

131. Determination of the Configuration of Wine Lactone

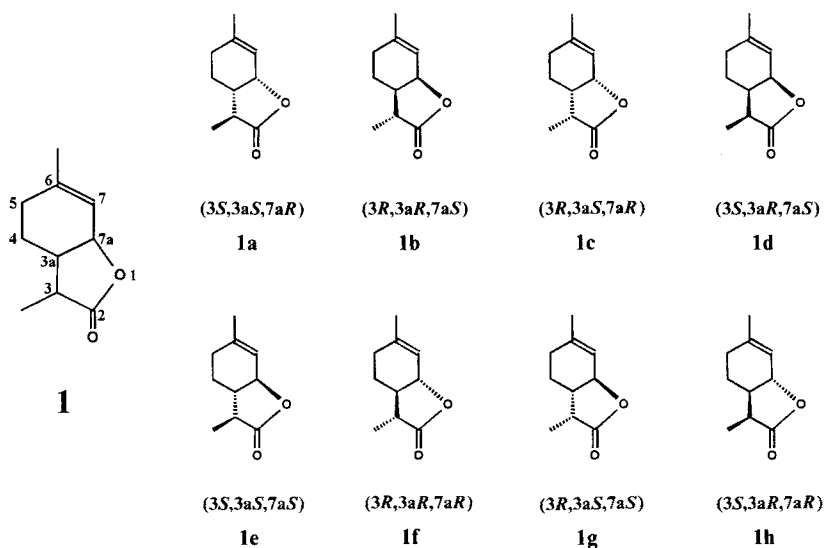
by Helmut Guth

Deutsche Forschungsanstalt für Lebensmittelchemie, Lichtenbergstrasse 4, D-85748 Garching

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The intense sweet and coconut-like smelling odorant **1**, named 'wine lactone', was isolated from different wine varieties. The chemical structure of this compound, which has not yet been detected in wine or a food, was identified by high-resolution mass spectrometry (HR-MS) as 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one. For the evaluation of the configuration of wine lactone, stereochemically controlled syntheses were developed. All eight isomers were characterized by NMR, MS, IR, and CD measurements. The configuration of 'wine lactone' was in agreement with synthesized (3*S*,3a*S*,7a*R*)-enantiomer (**1a**) on the basis of enantioselective GC. For this isomer, the lowest odor threshold (0.02 pg/l air) was detected.

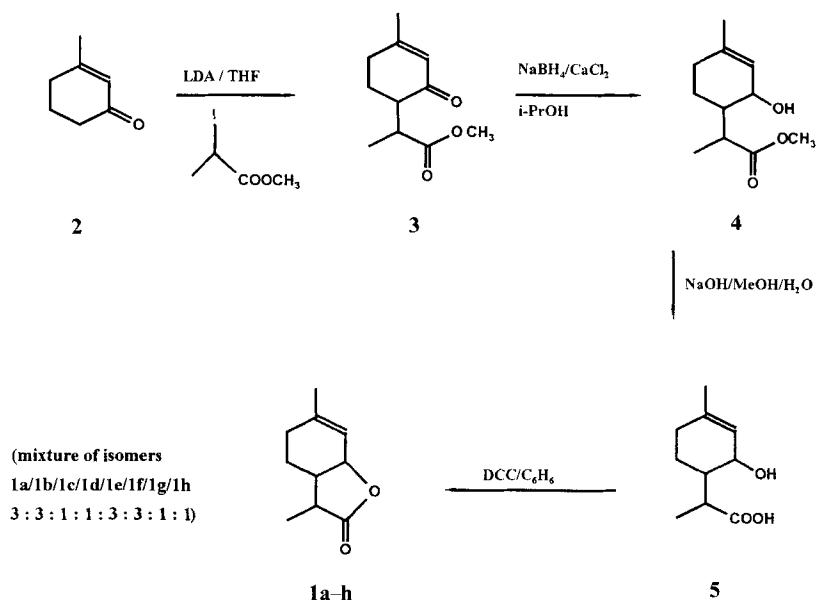
Introduction. – The odorants of different white wine varieties have recently been evaluated [1], and it has been shown that 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one (**1**) belongs to the most important flavor compounds. This trace component in wine with coconut and sweet odor was named 'wine lactone'. To our knowledge, this monoterpene has not yet been detected in wine or a food. *Southwell* [2], who investigated the essential-oil metabolism of koala animals after feeding of the leaf of *Eucalyptus punctata*, identified compound **1** tentatively by ¹H-NMR in the excreted urine. In 1981, *Bartlett and Pizzo* [3] reported about the evaluation of the rearrangement of cyclohex-2-



enols for the stereoselective construction of terpene compounds. In the course of their syntheses, the authors prepared a mixture of two racemic *cis*-fused bicyclic lactones **1a/1b** and **1c/1d**, but without assignment of the configuration of the enantiomers. To identify the configuration of **1** in wine, stereochemically controlled syntheses for the eight isomers were developed. The details of the syntheses, assignment of configuration, analytical properties, and evaluation of odor threshold of the stereoisomers are described in the present paper.

Results and Discussion. – *Syntheses of the Target 3a,4,5,7a-Tetrahydro-3,6-dimethyl-benzofuran-2(3H)-one Isomers 1a–h.* Preparation of stereoisomeric lactones **1a–h** followed a route according to [4] using 3-methylcyclohex-2-enon (**2**) as starting material (see Scheme 1). Treatment with LDA as base formed the enolate anion at C(6); the following reaction with methyl 2-iodopropanoate yielded methyl 2-(4-methyl-2-oxocyclohex-3-enyl)propanoate (**3**) as a 1:1 mixture of diastereoisomers (GC). A selective 1,2-reduction of the conjugated ketone group was performed with NaBH₄ in the presence of CaCl₂ [5] and yielded methyl 2-(2-hydroxy-4-methylcyclohex-3-enyl)propanoate (**4**). Saponification with NaOH and lactonization of the corresponding hydroxy-acid precursors **5** in benzene with addition of catalytic amounts of TsOH formed diastereoisomeric *cis*-fused racemic lactones **1a/1b** and **1c/1d** in *ca.* 3:1 mixture. No *trans*-configured lactones were generated during this procedure. On the other hand, if lactonization of hydroxy acids was performed with *N,N'*-dicyclohexylcarbodiimide (DCC) in benzene [8], there resulted a mixture (3:1:3:1) of racemic *cis*- (**1a/1b**, **1c/1d**) and *trans*-configured lactones (**1e/1f**, **1g/1h**).

Scheme 1



Separation of isomeric lactones **1a–h** was performed on different stationary GC phases and by HPLC; RI and t_R values are summarized in *Table 1*. Capillary GC on a chiral stationary phase (see *Fig. 1* and *Table 1*) showed that each enantiomeric pair has a 1:1 quantitative relation of isomers. After separating the mixture of lactones by HPLC chromatography (*Table 1*), the NMR, HR-MS, and IR experiments were performed with the obtained diastereoisomerically pure compounds.

