ago we reported on syntheses of dihydroxyisobenzofuranones [1–6] as models of the antimicrobial natural product garlicin [7], but these compounds showed no significant antimicrobial activity. This convinced us that a simple lactone ring was not sufficient to obtain antimicrobial active isobenzofuranones; a second pharmacophoric group should be present in the molecules. Now we turned our interest to oxiranylisobenzofuranones. A combination of the pharmacophoric epoxide and lactone substructures occurs in many antimicrobial natural products [8], especially in sesquiterpene lactones.

Heptelidic acid (**1**) is a well investigated epoxylactone of fungal origin [9] which has shown activity against anaerobic bacteria, especially *Bacteroides fragilis* [10]. Studies on the mechanism of action of **1** revealed a selective inhibition of




**Scheme 1**

glyceraldehyde-3-phosphate dehydrogenase [11, 12]. The epoxide moiety of **1** was postulated to be the essential structure pattern responsible for enzyme inactivation caused by covalent binding of **1** to the thiol groups at the active site of this enzyme [12].

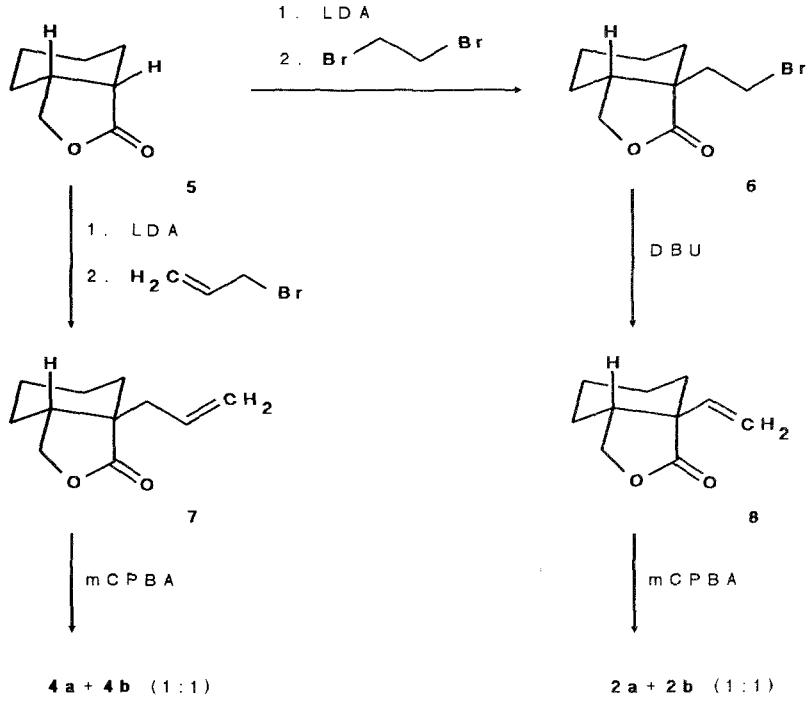
In this paper we want to report on epoxylactones based on the isobenzofuranone skeleton, especially on syntheses of $\beta$-epoxylactones **2a** and **2b**, the spirocyclic $\beta$-epoxylactone **3**, and $\gamma$-epoxylactones **4a** and **4b** (Scheme 1) which show some structural similarity to heptelidic acid (**1**).

## Results and Discussion

The readily available isobenzofuranone **5** [13] was used as starting compound for the syntheses of desired epoxylactones **2a**, **2b**, **4a**, and **4b**. Lithiation of **5** by standard methods (*LDA*, $-78\,^{\circ}C$) [14, 15] and treatment with 3-bromopropene gave the 7a-allyl substituted derivative **7** in excellent yield (98%). Using 1,2-dibromoethane as electrophile led to a mixture of starting material **5** and 2-bromoethyl derivative **6**, from which the latter could easily be separated by distillation [15]. Reaction of **6** with *DBU* resulted in elimination of HBr to give the 7a-vinyl substituted isobenzofuranone **8** in acceptable yield (62%). Spectroscopic properties of the new isobenzofuranones **7** and **8** were fully in accordance with the postulated structures and indicated that the substitution of **5** proceeded exclusively with retention of configuration at C-7a which is in accordance with previous results [15].

Epoxidation of unsaturated lactones **7** and **8** with 3-chloroperbenzoic acid (*mCPBA*) proceeded under rather drastic conditions but was complete after refluxing in $CHCl_3$ for 16 h. On reaction of **8**, we obtained a mixture of $\beta$-epoxylactones **2a** and **2b** (1:1, 77%), and on treatment of **7** a mixture of $\gamma$-epoxylactones **4a** and **4b** (1:1, 91%). Separation by flash chromatography and purification by crystallization or distillation yielded the diastereomerically pure epoxylactones **2a** (24%), **2b** (32%), **4a**, (37%) and **4b** (36%), respectively.

**2a**, **2b**, **4a**, and **4b** gave well separated signals in the respective $^1H$ and $^{13}C$ NMR-spectra (Table 1) which were in accordance with the postulated



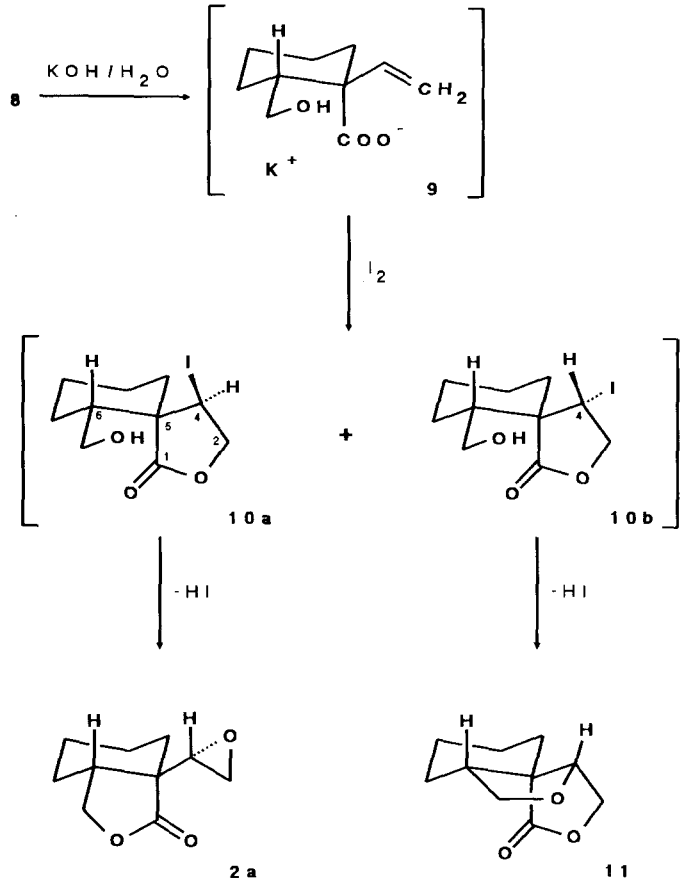

**Scheme 2**

**Table 1.** $^{13}C$ NMR shifts of isobenzofuranones **2–8** and **17–19** ($\delta$, ppm)

| | **2a** | **2b** | **3** | **4a** | **4b** | **7** | **8** | **17** | **18** | **19** |
|---|---|---|---|---|---|---|---|---|---|---|
| C-1 | 176.3 | 178.1 | 174.8 | 180.4 | 180.0 | 180.2 | 178.3 | 178.3 | 171.9 | 176.1 |
| C-3 | 70.8 | 69.9 | 72.0 | 68.6 | 69.4 | 69.1 | 69.8 | 72.2 | 71.4 | 71.6 |
| C-3a | 40.2 | 35.1 | 35.6 | 37.7 | 39.0 | 37.4 | 39.5 | 36.7 | 38.4 | 37.8 |
| C-4 | 27.2 | 25.8 | 26.4 | 23.2 | 25.4 | 24.8 | 26.0 | 26.0 | 25.1 | 24.6 |
| C-5 | 22.0 | 21.5 | 21.0 | 21.0 | 21.8 | 21.5 | 22.0 | 21.6 | 22.3 | 26.6 |
| C-6 | 22.5 | 21.7 | 30.5 | 21.1 | 22.0 | 21.7 | 22.6 | 32.3 | 39.3 | 32.3 |
| C-7 | 27.5 | 26.6 | 55.3 | 29.7 | 28.9 | 29.1 | 30.3 | 67.8 | 202.9 | 140.7 |
| C-7a | 47.2 | 45.4 | 47.3 | 44.3 | 44.4 | 44.8 | 49.4 | 44.0 | 53.5 | 48.0 |

structures. Attempts to determine the relative configuration at the asymmetric epoxide carbons of **2a** and **2b** (C-1′) and **4a** and **4b** (C-2′) by spectroscopic methods failed.

Hoping for a more selective access to epoxylactones **2a** and **2b**, we further investigated epoxidation of unsaturated lactone **8** *via* iodolactones (Scheme 3). We considered spirocyclic iodolactones **10a** and **10b** to be valuable targets for spectroscopic studies concerning the assignment of relative configuration at the asymmetric carbons. In a second step, we intended to transform iodolactones **10a** and **10b** to epoxylactones **2a** and **2b** by a reaction sequence previously reported by *P. A. Bartlett* [16]. Thus, the unsaturated lactone **8** was hydrolyzed by ethanolic KOH to yield the potassium salt **9** which was reacted with an equimolar amount




**Scheme 3**

of iodine. Unfortunately, the reaction could not be stopped at the level of the desired iodolactones **10a** and **10b**, but proceeded to yield a mixture of epoxylactone **2a** and tricyclic lactone **11** (1:1, 85%).