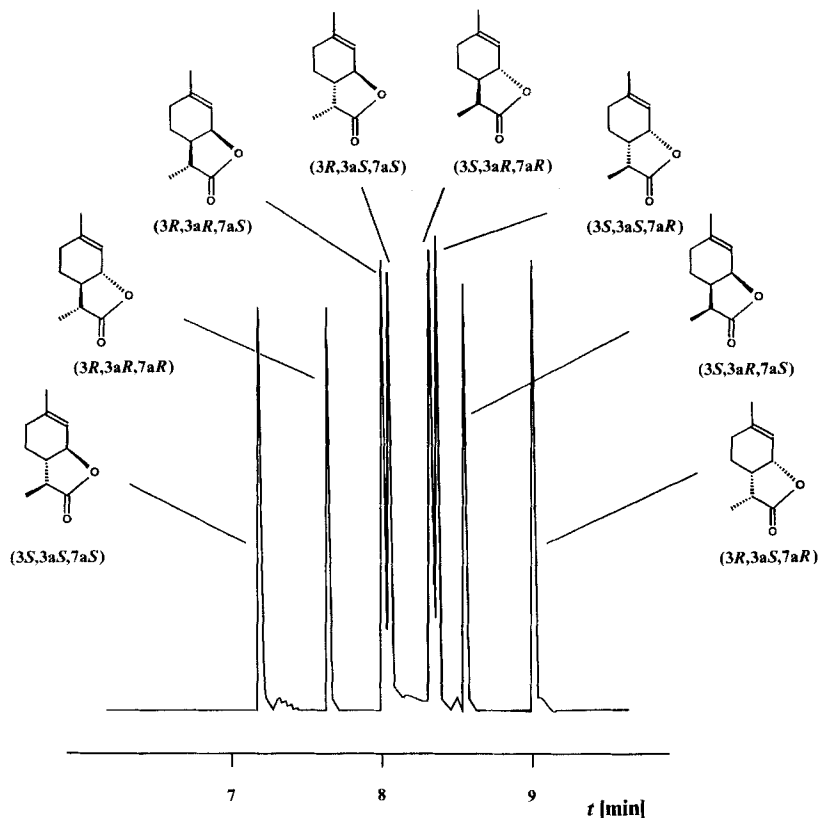


Fig. 1. Separation of 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)one isomers **1a–h** by capillary GC on a chiral stationary phase

Racemic lactones **1a/b–1g/h** all showed strong C=O stretching absorption bands in the IR region at 1775–1785 cm^{-1} (see *Exper. Part*). For the epimeric *cis*-configured lactones **1a/1b** and **1c/1d**, lower absorption bands (1775 cm^{-1}) were observed than for *trans*-analogues **1e/1f** and **1g/1h** (1785 cm^{-1}). The same differences in C=O absorption for *cis*- and *trans*-lactones of 2-(2-hydroxycyclohexyl)acetic acid were found by Klein [9].

High-resolution EI-MS of **1a/b–1g/h** led to the same sum formula and molecular-fragment ions for each enantiomeric pair (*Table 2*). However, the isomers differ in the intensities of the fragment ions: **1a/1b**, **1e/1f**, and **1g/1h** showed base peak at m/z 151

Table 1. GC and HPLC Data of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Stereoisomers

Stereoisomer	Capillary GC ^{a)}			Analytical HPLC ^{b)}
	FFAP (RI)	DB-5 (RI)	Chiral phase (<i>t</i> _R [min])	Silica gel (<i>t</i> _R [min])
Wine lactone	2192	1455	8.4	7.7
1a (3 <i>S</i> ,3 <i>aS</i> ,7 <i>aR</i>)	2192	1455	8.4	7.7
1b (3 <i>R</i> ,3 <i>aR</i> ,7 <i>aS</i>)	2192	1455	8.0	7.7
1c (3 <i>R</i> ,3 <i>aS</i> ,7 <i>aR</i>)	2314	1496	9.0	9.5
1d (3 <i>S</i> ,3 <i>aR</i> ,7 <i>aS</i>)	2314	1496	8.6	9.5
1e (3 <i>S</i> ,3 <i>aS</i> ,7 <i>aS</i>)	2129	1422	7.3	6.0
1f (3 <i>R</i> ,3 <i>aR</i> ,7 <i>aR</i>)	2129	1422	7.7	6.0
1g (3 <i>R</i> ,3 <i>aS</i> ,7 <i>aS</i>)	2206	1466	8.1	6.9
1h (3 <i>S</i> ,3 <i>aR</i> ,7 <i>aR</i>)	2206	1466	8.3	6.9

a) Capillary GC: FFAP and DB-5, and calculation of retention indices (RI), as described in [6] [7]. Separation of the enantiomers was performed on a borosilicate glass capillary (20 m × 0.25 mm) coated with a chiral stationary phase (octakis(3-*O*-butyryl-2,6-di-*O*-pentyl) γ -cyclodextrin).

b) Hypersil silica gel 60, 5 μ m, 500 × 4.6 mm; isocratic elution with pentane/Et₂O 7:3; flow rate 2 ml/min; UV detection at 215 nm [6].

Table 2. Key Ions (*m/z*, intensity [%]) Obtained by High-Resolution Mass Spectrometry^{a)} of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Isomers

Stereoisomers ^{b)}	166	151	138	123	122	109	107	95	93	91	79	77	55
Wine lactone	42	100	10	16	7	7	23	15	46	23	26	15	24
1a (3 <i>S</i> ,3 <i>aS</i> ,7 <i>aR</i>)	42	100	10	16	6	6	22	15	46	22	26	15	23
1b (3 <i>R</i> ,3 <i>aR</i> ,7 <i>aS</i>)													
1c (3 <i>R</i> ,3 <i>aS</i> ,7 <i>aR</i>)	34	64	8	18	25	5	46	22	100	54	58	38	40
1d (3 <i>S</i> ,3 <i>aR</i> ,7 <i>aS</i>)													
1e (3 <i>S</i> ,3 <i>aS</i> ,7 <i>aS</i>)	31	100	16	30	7	17	11	38	25	18	20	18	60
1f (3 <i>R</i> ,3 <i>aR</i> ,7 <i>aR</i>)													
1g (3 <i>R</i> ,3 <i>aS</i> ,7 <i>aS</i>)	31	100	16	27	6	16	12	38	22	18	21	14	75
1h (3 <i>S</i> ,3 <i>aR</i> ,7 <i>aR</i>)													

a) Analyses were performed with a 8230 mass spectrometer (Finnigan, Bremen, FRG) in the electron-impact mode (EI) by using perfluorokerosene (PFK) as the reference.

b) Sum formula of fragment (*m/z*): 166 (C₁₀H₁₄O₂), 151 (C₉H₁₁O₂), 138 (C₈H₁₀O₂), 123 (C₈H₁₁O), 122 (C₉H₁₄), 109 (C₇H₉O), 107 (C₈H₁₁), 95 (C₆H₇O/C₇H₁₁), 93 (C₇H₉), 91 (C₇H₇), 79 (C₆H₇), 77 (C₆H₅), 55 (C₃H₃O); the racemic mixture of lactones was used for measurements.

corresponding to the [*M*–CH₃]⁺ ion. In contrast, for racemic **1c/1d** a relative abundance of 64% of this ion and a base peak at *m/z* 93 [*M*–C₃H₅O₂]⁺ has been observed. For stereoisomeric *trans*-lactones, a higher abundance of *m/z* 55 has been found than for the *cis*-lactones. The molecular ion (*m/z* 166) of lactones was confirmed by CI-MS (isobutane).

The results of the IR and MS experiments are consistent with the proposed structures of **1a/1b–1g/1h**.