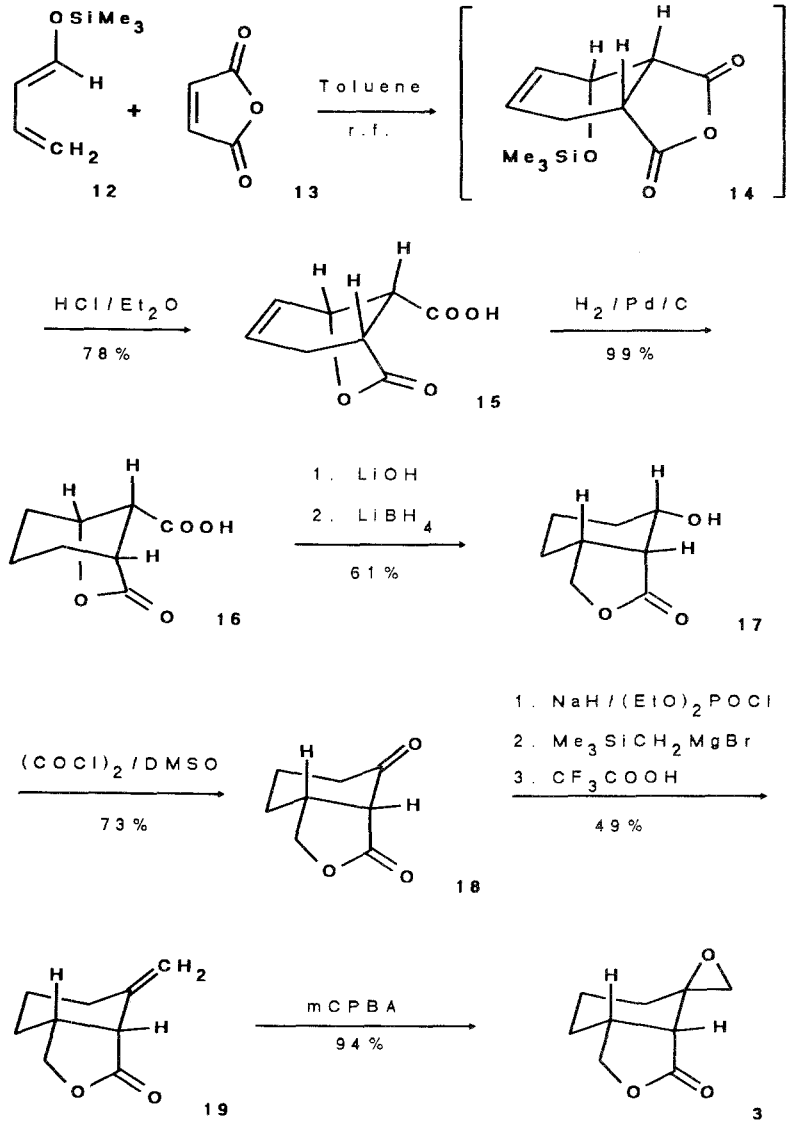
Obviously, iodolactone **10a** reacted in the predicted manner to epoxylactone **2a** by translactonization and subsequent epoxidation, whereas the epimeric iodolactone **10b** gave exclusively the tricyclic lactone **11** instead of the expected epoxylactone **2b**. We considered a nucleophilic attack at C-4 by the suitable disposed hydroxy group with concomitant elimination of iodide to be the mechanism leading to the formation of **11** starting from **10b**. Consequently, we postulated the outlined configuration of **2a** and **2b**.

Epoxidation of unsaturated lactone **7** *via* iodolactones resulted in a mixture of epoxylactones **4a** and **4b** (1:1, 90%). Intermediate iodolactones or side products which were homologous to **11** could not be detected; therefore we were unable to deduce the configuration of **4a** and **4b** by mechanistic considerations.

Furthermore, we want to present an access to spirocyclic epoxylactone **3** which we regarded to be the most valuable model of **1** in our series of epoxylactones. We started our sequence of synthesis (Scheme 4) with a *Diels-Alder* reaction of maleic anhydride (**12**) and 1-trimethylsilyloxy-butadiene (**13**). The *Diels-Alder* adduct **14** was not isolated but was immediately reacted with hydrochloric acid in ether yielding the bicyclic lactone **15** which precipitated from the ether solution to give

pure crystals (78%). After catalytic hydrogenation of the double bond in **15**, we obtained the bicyclic lactone **16** in excellent yield (99%). Treatment of **16** with $LiBH_4$ and subsequent workup at acidic conditions resulted in a chemoselective reduction of the lactone carboxyl group and lactonization of the free carboxylic function to give 7-hydroxyisobenzofuranone **17** (61%). *Swern* oxidation of **17** led to β-ketolactone **18** (73%) which proved to be a key intermediate towards the synthesis of spirocyclic epoxylactone **3**.

First, we considered *Corey*'s procedure for one step epoxidation of ketones using dimethylsulfonium methylide or dimethylsulfoxonium methylide [17] to be the method of choice to prepare epoxylactone **3**, but reaction failed due to a high tendency of **18** to enolization. Thus, we transformed β-ketolactone **18** to its methylene derivative **19** using a method previously published by *S. J. Danishefsky*




**Scheme 4**

[18]. Finally, reaction of **19** with *mCPBA* gave the well crystallizing epoxylactone **3** as the single diastereomer (94%). The high stereoselectivity on epoxidation of **19** may be explained by an attack of the oxidant at the less hindered face of the *cis* fused isobenzofuranone skeleton which was consistent to results [6] previously obtained in this series.

In a preliminary screening model we evaluated the cytotoxic potency of epoxylactones using a simple growth inhibition test of baker's yeast [19]. High $IC_{50}$ values indicated low toxicity of lactones **2a** ($IC_{50} = 852\,\mu g/ml$), **2b** ($IC_{50} = 1066\,\mu g/ml$), **4a** ($IC_{50} = 537\,\mu g/ml$) and **4b** ($IC_{50} = 1995\,\mu g/ml$) [20]. We hope that the low cytotoxicity of epoxylactones **2a**, **2b**, **4a**, and **4b** will increase interest for an intended antimicrobial testing.

## Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected. $^1H$ NMR spectra were measured on Bruker WM-250 or AM-400 WB spectrometers; $^{13}C$ NMR spectra were recorded on Bruker AC 80 or Varian Unity Plus 300 spectrometers (*TMS* as internal standard, $\delta$ in ppm). Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Mass spectra were detected on a MAT CH-7 spectrograph by *L. Jirovetz*. Microanalyses were preformed by *J. Theiner* (Institute of Physical Chemistry, Vienna University).

*Epoxidation of Isobenzofuranone* **8**

A solution of **8** (2.54 g, 15.3 mmol) and *mCPBA* (7.02 g, 75%, 30.5 mmol) in chloroform (50 ml) was refluxed for 16 h. The organic layer was washed with a solution of $Na_2SO_3$ (5%, 2 × 50 ml) and $Na_2CO_3$ (1 *M*, 2 × 50 ml), dried with $Na_2SO_4$, and the solvent was distilled off at reduced pressure to give a mixture of **2a** and **2b** (1:1, 2.14 g, 77%). Separation by flash chromatography (silica gel, hexane:ether = 1:1) yielded **2a** (670 mg, 24%, colourless oil, b.p.: 120 °C/0.02 torr) and **2b** (890 mg, 32%, colourless crystals from ether, m.p.: 64 °C).

*(3aRS, 7aSR, 1'SR)-7a-Oxiranyl-perhydroisobenzofuranone* (**2a**)

IR (KBr): $\tilde{\nu} = 1773\,cm^{-1}$ (lactone); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 4.48$ (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 3.92 (dd, $J = 9.0$ and 2.0 Hz, 1H, 3-H), 2.98 (dd, $J = 4.0$ and 3.0 Hz, 1H, 1'-H), 2.76 (dd, $J = 4.0$ and 3.0 Hz, 1H, 2'-H), 2.70 (t, $J = 4.0$ Hz, 1H, 2'-H), 2.46 (m, 1H, 3a-H), 2.05–1.90 (m, 2H), 1.75–1.60 (m, 2H), 1.55 (m, 1H), 1.35–1.20 (m, 3H); $^{13}C$ NMR (20 MHz, $CDCl_3$): $\delta = 55.6$ (C-1'), 42.9 (C-2'); for further signals see Table 1; $C_{10}H_{14}O_3$ (182.2); calcd.: C, 65.92, H, 7.74; found: C, 65.72, H, 7.70.

*(3aRS, 7aSR, 1'RS)-7a-Oxiranyl-perhydroisobenzofuranone* (**2b**)

IR (KBr): $\tilde{\nu} = 1770\,cm^{-1}$ (lactone); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 4.36$ (dd, $J = 9.0$ and 7.0 Hz, 1H, 3-H), 3.95 (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 3.14 (dd, $J = 4.0$ and 3.0 Hz, 1H, 1'-H), 2.82 (t, $J = 4.0$ Hz, 1H, 2'-H), 2.74 (dd, $J = 4.0$ and 3.0 Hz, 1H, 2'-H), 2.34 (m, 1H, 3a-H), 2.00–1.75 (m, 2H), 1.65–1.50 (m, 3H), 1.45–1.30 (m, 3H); $^{13}C$ NMR (20 MHz, $CDCl_3$): $\delta = 54.3$ (C-1'), 44.3 (C-2'); for further signals see Table 1; $C_{10}H_{14}O_3$ (182.2); calcd.: 65.92, H, 7.74; found: C, 65.84, H, 7.73.

*(3aRS, 7RS, 7aRS)-Perhydro-spiro[isobenzofuran-7,2'-oxiran]-1-one* (**3**)

A solution of **19** (420 mg, 2.76 mmol) and *mCPBA* (953 mg, 50%, 2.76 mmol) in dichloromethane (20 ml) was refluxed for 4 h. The organic layer was washed with a solution of $Na_2SO_3$ (5%, 2 × 20 ml) and

$Na_2CO_3$ (1 *M*, 2 × 20 ml), dried with $Na_2SO_4$, the solvent was distilled off at reduced pressure, and the residue was crystallized from ether to yield **3** (435 mg, 94%, colourless crystals, m.p.: 89 °C). IR (KBr): $\tilde{\nu} = 1765\,cm^{-1}$ (lactone); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 4.24$ (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 4.05 (d, $J = 9.0$ Hz, 1H, 3-H), 2.95 (d, $J = 4.0$ Hz, 1H, 2'-H), 2.85 (d, $J = 4.0$ Hz, 1H, 2'-H), 2.77 (m, 1H, 3a-H), 2.28 (d, $J = 7.0$ Hz, 1H, 7a-H), 1.97 (m, 1H), 1.90–1.70 (m, 2H), 1.64 (qt, $J = 3.0$ and 13.0 Hz, 1H), 1.38–1.25 (m, 2H); $^{13}C$ NMR (20 MHz, $CDCl_3$): $\delta = 52.4$ (C-2'); for further signals see Table 1; MS (70 eV): *m/z* (%): 168 (100) [$M^+$], 140 (79) [$M^+$–CO], 124 (33) [$M^+$–$CO_2$]; $C_9H_{12}O_3$ (168.2); calcd.: C, 64.27, H, 7.19; found: C, 64.31, H, 7.41.