NMR Analysis of 1a/1b–1g/1h. In the ¹H-NMR spectrum (Table 3) of the four racemic lactones, nine different signals were detectable, which are assigned in connection with the structure of 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one. The spin systems of the diastereoisomeric lactones were identified from a TOCSY spectrum, and

Table 3. ^1H Chemical Shifts (δ [ppm])^{a)} and Coupling Constants [Hz]^{b)} of Selected Protons of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Stereoisomers

Stereoisomer ^{c)}	H–C(7)	H–C(7a)	H–C(3)	H–C(3a)	CH ₃ –C(6)	CH ₂ (5)	H _{eq} –C(4)	H _{ax} –C(4)	CH ₃ –C(3)
1a (3S,3aS,7aR) (C ₆ D ₆)	5.34 (dq)	4.42 (ddd)	2.02 (dq)	1.52 (ddt)	1.39 (s)	1.36 (m)	1.14 (m)	1.14 (m)	0.98 (d)
1b (3R,3aR,7aS) (CDCl ₃)	5.50 (dq)	4.87 (ddd)	2.40 (dq)	2.25 (ddt)	1.71 (s)	1.94 (m)	1.81 (m)	1.71 (m)	1.24 (d)
1c (3R,3aS,7aR) (C ₆ D ₆)	5.50 (m)	4.06 (br. t)	2.20 (dq)	1.48 (m)	1.47 (s)	1.44 (m)	0.99 (m)	0.77 (m)	0.98 (d)
1d (3S,3aR,7aS) (CD ₂ Cl ₂)	5.65 (m)	4.60 (br. t)	2.86 (dq)	2.33 (dddd)	1.77 (s)	2.01 (m)	1.67 (dddd)	1.20 (m)	1.13 (d)
1e (3S,3aS,7aS) (C ₆ D ₆)	5.70 (s)	3.90 (br. d)	1.70 (dq)	1.29 (m)	1.39 (s)	1.61 (m)	1.37 (m)	0.89 (m)	1.02 (d)
1f (3R,3aR,7aR) (CD ₂ Cl ₂)	5.78 (s)	4.35 (br. d)	2.29 (dq)	1.71 (dddd)	1.69 (s)	2.16 (m)	2.01 (m)	1.56 (m)	1.19 (d)
1g (3R,3aS,7aS) (C ₆ D ₆)	5.71 (s)	4.17 (br. d)	2.26 (dq)	1.61 (dddd)	1.39 (s)	1.58 (m)	1.08 (m)	0.88 (m)	0.76 (d)
1h (3S,3aR,7aR)									

Stereoisomer ^{b)}	J (7,7a)	J (7,CH ₃ (6))	J (7a,CH ₃ (6))	J (7a,3a)	J (3a,4 _{ax})	J (3a,4 _{eq})	J (3,3a)	J (3,CH ₃ (3))
1a (3S,3aS,7aR) (C ₆ D ₆)	3.1	1.5	1.6	6.8	5.1	5.1	9.1	7.0
1b (3R,3aR,7aS) (CDCl ₃)	3.1	1.3	1.7	6.5	6.6	4.4	8.9	7.1
1c (3R,3aS,7aR)	4.4	1.6	≈ 1	4.4	13.6	4.4	7.6	7.1
1d (3S,3aR,7aS)								
1e (3S,3aS,7aS)	< 1	< 1	2.7	9.7	12.5	2.7	13.1	7.1
1f (3R,3aR,7aR)								
1g (3R,3aS,7aS)	< 1	< 1	≈ 2	10.2	13.3	3.1	7.5	8.0
1h (3S,3aR,7aR)								

^{a)} The ^1H chemical shifts are given in relation to C₆D₆ (δ (H) 7.20 ppm), CDCl₃ (δ (H) 7.24 ppm), and CD₂Cl₂ (δ (H) 5.32 ppm). Assignments based on TOCSY and DQF-COSY.

^{b)} Determined from 1D spectrum.

^{c)} The racemic mixture of lactones (1:1) was used for measurements.

Table 4. ^{13}C Chemical Shifts (δ [ppm])^{a)} of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Stereoisomers

Stereoisomer ^{b)}	C(2)	C(6)	C(7)	C(7a)	C(3a)	C(3)	C(5)	CH ₃ –C(6)	C(4)	CH ₃ –C(3)
1a (3S,3aS,7aR)	178.1	139.6	119.7	74.5	40.2	37.3	25.7	23.4	22.1	14.0
1b (3R,3aR,7aS)										
1c (3R,3aS,7aR)	177.4	142.7	118.0	73.8	37.7	40.0	28.8	23.5	19.6	9.4
1d (3S,3aR,7aS)										
1e (3S,3aS,7aS)	178.4	137.0	121.0	79.5	48.9	41.2	30.7	22.8	22.7	12.6
1f (3R,3aR,7aR)										
1g (3R,3aS,7aS)	176.5	136.9	121.4	78.3	44.1	38.6	30.5	22.5	19.9	8.6
1h (3S,3aR,7aR)										

^{a)} The ^{13}C chemical shifts are given in relation to C₆D₆ (δ (H) 128.0 ppm). Assignment based on DEPT, HMQC, and HMBC measurements.

^{b)} The racemic mixture of lactones (1:1) was used for measurements.

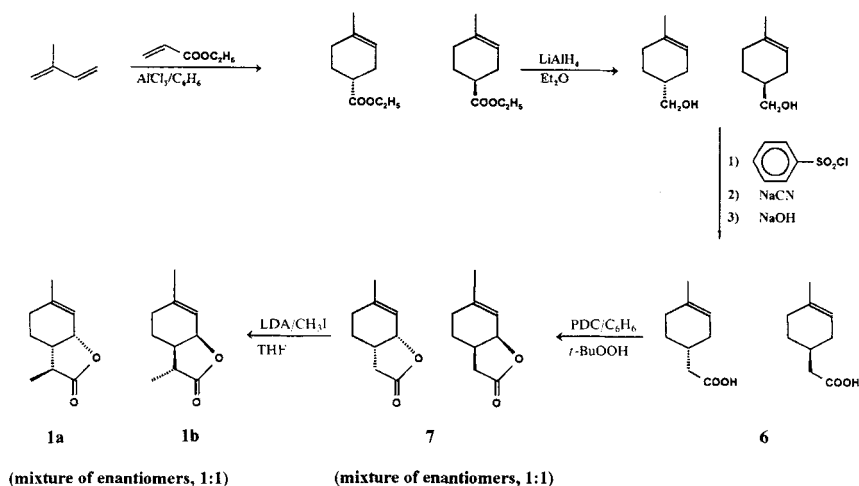
all individual protons could be assigned unequivocally by double quantum-filtered COSY (Table 3). To investigate multiple overlapping ^1H signals ($\text{H}-\text{C}(3\text{a})$, $\text{CH}_2(4)$, $\text{CH}_2(5)$) in C_6D_6 , the solvent was substituted in some cases by CD_2Cl_2 and CDCl_3 , respectively. *cis*- or *trans*-nature of ring junction of the lactone isomers was assigned from the observed coupling constants $^3J(7\text{a},3\text{a})$ and $^3J(7\text{a},7)$. Strong cross-peaks between $\text{H}-\text{C}(7\text{a})/\text{H}-\text{C}(3\text{a})$ and $\text{H}-\text{C}(7\text{a})/\text{H}-\text{C}(7)$ protons as well as corresponding coupling constants confirmed *cis*-ring fusion for **1a/1b** and **1c/1d**. In contrast to the above mentioned lactones, the $\text{H}-\text{C}(7)$ resonance of **1e/1f** and **1g/1h** appeared as a br. s at 5.70 and 5.71, respectively, and no cross-peak to $\text{H}-\text{C}(7\text{a})$ proton was observed in the DQF-COSY experiment. Molecular-dynamics simulations (data not shown) suggested, as energy-minimized conformations, structures with dihedral angles between $\text{H}-\text{C}(7\text{a})$ and $\text{H}-\text{C}(7)$ (see Fig. 2) of ca. 105° for *trans*-lactones (**1e/1f** and **1g/1h**) and 60 – 62° for *cis*-lactones (**1a/1b** and **1c/1d**). The predicted coupling constant, based upon the Karplus equation, would be between 2 and 3 Hz for a dihedral angle of 60° , and ca. 1 Hz for an angle of 105° . The observed coupling constants of the allylic proton $\text{H}-\text{C}(7\text{a})$ with $\text{H}-\text{C}(7)$ are in agreement with the experimental data and consistent with *trans*-configuration for **1e/1f** and **1g/1h**. Furthermore, the vicinal coupling constant $^3J(7\text{a},3\text{a})$ for isomers **1e/1f** and **1g/1h** are higher ($J = 9.7$ and 10.2 , resp.) than observed for the isomers **1a/1b** and **1c/1d** ($J = 6.8$ and 4.4 , resp.). Such a large coupling was only observed for *trans*-lactones with diequatorially fused rings and axial *trans*-H-atoms at the ring fusion [10]. From the DQF-COSY spectrum of lactone isomers, it was apparent that the proton $\text{H}-\text{C}(7\text{a})$ coupled also weakly with $\text{Me}-\text{C}(7)$, indicating that it was in homoallylic position to the Me group.