*Epoxidation of Isobenzofuranone* **7** *with mCPBA*

A solution of **7** (1.53 g, 8.5 mmol) and *mCPBA* (2.2 g, 75%, 9.6 mmol) in chloroform (50 ml) was refluxed for 16 h. The organic layer was washed with a solution of $Na_2SO_3$ (5%, 2 × 50 ml) and $Na_2CO_3$ (1 *M*, 2 × 50 ml), dried with $Na_2SO_4$, and the solvent was distilled off at reduced pressure to give a mixture of **4a** and **4b** (1:1, 1.52 g, 91%). Separation by flash chromatography (silica gel, hexane:ether = 2:1) yielded **4a** (617 mg, 37%, colourless crystals from ether/hexane, m.p.: 49 °C) and **4b** (600 mg, 36%, colourless crystals from ether, m.p.: 57 °C).

*Epoxidation of Isobenzofuranone* **7** *via Iodolactones*

A solution of **7** (2.80 g, 15.5 mmol) in ethanol (12 ml) was mixed with a solution of KOH (4.35 g, 77.5 mmol) in $H_2O$ (6 ml) and then refluxed for 16 h. After evaporation of the solvent, the residue was dissolved in $H_2O$ (100 ml), and $CO_2$ was bubbled through the solution until *pH* 7 was reached. The resulting mixture was washed with dichloromethane (2 × 50 ml) and a solution of KI (8.07 g, 48.6 mmol); $I_2$ (4.11 g, 16.5 mmol) in $H_2O$ (20 ml) was added, and the mixture was stirred at 20 °C for 16 h. Then the reaction mixture was decoloured with $Na_2S_2O_3$ and extracted with dichloromethane (2 × 50 ml). The organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 50 ml) and dried with $Na_2SO_4$. Evaporation of the solvent gave a mixture of **4a** and **4b** (1:1, 2.74 g, 90%). Separation and purification was performed as given above.

*(3aRS, 7aSR)-7a-(Oxiranylmethyl)-perhydroisobenzofuranone* (**4a**)

IR (KBr): $\tilde{\nu} = 1760\,cm^{-1}$ (lactone): $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 4.34$ (dd, $J = 9.0$ and 7.0 Hz, 1H, 3-H), 4.11 (t, $J = 9.0$ Hz, 1H, 3-H), 2.96 (ddt, $J = 8.0$, 2.0 and 4.0 Hz, 1H, 2'-H), 2.78 (t, $J = 4.0$ Hz, 1H, 3'-H), 2.69 (m, 1H, 3a-H), 2.49 (dd, $J = 4.0$ and 2.0 Hz, 1H, 3'-H), 2.02 (dd, $J = 14.0$ and 4.0 Hz, 1H, 1'-H), 1.85–1.70 (m, 2H), 1.73 (dd, $J = 14.0$ and 8.0 Hz, 1H, 1'-H), 1.60–1.35 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 48.8$ (C-2'), 46.1 (C-3'), 36.8 (C-1'); for further signals see Table 1; $C_{11}H_{16}O_3$ (196.3); calcd.: C, 67.32, H, 8.22; found: C, 67.36, H, 8.48.

*(3aRS, 7aSR)-7a-(Oxiranylmethyl)-perhydroisobenzofuranone* (**4b**)

IR (KBr): $\tilde{\nu} = 1760\,cm^{-1}$ (lactone); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 4.33$ (dd, $J = 9.0$ and 6.0 Hz, 1H, 3-H), 4.01 (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 3.14 (ddt, $J = 7.0$, 2.0 and 4.0 Hz, 1H, 2'-H), 2.80 (t, $J = 4.0$ Hz, 1H, 3'-H), 2.48 (dd, $J = 4.0$ and 2.0 Hz, 1H, 3'-H), 2.44 (m, 1H, 3a-H), 1.97 (m, 1H), 1.88 (dd, $J = 14.0$ and 4.0 Hz, 1H, 1'-H), 1.79 (m, 1H), 1.72 (dd, $J = 14.0$ and 7.0 Hz, 1H, 1'-H), 1.75–1.30 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 48.3$ (C-2'), 46.5 (C-3'), 37.7 (C-1'); for further signals see Table 1; $C_{11}H_{16}O_3$ (196.3); calcd.: C, 67.32, H, 8.22; found: C, 67.45, H, 8.21.

*(3aRS, 7aRS)-7a-(2-Propenyl)-perhydroisobenzofuranone* (**7**)

In an argon atmosphere a solution of diisopropylamine (5.14 ml, 39.2 mmol) in *THF* (8.66 ml) was cooled to 0 °C and reacted with *n*-BuLi (26.1 ml, 1.5 *M* in hexane, 39.3 mmol). This solution was added