The ^{13}C -NMR spectrum of the isomers of **1** showed ten signals (Table 4). Assignments based on ^1H , ^{13}C -correlation experiments (HMOC, HMBC). The chemical-shift differences of $\text{Me}-\text{C}(7)$ for the isomers allowed assignments of the relative configuration of the Me group. Due to the rather small ^{13}C -NMR shift of **1c/1d** (9.4 ppm) and **1g/1h** (8.6 ppm) in comparison to **1a/1b** (14.0 ppm) and **1e/1f** (12.6 ppm), the Me group of **1c/1d** and **1g/1h**, therefore, must have 'endo'-configuration (shielding of the Me group by the $\text{C}=\text{C}$ bond), these of **1a/1b** and **1e/1f** 'exo'-configuration. Similar shift differences were observed by Blank *et al.* [11] for diastereoisomeric 2,3,3a,4,5,7a-hexahydro-3,6-dimethylbenzofurans.

Synthesis of (3SR,3aSR,7aRS)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one (1a/1b). For further confirmation of the above suggested relative configuration of the Me group at C(3), a stereoselective synthesis (Scheme 2) was developed. Key step of the synthesis was the alkylation of **7** with iodomethane. This alkylation is highly stereoselective and takes place from the less hindered side of the *cis*-fused bicyclic enolate anion with formation of the 'exo'-Me enantiomers **1a/1b**. The same strategy for stereocontrol has been employed in a number of similar systems [3] [8] [12]. HPLC as well as GC analysis indicate a diastereoisomerically pure lactone **1a/1b** ($> 95\%$). The enantiomeric distribution of **1a** and **1b**, determined by enantioselective GC, was 1:1. ^1H - and ^{13}C -NMR characteristics of **1a/1b** are in agreement with the proposed structures (Tables 3 and 4).

Assignment of Absolute Configuration of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-ones 1a–h by Synthesis. To achieve the synthesis of enantiomerically pure lactones, the strategies shown in Scheme 3 were devised. Starting from (+)-(4*R*)-limonene (**8a**), intermediates **9a** and **9b** were prepared as a 1:1 mixture of two diastereoisomers;

Scheme 2



oxidation yielded the two diastereoisomeric acids **10a** and **10b**. Using a mixture of PDC and *t*-BuOOH in benzene for cyclization of **10a** and **10b** resulted in *cis*-lactones **1a** (3*S*,3*aS*,7*aR*) and **1c** (3*R*,3*aS*,7*aR*). Analogously, lactones **1b** (3*R*,3*aR*,7*aS*) and **1d** (3*S*,3*aR*,7*aS*) were obtained in moderate yields (30%) as a 1:1 mixture starting from (–)-(4*S*)-limonene (**8b**). GC Analyses on chiral and achiral phases indicated the high regio- and stereoselectivity of the cyclization process. For the preparation of enantiomerically pure *trans*-lactones **1e–h**, the diastereoisomeric acids **10a** and **10b** were converted into the corresponding methyl esters **11a** and **11b** (Scheme 3); allylic oxidation followed by hydride reduction gave the allylic alcohols **4a** and **4b**, which were then saponified into the *trans*-hydroxy acids **5a** and **5b**. Cyclization with DCC yielded **1e** (3*S*,3*aS*,7*aS*) and **1g** (3*R*,3*aS*,7*aS*). Analogously **1f** (3*R*,3*aR*,7*aR*) and **1h** (3*S*,3*aR*,7*aR*) were obtained from the above described synthetical pathway when starting with (–)-(4*S*)-limonene. The mixtures of diastereoisomeric lactones, resulting from both pathways (Scheme 3), were cleanly separated by HPLC chromatography into the corresponding pure enantiomers. The ¹H- and ¹³C-NMR chemical shifts of these isolated compounds corresponded to the expected lactone structures.

Inversion of Ring Junction. The configurations of *trans*-fused lactones were additionally confirmed by rearrangement experiments, shown in Scheme 3. Saponification of **1e** and **1g**, followed by acid-catalyzed ring closure, afforded enantiomerically pure **1a** in both cases. Under these conditions, the *cis*-lactone is assumed to be derived from the *trans*-compound by inversion of configuration at C(7*a*). This re-lactonization presumably proceeds *via* intramolecular attack of the carboxylic-acid group at an intermediate allylic carbonium ion, which favored the *cis*-ring fusion [8] [12]. Furthermore, a complete epimerization of **1g** at C(3) was observed during this procedure thus leading to **1a**.

Characterization of Synthesized Lactones 1a–h by Circular Dichroism (CD) Measurements. UV and CD data are summarized in Table 5. The correlation of the configuration at C(3) of the isomeric lactones with the sign of the Cotton effect in their CD spectra as proposed by Beecham [13] for γ -lactones (configuration of C(α) determines the sign of the