to a solution of **5** [13] (5.0 g, 35.6 mmol) in dry *THF* (50 ml) at −78 °C, and the mixture was stirred at −78 °C for 1 h. Then, 3-bromoprop-1-ene (3.4 ml, 39.2 mmol) was added at −78 °C, the mixture was allowed to warm up to 20 °C, and stirring was continued for 16 h. After the solvent was evaporated, the residue was dissolved in dichloromethane (20 ml) and washed with 2 *M* HCl (2 × 20 ml). The organic layer was dried with $Na_2SO_4$, the solvent was evaporated, and the residue was distilled to give pure **7** (6.29 g, 98%, b.p.: 94 °C/0.1 torr). IR (KBr): $\tilde{\nu} = 1773\ cm^{-1}$ (lactone); $^1H$ NMR (250 MHz, $CDCl_3$): $\delta = 5.77$ (ddt, $J = 18.0$, 10.0 and 7.0 Hz, 1H, 2′-H), 5.12 (d, $J = 10.0$ Hz, 1H, 3′-H), 5.14 (d, $J = 18.0$ Hz, 1H, 3′-H), 4.30 (dd, $J = 9.0$ and 6.5 Hz, 1H, 3-H), 3.99 (dd, $J = 9.0$ and 6.0 Hz, 1H, 3-H), 2.37 (m, 1H, 3a-H), 2.36 (d, $J = 7$ Hz, 2H, 1′-H), 1.90–1.70 (m, 2H), 1.60–1.30 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 132.7$ (C-2′), 118.7 (C-3′), 38.6 (C-1′); for further signals see Table 1; MS (70 eV): *m/z* (%): 180 (100) [$M^+$], 136 (10) [$M^+-CO_2$]; $C_{11}H_{16}O_2$ (180.3); calcd.: C, 73.30, H, 8.95; found: C, 73.04, H, 8.95.

*(3aRS, 7aRS)-7a-Ethenyl-perhydroisobenzofuranone* (**8**)

A solution of **6** [15] (20 g, 80.9 mmol) and *DBU* (13.5 g, 89 mmol) in toluene (200 ml) was refluxed for 16 h. Then, the organic layer was washed with 2 *M* HCl, dried with $Na_2SO_4$, and the solvent was removed at reduced pressure. The residue was submitted to bulb-to-bulb distillation to give pure **8** (8.34 g, 62%, b.p.: 110 °C/0.06 torr); IR (KBr): $\tilde{\nu} = 1777\ cm^{-1}$ (lactone); $^1H$ NMR (250 MHz, $CDCl_3$): $\delta = 5.78$ (dd, $J = 17.0$ and 10.0 Hz, 1H, 1′-H), 5.23 (d, $J = 10.0$ Hz, 1H, 2′-H), 5.18 (d, $J = 17.0$ Hz, 1H, 2′-H), 4.27 (dd, $J = 9.0$ and 6.0 Hz, 1H, 3-H), 3.93 (dd, $J = 9.0$ and 4.0 Hz, 1H, 3-H), 2.36 (m, 1H, 3a-H), 2.00 (m, 1H), 1.86 (m, 1H), 1.70–1.45 (m, 3H), 1.45–1.20 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 138.1$ (C-1′), 115.7 (C-2′); for further signals see Table 1; MS (70 eV): *m/z* (%): 166 (2) [$M^+$], 122 (100) [$M^+-CO_2$]; $C_{10}H_{14}O_2$ (166.2); calcd.: C, 72.26, H, 8.49; found: C, 72.35, H, 8.58.

*(3aRS, 5aRS, 9aSR)-1H-Perhydro-furo[3,4-c]isobenzofuranone* (**11**)

A solution of **8** (1.66 g, 10 mmol) in ethanol (10 ml) was mixed with a soltion of KOH (2.81 g, 50 mmol) in $H_2O$ (4 ml) and then refluxed for 16 h. After evaporation of the solvent, the residue was dissolved in $H_2O$ (100 ml) and $CO_2$ was bubbled through the solution until *pH* 7 was reached. The resulting mixture was washed with dichloromethane (2 × 50 ml) and a solution of KI (5.23 g, 31.5 mmol); $I_2$ (2.67 g, 10.5 mmol) in $H_2O$ (15 ml) was added, and the mixture was stirred at 20 °C for 16 h. Then, the reaction mixture was decoloured with $Na_2S_2O_3$ and extracted with dichloromethane (2 × 50 ml). The organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 50 ml) and dried with $Na_2SO_4$. Evaporation of the solvent gave a mixture of **2a** and **11** (1:1, 1.55 g, 85%). Separation by flash chromatography (silica gel, hexane:dichloromethane = 1:1) yielded **2a** (675 mg, 37%, colourless oil, b.p.: 120 °C/0.02 torr, analytical data see above) and **11** (585 mg, 32%, colourless crystals from EtOAc, m.p.: 87 °C). IR (KBr): $\tilde{\nu} = 1765\ cm^{-1}$ (lactone); $^1H$ NMR (250 MHz, $CDCl_3$): $\delta = 4.37$ (d, $J = 10.0$ Hz, 1H, 3-H), 4.27 (dd, $J = 10.0$ and 3.0 Hz, 1H, 3-H), 4.18 (d, $J = 3.0$ Hz, 1H, 3a-H), 3.99 (t, $J = 7.5$ Hz, 1H, 5-H), 3.45 (dd, $J = 12.0$ and 7.5 Hz, 1H, 5-H), 2.25–1.85 (m, 5H), 1.75–1.45 (m, 3H), 1.32 (m, 1H); $^{13}C$ NMR (20 MHz, $CDCl_3$): $\delta = 177.3$ (C-1), 83.3 (C-3a), 71.5 (C-3), 71.3 (C-5), 52.4 (C-9a), 48.2 (C-5a), 29.1 (C-9), 24.8 (C-6), 20.0 (C-8), 19.9 (C-7); $C_{10}H_{14}O_3$ (182.2); calcd.: C, 65.92, H, 7.74; found: C, 65.84, H, 7.66.

*(IRS, 5SR, 8RS)-7-Oxo-6-oxabicyclo[3.2.1]oct-3-ene-8-carboxylic acid* (**15**)

In an argon atmosphere, **12** (35.1 g, 358 mmol) was dissolved in dry toluene (500 ml). **13** (50.9 g, 358 mmol) was added, and the mixture was refluxed for 16 h. Then the solvent was distilled off at reduced pressure, the residue was dissolved in dry ether (500 ml), HCl (7.7 *M* in ether, 52 ml, 400 mmol) was added, and the mixture was refluxed for 48 h. During removal of the solvent, yellow crystals were precipitated which were collected by filtration and recrystallized from chloroform to give pure **15** (46.95 g, 78%), colourless crystals, m.p.: 134–135 °C. IR (KBr): $\tilde{\nu} = 1795\ cm^{-1}$ (lactone), 1715 $cm^{-1}$

(COOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (m, br., 1H, COOH), 6.29 (ddt, $J = 10.0$, 6.0 and 2.0 Hz, 1H, 4-H), 5.92 (dt, $J = 10.0$ and 3.0 Hz, 1H, 3-H), 5.02 (d, $J = 6.0$ Hz, 1H, 5-H), 3.26 (dt, $J = 2.0$ and 3.0 Hz, 1H, 1-H), 3.07 (s, 1H, 8-H), 2.58 (m, 2H, 2-H); $^{13}$C NMR (20 MHz, *DMSO*-$d_6$): $\delta = 177.5$ (C-7), 172.4 (COOH), 131.1 (C-4), 129.0 (C-3), 74.5 (C-5), 49.4 (C-8), 39.9 (C-1), 29.0 (C-2); MS (70 eV): *m/z* (%): 168 (9) [$M^+$], 151 (7) [$M^+$–OH], 124 (100) [$M^+$–$CO_2$]; $C_8H_8O_4$ (168.2); calcd.: C, 57.14, H, 4.80; found: C, 57.08, H, 5.03.

*(1RS, 5SR, 8RS)-7-Oxo-6-oxabicyclo[3.2.1]octane-8-carboxylic acid* (**16**)

Olefine **15** (16.3 g, 97 mmol) was dissolved in ethyl acetate. Pd on activated carbon (10%, 1 g) was added, and the mixture was stirred in a hydrogen atmosphere (1 bar) until no more hydrogen was absorbed. After removal of the catalyst by filtration and of the solvent by evaporation, the residue was recrystallized from ethyl acetate to give **16** (16.3 g, 99%), colourless crystals, m.p. 105–107 °C. IR (KBr): $\tilde{\nu} = 1780\ cm^{-1}$ (lactone), $1715\ cm^{-1}$ (COOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (m, br., 1H, COOH), 5.07 (d, $J = 4.0$ Hz, 1H, 5-H), 3.02 (d, $J = 4.0$ Hz, 1H, 1-H), 2.78 (s, 1H, 8-H), 2.20–2.00 (m, 2H), 1.90–1.60 (m, 4H); $^{13}$C NMR (20 MHz, *DMSO*-$d_6$): $\delta = 176.9$ (C-7), 172.7 (COOH), 79.2 (C-5), 52.4 (C-8), 41.0 (C-1), 27.9 (C-4), 25.2 (C-2), 17.4 (C-3); MS (70 eV): *m/z* (%): 170 (4) [$M^+$], 153 (6) [$M^+$–OH], 126 (100) [$M^+$–$CO_2$]; $C_8H_{10}O_4$ (170.2); calcd.: C, 56.46, H, 5.93; found: C, 56.50, H, 6.16.

*(3aRS, 7SR, 7aRS)-7-Hydroxy-perhydroisobenzofuranone* (**17**)

Carboxylic acid **16** (8.51 g, 50 mmol) was dissolved in MeOH (15 ml), a solution of $LiOH \cdot H_2O$ (2.1 g, 50 mmol) in MeOH (10 ml) was added, and the solvent was removed at reduced pressure. The lithium salt was suspended in dry *THF* (250 ml) in an argon atmosphere, a solution of $LiBH_4$ (2 *M* in *THF*, 50 ml, 100 mmol) was added, and the mixture was refluxed for 4 h. After cooling to 20 °C, MeOH (10 ml) was slowly added and the mixture was further refluxed for 1 h. Then, 2 *M* HCl (200 ml) was added, the mixture was extracted with ethyl acetate (4 × 100 ml), the organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 100 ml), dried with $Na_2SO_4$, and the solvent was removed at reduced pressure. The residue was crystallized from ether to yield **17** (4.75 g, 61%), colourless crystals, m.p. 62–64 °C. IR (KBr): $\tilde{\nu} = 3500\ cm^{-1}$ (OH), $1760\ cm^{-1}$ (lactone); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 4.25$ (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 4.03 (d, $J = 9.0$ Hz, 1H, 3-H), 3.99 (d, $J = 11.0$ Hz, 1H, OH), 3.86 (ddt, $J = 6.0$, 4.0 and 11.0 Hz, 1H, 7-H), 2.96 (t, $J = 6.0$ Hz, 1H, 7a-H), (ddt, $J = 12.0$, 6.0 and 5.0 Hz, 1H, 3a-H), 2.03 (m, 1H), 1.85–1.75 (m, 2H), 1.35–1.12 (m, 3H); $^{13}$C NMR (20 MHz, $CDCl_3$): see Table 1; MS (70 eV): *m/z* (%) 156 (6) [$M^+$], 138 (8) [$M^+$–$H_2O$], 128 (100) [$M^+$–CO]; $C_8H_{12}O_3$ (156.2); calcd.: C, 61.52, H, 7.74; found: C, 61.59, H, 7.86.