Scheme 3

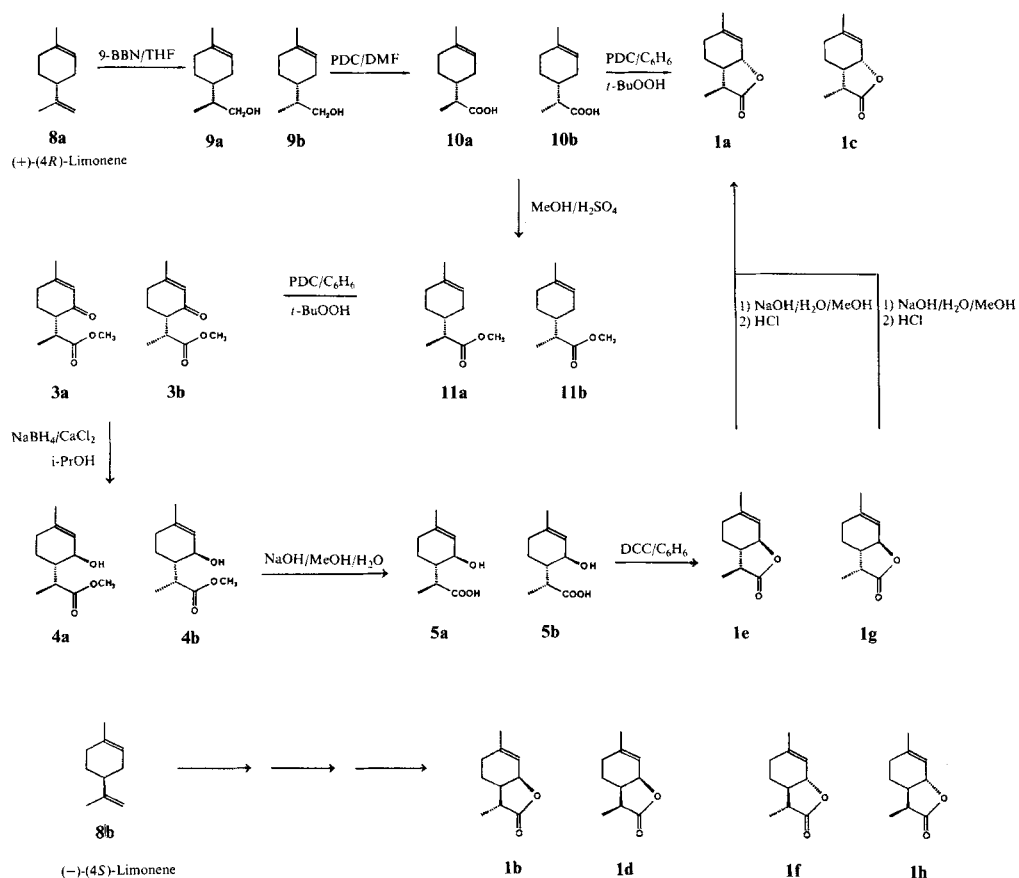


Table 5. Comparison of Observed UV ($\lambda_{\max}$, molar extinction [$\epsilon_{\max}$]) and CD Maxima ($\lambda_{\max}$, molar ellipticity [θ]) of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Stereoisomers

Stereoisomer	UV		CD		Handedness of helix ^{a)} C=C—C—O
	λ [nm]	$\epsilon_{\max}$	λ [nm]	θ	
1a (3 <i>S</i> ,3a <i>S</i> ,7a <i>R</i>)	207	4040	211	+ 5333	right
1b (3 <i>R</i> ,3a <i>R</i> ,7a <i>S</i>)	207	4100	211	− 4707	left
1c (3 <i>R</i> ,3a <i>S</i> ,7a <i>R</i>)	204	6240	209	+ 3238	right
1d (3 <i>S</i> ,3a <i>R</i> ,7a <i>S</i>)	204	6200	209	− 3333	left
1e (3 <i>S</i> ,3a <i>S</i> ,7a <i>S</i>)	208	4250	214	− 800	left
1f (3 <i>R</i> ,3a <i>R</i> ,7a <i>R</i>)	208	4400	214	+ 825	right
1g (3 <i>R</i> ,3a <i>S</i> ,7a <i>S</i>)	209	6900	215	− 1090	left
1h (3 <i>S</i> ,3a <i>R</i> ,7a <i>R</i>)	209	6931	215	+ 1056	right

^{a)} Relationships between CD sign and helical sense of the allylic oxygen system of 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one stereoisomers.

Cotton effect for the $n \rightarrow \pi^*$ transition at 215–217 nm) did not apply to the bicyclic lactones **1a–h**. For bridged-ring lactones, *Beecham* [14] found that the sign of the $n \rightarrow \pi^*$ *Cotton* effect depends solely on the enantiomeric nature of the bridged-ring system and not at all on molecular asymmetry peripheral to this. In the case of chiral lactones **1a–h**, a relationship between sign of the $\pi \rightarrow \pi^*$ *Cotton* effect and helical sense of the allylic oxygen function is observed (*Table 4*): each of the lactones **1a–h** exhibits a strong *Cotton* effect at *ca.* 209–215 nm, positive in sign in the case of **1a**, **1c**, **1f**, and **1h**, in which the chirality of the C=C–C–O bond helix is right-handed ((*R*)-configuration at C(7a)), and negative ((*S*)-configuration at C(7a)) in **1b**, **1d**, **1e**, and **1g**, in which it is left-handed. These results confirm the allylic oxygen rule of *Beecham* [15]. The fact that the chirality rules for lactones did not apply to the present compounds is probably due to the overlapped $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of which the former determines the sign of the *Cotton* effect. The large extinction coefficients of the UV maxima (*Table 4*) near the CD maxima confirm these results.

Conformational Aspects of Stereoisomeric Lactones. The coupling constants of ^1H -NMR (*Table 3*) observed for **1a–h** correspond to the pattern expected for a cyclohexenyl ring in a half-chair conformation. Significant differences between the isomers occur in the large $^3J(3a,4_{ax})$ coupling for isomers **1c/1d**, **1e/1f**, and **1g/1h** ($J = 12.5\text{--}13.6$ Hz), whereas the same protons in **1a/1b** coupled with $J = 5.1$ Hz (C_6D_6). These results are only consistent with a H–C(3a)/H_{ax}–C(4) axial-axial coupling constant for **1c/1d–1g/1h** and a more equatorial-axial coupling of **1a/1b**. The protons CH₂(4) of **1a/1b** are nearly equivalent at 1.14 ppm, whereas for isomers **1c/1d–1g/1h** prominent differences of the chemical shifts in C_6D_6 were observed ($\Delta\delta(\text{H}_{eq}\text{--C}(4)/\text{H}_{ax}\text{--C}(4))$: 0.22 ppm for **1c/1d**; 0.48 ppm for **1e/1f**; 0.20 ppm for **1g/1h**) and, therefore, showed the extent of diastereotopic splitting. As the ring inversion of the two conformers of **1a/1b** (*Fig. 2*; conformers **1a**, and **1a**₂ of enantiomer **1a** are shown) is very rapid in the typical chemical-shift time scale of the NMR experiment, one sole averaged resonance was observed for H_{eq}–C(4) and H_{ax}–C(4). Rapid ring inversion of cyclohexenyl systems on the NMR time scale was also observed by *Jensen* and *Bushweller* [16]. Consequently, the conformation of the cyclohexenyl skeleton concerning the CH₂(4) and CH₂(5) groups differed in isomer **1a/1b** from that of **1c/1d–1g/1h** (*Fig. 2*). Coupling constant of the enantiomer **1a** revealed the preference of conformer **1a**₁, with a quasi-diaxial ring fusion (in C_6D_6). As shown in *Tables 3* and *4* for **1a/1b**, the ring inversion was solvent-dependent. It is obvious from the data in *Tables 3* and *4* that **1c/1d** favored the conformation with a quasi-diequatorially ring fusion (see *Fig. 2*), probably due to the steric hindrance of Me group at C(3) with the cyclohexenyl ring in the other conformer. The large downfield shift of the allylic proton H–C(7a) of **1a/1b** which resonated at 4.42 ppm (C_6D_6) suggests that the proton is in a more deshielded environment, and, therefore, resides a more quasi-equatorial position and confirms the above mentioned results. The assignment of H–C(7a) of **1c/1d** (δ 4.04 ppm; C_6D_6), **1e/1f** (δ 3.90 ppm; C_6D_6), and **1g/1h** (δ 4.17 ppm; C_6D_6), which are more shielded, must, therefore, be quasi-axial.

Determination of Odor Threshold Values of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Isomers 1a–h. – The odor thresholds of the coconut, sweet smelling lactones **1a–h** are compared in *Table 6*. Low values were found for **1a**, **1e**, and **1h**. Comparison of the two compounds of each enantiomeric pair showed that (*3S*)-configuration correlated with a lower threshold. The large differences of the odor threshold

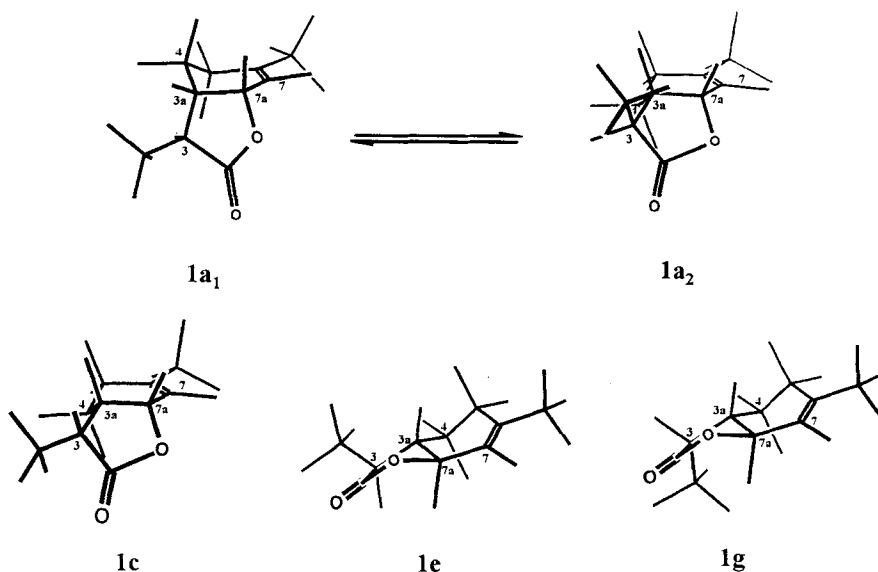


Fig. 2. Conformations of 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one enantiomers **1a** (3*S*,3a*S*,7a*R*), **1c** (3*R*,3a*S*,7a*R*), **1e** (3*S*,3a*S*,7a*S*), and **1g** (3*R*,3a*S*,7a*S*). Dihedral angle H–C(3a)/H_{ax}–C(4): 75° (**1a**₁), 170° (**1a**₂), 170° (**1c**), 180° (**1e**, **1g**); dihedral angle H–C(3a)/H–C(7a): 30° (**1a**₁), 28° (**1a**₂), 27° (**1c**), 167° (**1e**, **1g**); dihedral angle H–C(7a)/H–C(7): 60° (**1a**₁), 60° (**1a**₂), 62° (**1c**), 105° (**1e**, **1g**); dihedral angle H–C(3a)/H–C(3): 155° (**1a**₁), 105° (**1a**₂), 16° (**1c**), 152° (**1e**), 30° (**1g**).

Table 6. Odor Threshold Values [ng/l of Air]^a) of 3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one Stereoisomers

Stereoisomer	Odor threshold (ng/l air)
1a (3 <i>S</i> ,3a <i>S</i> ,7a <i>R</i>)	0.00001–0.00004
1b (3 <i>R</i> ,3a <i>R</i> ,7a <i>S</i>)	> 1000
1c (3 <i>R</i> ,3a <i>S</i> ,7a <i>R</i>)	> 1000
1d (3 <i>S</i> ,3a <i>R</i> ,7a <i>S</i>)	80–160
1e (3 <i>S</i> ,3a <i>S</i> ,7a <i>S</i>)	0.007–0.014
1f (3 <i>R</i> ,3a <i>R</i> ,7a <i>R</i>)	14–28
1g (3 <i>R</i> ,3a <i>S</i> ,7a <i>S</i>)	8–16
1h (3 <i>S</i> ,3a <i>R</i> ,7a <i>R</i>)	0.05–0.2

^a) Odor thresholds were determined by a gas-chromatographic olfactometric method [17] using (*E*)-dec-2-enal (odor threshold 2.7 ng/l air) as the standard. Data are reported in the range for the lowest and highest value found in triplicates.

values observed for, e.g. **1a** (0.00001 ng/l air) and **1b** (> 1000 ng/l air), clearly demonstrate that the threshold was significantly influenced by the configuration of the odorant.

Determination of the Configuration of Wine Lactone. Comparison of MS and chromatographic data (Tables 1 and 2) of compound **1**, isolated from different white wine varieties, with those of the synthesized lactones **1a–h** indicated that wine lactone is identical with the (3*S*,3a*S*,7a*R*)-3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one (**1a**).

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Experimental Part

General. Wine lactone (= (3*S*,3*aS*,7*aR*)-3*a*,4,5,7*a*-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one; **1**) was isolated from *Gewürztraminer* wine (10 l) by solvent extraction with pentane and purified by column chromatography (CC) on silica gel and, in addition, by HPLC and prep. GC [1]. The following compounds were obtained commercially: (–)-(4*S*)-limonene, (+)-(4*R*)-limonene, 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (0.5 mol/l), *N,N'*-dicyclohexylcarbodiimide (DCC), 3-methylcyclohex-2-enon (**2**), methyl (±)-2-bromopropanoate, sodium borohydride, BuLi, (i-Pr)₂NH, MeI, isoprene, ethyl prop-2-enoate (*Aldrich*, Steinheim, FRG); pyridinium dichromate (PDC) (*Merck*, Darmstadt, FRG). Pentane, Et₂O, and MeOH were 'for HPLC' (*Aldrich*, Steinheim, FRG). (D₆)Benzene, CD₂Cl₂, and CD₃Cl were from *Isocom* (Landshut, FRG). Separation of the enantiomers of **1** on an octakis(3-*O*-butyryl-2,6-*cis-O*-pentylyl) γ -cyclodextrin borosilicate glass capillary (20 m $\times$ 0.25 mm), which was a gift of *W.A. König*, University of Hamburg, Germany, trade-name *Lipodex E*. On column injection of the sample; temp. 70° for 1 min, then raised with 40°/min to 170° and further with 8°/min to 200°, hold for 10 min. CD Spectra: solns. in pentane (200 μ l, 1–6 μ mol) spectralpolarimeter *Jasco J-500 A* (*Biotronik*, Maintal, FRG) equipped with a 450-W Xe lamp; at 24° in 1-mm quartz cell, range 300–180 nm. IR Spectra: solns. in CS₂ (1–2 mg/200 μ l); IR spectrometer 299 *B* (*Perkin Elmer*, Überlingen, FRG). NMR Spectra: *Bruker-AM-360* spectrometer, at 297 K, samples (ca. 2 mg), in C₆D₆, CD₂Cl₂, and CDCl₃, in a *Wilmad 535-PP* tube for ¹H- and ¹³C-NMR, and DEPT experiments; *Bruker-AC-200* for DQF-COSY, TOCSY, HMQC, and HMBC experiments. ¹H-NMR: transmitter frequency 360.13 MHz; recorded with 32 K data points and a spectral width of 7200 Hz and multiplied with a *Lorentz-Gaussian* function prior to transformation; repetition time 3.2 s. ¹³C-NMR: transmitter frequency 90.56 MHz; recorded with 64 K data points and a spectral width of 21 700 Hz; repetition time 2.5 s; 1 Hz line broadening. ¹H-COSY: a phase-sensitive double-quantum-filtered COSY was performed (DQF-COSY); relaxation delay 3 s, 2 K data points in *F*₂ and 400 experiments in *F*₁, 32 scans, 2 dummy scans, spectral width 2000 Hz and resolution 2 Hz/point in both dimensions; sine-bell multiplication gives 1 K $\times$ 1 K complex points. TOCSY: MLEV-17 mixing sequence $\tau_{\text{mix}} = 8$ ms with 2.5 ms trim pulses; 2 K data points in *F*₂ and 200 experiments in *F*₁, 4 scans, spectral width 2000 Hz in both dimensions. HMQC, HMBC: the pulse sequence described by *Bax* and *Summers* [18], with a BIRD puls to suppress protons connected to ¹²C, was used; 2 experiments with magnetization transfer optimized for coupling constants of 145 and 8.3 Hz, giving delays of 3.45 and 60 ms, resp.; relaxations delay 2 s; 32 scans preceded by 2 dummy scans were recorded for 200 *t*₁ values and zero-filled; spectral width 2000 Hz in *F*₂ and 9615 Hz in *F*₁; sine bell apodization and magnitude calculation in *F*₂ (HMBC), gives a data matrix of 512 $\times$ 512.