*(3aRS, 7aRS)-Perhydroisobenzofurane-1,7-dione* (**18**)

In an argon atmosphere, a solution of $(COCl)_2$ (4.44 g, 35 mmol) in dry $CH_2Cl_2$ (100 ml) was cooled to −60 °C, reacted with *DMSO* (10 ml), and stirred for 10 min. Then, a solution of **17** (5 g, 32 mmol) in $CH_2Cl_2$ (25 ml) and *DMSO* (10 ml), which was prepared in a second flask, was added dropwise to the above mixture at −60 °C. After 30 min, $Et_3N$ (14.2 g, 140 mmol) was added, and the mixture was allowed to warm up to 20 °C. Then, a solution of $Na_2CO_3$ (1 *M*, 100 ml) was added, extracted with $CH_2Cl_2$ (2 × 100 ml), the combined organic layers were washed with a solution of $Na_2CO_3$ (2 × 100 ml), dried with $Na_2SO_4$, the solvent was evaporated, and the residue recrystallized from methanol to give **18** (3.58 g, 73%), colourless crystals, m.p. 61 °C; IR (KBr): $\tilde{\nu} = 1775\ cm^{-1}$ (lactone), $1715\ cm^{-1}$ (ketone); $^1$H NMR (400 MHz, $CDCl_3$): ketone:enol = 85:15; $\delta$(ketone) = 4.32 (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 4.16 (dd, $J = 9.0$ and 2.0 Hz, 1H, 3-H), 3.44 (d, $J = 8.0$ Hz, 1H, 7a-H), 3.00 (m, 1H, 3a-H), 2.50 (m, 1H), 2.36 (m, 1H), 2.06 (m, 2H), 1.80–1.60 (m, 2H); $\delta$(enol, separated signals) = 8.93 (s, 1H, enol-H), 4.59 (t, $J = 8.0$ Hz, 1H, 3-H), 3.85 (dd, $J = 10.0$ and 8.0 Hz, 1H, 3-H); $^{13}$C NMR (20 MHz, *DMSO*-$d_6$): see Table 1; $C_8H_{10}O_3$ (154.2); calcd.: C, 62.33, H, 6.54; found: C, 62.55, H, 6.61.

*(3aRS, 7aRS)-7-Methylenperhydroisobenzofuranone* (**19**)

*7-Methylenperhydroisobenzofuranone* (**19**)

A solution of **18** (2 g, 13 mmol) in *THF* (10 ml) was added dropwise to a slurry of hexane-washed NaH (70% dispersion, 490 mg, 14.3 mmol) in *THF* (10 ml) at 0 °C. The solution was warmed to 20 °C for 20 min, cooled to 0 °C again and $(EtO)_2POCl$ (1.88 ml, 13 mmol) was added. After 2 h at 0 °C, the solution was transferred to a flask filled with nickel acetylacetonate (333 mg, 1.3 mmol). Then, a solution of $Me_3SiCH_2MgCl$ (32.5 ml, 1 *M* in $Et_2O$, 32.5 mmol) was added, and the mixture was stirred for 16 h. The reaction was quenched with an aqueous solution of $NH_4Cl$ (20%, 100 ml), the mixture was extracted with ether (3 × 100 ml), the organic layer was washed with an aqueous solution of $NaHCO_3$ (5%, 100 ml) and dried with $Na_2SO_4$. After evaporation of the solvent, the residue was dissolved in $CH_2Cl_2$ (15 ml), cooled to 0 °C, $CF_3COOH$ (10 ml) was slowly added, and the solution was warmed to 20 °C for 16 h. After evaporation of the solvent, the residue was purified by flash chromatography (silica gel, hexane:$CH_2Cl_2$ = 1:1) to give **19** (970 mg, 49%, colourless oil); IR (KBr): $\tilde{\nu} = 1770\,cm^{-1}$ (lactone); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 5.07$ (s, 1H, 1′-H), 4.94 (s, 1H, 1′-H), 4.26 (dd, $J = 9.0$ and 5.0 Hz, 1H, 3-H), 4.02 (dd, $J = 9.0$ and 2.0 Hz, 1H, 3-H), 3.28 (d, $J = 7.0$ Hz, 1H, 7a-H), 2.59 (m, 1H, 3a-H), 2.29 (dt, $J = 14.0$ and 3.0 Hz, 1H, 6-H), 2.02 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.46–1.25 (m, 2H); $^{13}C$ NMR (20 MHz, $CDCl_3$): $\delta = 114.4$ (C-1′); for further signals see Table 1. $C_9H_{12}O_2$ (152.2); calcd.: C, 71.03, H, 7.95; found: C, 70.78, H, 8.06.

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