Methyl 2-(4-Methyl-2-oxocyclohex-3-enyl)propanoate (3). According to *Hijfte* and *Vandewalle* [4], LDA was prepared from (i-Pr)₂NH (3.5 g, 35 mmol) in THF (20 ml) and BuLi (1.6M in hexane, 20 ml; 33 mmol) at –10°. After cooling at –78°, a soln. of 3-methylcyclohex-2-enon (3.3 g, 30 mmol) in THF (20 ml) was added dropwise. After stirring for 1 h, HMPA (15 ml) and methyl 2-iodopropanoate (35 mmol; prepared from NaI and methyl (±)-2-bromopropanoate in acetone) were added. The resulting mixture was stirred at –20° for 2 h. Then, the mixture was allowed to warm up to r.t. and was quenched with a sat. aq. soln. of NH₄Cl (50 ml). Extraction was performed with Et₂O (2 $\times$ 50 ml) and the combined org. phases were dried (Na₂SO₄) and concentrated. Purification by CC (silica gel, 30 $\times$ 2 cm, pentane/Et₂O, 6:4) yielded 2.9 g (50%) of pure **3** as a 1:1 mixture of diastereoisomers (GC). EI-MS: 196 (3, *M*⁺), 165 (6), 137 (8), 110 (52), 109 (22), 82 (100), 54 (22), 39 (25). RI (FFAP): 2262, 2269.

Methyl 2-(2-Hydroxy-4-methylcyclohex-3-enyl)propanoate (4). Compound **3** (2 g, 10 mmol) was reduced with a soln. of CaCl₂ (2.2 g, 20 mmol) and NaBH₄ (0.55 g, 15 mmol) in i-PrOH (50 ml) according to the general procedure in [5] with some modifications. The mixture was stirred for 2 h at 0° and was used without purification for the preparation of **5**.

2-(2-Hydroxy-4-methylcyclohex-3-enyl)propanoic Acid (5). The soln. of **4** was added to a mixture of NaOH (1.2 g, 30 mmol) in MeOH/H₂O (1:1, 20 ml) and stirred for 12 h at r.t. Careful acidification with 1M HCl to pH 6, followed by extraction with Et₂O, and evaporation of solvent yielded crude **5** (0.8 g).

3*a*,4,5,7*a*-Tetrahydro-2(3*H*)-one Isomers 1*a*–1*h*. Cyclization of **5** (0.8 g) was performed with *N,N'*-dicyclohexylcarbodiimide (DCC; 1.0 g, 5 mmol) in benzene (20 ml) for 8 h at 25° [8]. The mixture was then diluted with hexane (80 ml), and an insoluble white solid removed by filtration. The filtrate was washed with 1M HCl (50 ml) and with a soln. of NaCl (10%, w/v, 50 ml). After drying (MgSO₄), the org. layer was concentrated, and the target compounds **1a–h** (400 mg, 50%) were purified by CC on a water-cooled glass column (30 $\times$ 1.5 cm) filled with silica gel. Elution was performed with pentane/Et₂O (9:1, 200 ml; *Fr. 1*) followed by pentane/Et₂O 7:3 (4 $\times$ 50 ml; *Fr. 2a–d*) and pentane/Et₂O 6:4 (100 ml; *Fr. 3*). *Fr. 2b* contains lactones **1e/1f**, *Fr. 2c 1a/1b* and **1g/1h**, *Fr. 2d 1a/1b*, and *Fr. 3 1c/1d*. These fractions were further purified for spectral measurements by HPLC on silica gel (see *Table 1*). IR (CS₂): **1a/1b**: 3040w, 2965w, 2920m, 2850w, 1775s, 1380m, 1320m, 1260w, 1210w, 1170m, 1145m, 1085m, 1050m, 990m, 955m, 815w. IR (CS₂): **1c/1d**: 3040w, 2970w, 2930m, 2850w, 1775s,

1710w, 1330w, 1280w, 1195w, 1165m, 1155m, 1125w, 1090w, 970w, 950m, 810w. IR (CS₂): **1e/1f**: 3040w, 2970w, 2930m, 2880w, 1785s, 1710w, 1655w, 1380w, 1340w, 1245w, 1190w, 1140w, 1125m, 1100w, 1055w, 1000s, 950w, 895w, 790w. ¹H- and ¹³C-NMR: *Tables 3 and 4*. EI-MS: *Table 2*.

2-[(1*RS*)-4-Methylcyclohex-3-enyl]acetic Acid (**6**). Isoprene (11.9 g, 175 mmol) was added to a stirred benzene soln. (90 ml) of ethyl prop-2-enoate (17.5 g, 175 mmol) and anhyd. AlCl₃ (293 mg, 2.2 mmol) at 10° as described in [19] [20]. After 3 h, the soln. was cooled to 0° and treated with 1M HCl (100 ml). The benzene layer was washed with H₂O, dried (Na₂SO₄), and concentrated. Fractional distillation afforded ethyl (1*RS*)-4-methylcyclohex-3-enecarboxylate (14.4 g, 46%). Reduction of ethyl (1*RS*)-4-methylcyclohex-3-enecarboxylate (10 g, 55 mmol) with LiAlH₄ (2.1 g, 55 mmol) in Et₂O (200 ml) yielded (1*RS*)-4-methylcyclohex-3-enemethanol (5.0 g, 73%). Compound **6** was prepared by the procedure described in [21] for (1*RS*)-4-methylcyclohex-3-enemethanol. EI-MS: 154 (10, *M*⁺), 136 (20), 94 (100), 79 (60), 67 (40), 55 (20).

(3*aRS*,7*aSR*)-3*a*,4,5,7*a*-Tetrahydro-6-methylbenzofuran-2(3*H*)-one (**7**). Pyridinium dichromate (PDC; 9.87 g, 26 mmol) and 70% (w/v) *t*-BuOOH (4.67 g, 52 mmol) were added to a stirred soln. of **6** (2.0 g, 13 mmol) in benzene (40 ml) and *Celite* (5.0 g). The mixture was stirred for 12 h at 30° and filtered, the precipitate washed with Et₂O (2 × 50 ml), and the combined filtrates stirred with 0.1M HCl (100 ml) for 15 min. The org. layer was separated and washed with a 0.5M soln. of Na₂CO₃ (2 × 100 ml) to remove unreacted acid **6**. Drying (Na₂SO₄) and concentration yielded pure **7** (490 mg, 25%) as 1:1 mixture of enantiomers. RI (FFAP): 2280. EI-MS: 152 (30, *M*⁺), 137 (100), 124 (12), 93 (28), 91 (16), 77 (16).

(3*SR*,3*aSR*,7*aRS*)-3*a*,4,5,7*a*-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one (**1a/1b**). An enantiomeric mixture **1a/1b** was prepared by alkylation of **7** (150 mg, 1 mmol) with LDA (1.1 mmol) and MeI (156 mg, 1.1 mmol) [13]. ¹H- and ¹³C-NMR: *Tables 3 and 4*. EI-MS: *Table 2*.

(2*RS*)-2-[(1*R*)-4-Methylcyclohex-3-enyl]propanol (**9a/9b**). (+)-(-)-4*R*-Limonene (**8a**) (2.7 g, 20 mmol) was regioselectively hydroborated with a soln. of 9-BBN in THF (40 ml) according to the general procedure in [22]. The organoborane was oxidized by adding, successively, EtOH (12 ml), 6M NaOH (4 ml), and 30% (w/v) H₂O₂ (8 ml). The mixture was heated for 1 h at 50°, then cooled to r.t. and saturated with NaCO₃. After addition of H₂O (80 ml), the mixture was extracted with Et₂O (2 × 100 ml). Drying (Na₂SO₄) and concentration of the org. layer yielded **9a/9b** (2.0 g, 65%) as a 1:1 mixture of diastereoisomers. EI-MS: 154 (24, *M*⁺), 121 (35), 107 (35), 95 (40), 94 (100), 93 (50), 79 (70), 68 (35), 67 (40), 55 (30).

(2*RS*)-2-[(1*R*)-4-Methylcyclohex-3-enyl]propanoic Acid (**10a/10b**). Oxidation of diastereoisomeric alcohols **9a/9b** (2 g, 12.9 mmol) was performed with PDC (45 mmol) in DMF (20 ml) [23]. After 12 h at 20°, the reaction was quenched by addition of H₂O (200 ml) and extracted with Et₂O (2 × 100 ml). The combined org. layers were extracted with a 0.5M soln. of Na₂CO₃ (2 × 100 ml), and the org. layer was discarded. The aq. layer was acidified (pH 5) and extracted with Et₂O (2 × 100 ml). The org. layer was washed with 0.1M HCl (100 ml) and saturated NaCl soln., dried (Na₂SO₄), and concentrated to afford 840 mg (39%) of a 1:1 diastereoisomeric mixture **10a/10b**. RI (FFAP): 2400, 2406. EI-MS: 168 (10, *M*⁺), 150 (8), 95 (40), 94 (100), 79 (60), 67 (24), 55 (16), 41 (22).

(3*S*,3*aS*,7*aR*)- and (3*R*,3*aS*,7*aR*)-3*a*,4,5,7*a*-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one (**1a** and **1c**, resp.). As described for **7**, **10a/10b** (400 mg, 2.4 mmol) was treated with PDC (1.8 g, 4.8 mmol), *Celite* (1 g), and aq. 70% (w/v) *t*-BuOOH (0.86 g, 9.6 mmol) in benzene (7 ml). Pure enantiomers **1a** and **1c** were obtained by CC and by HPLC on silica gel as described for **1a-h**. CD, UV: *Table 5*. ¹H- and ¹³C-NMR, and MS: data found for **1a** and **1c** are the same as obtained for **1a/1b** and **1c/1d**, resp., detailed in *Table 2* and *Tables 3 and 4*.

(3*R*,3*aR*,7*aS*)- and (3*S*,3*aR*,7*aS*)-3*a*,4,5,7*a*-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one (**1b** and **1d**, resp.). Starting from (-)-4*S*-limonene (**8b**) as described for **1a** and **1c**. Spectroscopic characteristics: see above.

Methyl (2*RS*)-2-[(1*R*)-4-Methylcyclohex-3-enyl]propanoate (**11a/11b**). A soln. of **10a/10b** (400 mg, 2.4 mmol) in MeOH (10 ml) and conc. H₂SO₄ (10 µl) was heated at 60° for 4 h, diluted with H₂O (50 ml), and extracted with Et₂O (2 × 50 ml). The org. layer was washed with 0.5M aq. Na₂CO₃ (50 ml), dried (Na₂SO₄), and concentrated to provide **11a/11b** (400 mg, 92%).

Methyl (2*RS*)-2-[(1*R*)-4-Methyl-2-oxocyclohex-3-enyl]propanoate (**3a/3b**). Using the procedure of Chidambaram and Chandrasekaran [24], an allylic oxidation of **11a/11b** (400 mg, 2.2 mmol) was performed with PDC (1.67 g, 4.4 mmol), 70% (w/v) aq. *t*-BuOOH (395 mg, 4.4 mmol), and *Celite* (1 g) in benzene (25 ml) for 24 h. After dilution with Et₂O (50 ml), the mixture was filtered, and washed with 0.1M HCl (50 ml). Drying (Na₂SO₄), concentration to 2 ml, and purification by CC on a glass column (30 × 1.5 cm) with pentane/Et₂O 1:1 yielded **3a/3b** (200 mg, 46%) as a 1:1 mixture (GC) of diastereoisomers. EI-MS: as described for **3**.

(3*S*,3*aS*,7*aS*)- and (3*R*,3*aS*,7*aS*)-3*a*,4,5,7*a*-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one (**1e** and **1f**, resp.). The procedure described for **1a-h** was applied to convert **3a/3b** (200 mg, 1 mmol) via **4a/4b** and **5a/5b** to **1e** and **1g** (10%, 3:1). Pure enantiomers of **1e** and **1g** were obtained after CC and HPLC on silica gel as described for **1a-h**. ¹H- and ¹³C-NMR, and MS: data found for **1e** and **1g** are the same as obtained for the enantiomeric mixture **1e/1f** and **1g/1h**, resp., summarized in *Tables 2-4*.

(3R,3aR,7aR)- and (3S,3aR,7aR)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one (**1f** and **1h**, resp.). Starting from (–)-(4S)-limonene (**8b**) as described for **1e/1g**. Spectroscopic data: see above.

Conversion of Lactones 1e (3S,3aS,7aS) and 1g (3R,3aS,7aS) into 1a (3S,3aS,7aR). A stirred soln. of **1e** and **1g** (2 mg, 12 μ mol), and MeOH (2 ml) and 0.1M aq. NaOH soln. (1 ml), resp., was heated at 80° for 2 h. Then, the mixture was adjusted with 1M HCl at pH 1 and heated for further 2 h at 80°. After addition of H₂O (10 ml), followed by Et₂O extraction (2 $\times$ 10 ml), drying (Na₂SO₄), and concentration to 2 ml, the soln. was investigated by GC (**1e** and **1g** not detectable; conversion to **1a**: 80–90%; ee > 95%).

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