Synthesis of Enantiomerically Pure (–)-Wine Lactone Based on a Palladium-Catalyzed Enantioselective Allylic Substitution

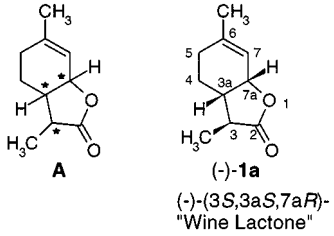
E. J. Bergner[a] and Günter Helmchen*[a]

Keywords: Asymmetric synthesis / Natural products / Palladium / Wine lactone / Allylic substitution

The first enantioselective synthesis of enantiomerically pure (–)-wine lactone, (–)-**1a**, a fragrance constituent of various white wines, and its epimer (+)-**1b**, was carried out. The key steps are allylic substitution of (±)-2-cyclohexen-1-yl acetate (**2**) with dimethylmalonate using palladium complexes of phosphanyldihydrooxazol **L1** or of the phosphanylcarboxylic acid **L2** as catalyst, subsequent decarboxylation, iodolactonization and elimination, furnishing enantiomerically pure bicyclic lactone (+)-**7** in 47% overall yield. The diastereoselective introduction of methyl groups by S_N2'-type substitution with an organocopper compound and by enolate alkylation gave lactone (–)-**1a** in 43% overall yield from (+)-**7**.

Introduction

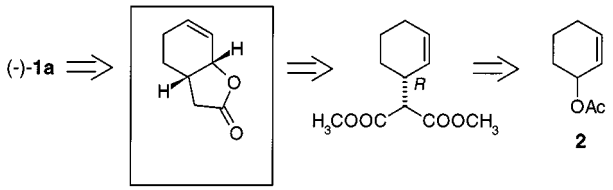
In 1975 Southwell identified a group of bicyclic terpenoid lactones[1] in the urine of koala animals. One of these lactones was assigned the constitution **A** [3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one]. In 1997 Guth identified one of the stereoisomers with constitution **A** in white wine types Gewürztraminer and Scheurebe as an important flavor component.[2] He then synthesized all the eight stereoisomers and compared their odor threshold values which differed considerably.[3] The compound with the highest odor activity was the lactone (–)-**1a**, which was found to be identical to the natural product and was named "wine lactone." The absolute configuration of wine lactone was assigned by spectroscopic comparison with the synthetic stereoisomers. The odor of (–)-**1a** is described as sweet, woody and coconut-like with an odor threshold as low as 0.02 pg/L of air; the odor activity of the enantiomer, (+)-**1a**, displaying a threshold value of >1 µg/L of air, is lower by a factor of $>10^8$. Recently wine lactone was also found in orange juice and black pepper.[4]



Starting from (+)- and (–)-limonene, Guth prepared the eight stereoisomers with constitution **A** as mixtures of diastereomers and separated these by chromatography. Prior to the discovery of wine lactone, a diastereoselective route was developed in 1981 by Bartlett and Pizzo who prepared racemic **1a** and its *endo*-C-3-epimer **1b** (cf. Scheme 5) by Claisen rearrangement from 2-cyclohexenol derivatives.[5]

Results and Discussion

We now report the first enantio- and in all steps highly diastereoselective synthesis of enantiomerically pure (–)-wine lactone and its C-3-epimer. The retrosynthetic analysis of our synthesis is displayed in Scheme 1. Enantioselectivity was provided by asymmetric palladium-catalyzed allylic substitution of 2-cyclohexen-1-yl acetate with dimethylmalonate, diastereoselectivity by iodolactonization and enolate alkylation.



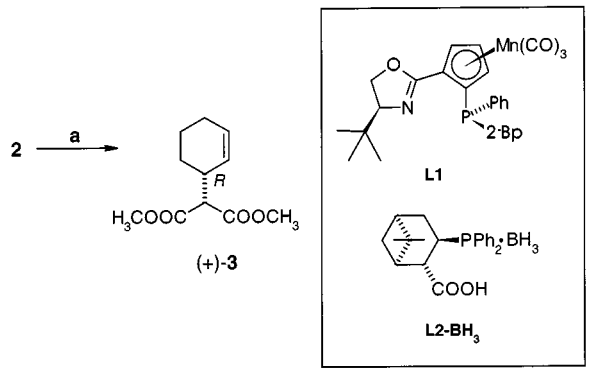
Scheme 1. Retrosynthetic analysis

For the enantioselective palladium-catalyzed alkylation[6] of racemic 2-cyclohexen-1-yl acetate (**2**)[7] with alkali metal dimethylmalonates we made use of the chiral ligands **L1** and **L2** which are particularly well suited for applications to cyclic substrates (Scheme 2).[8]

With the P,N-chelate **L1** as ligand, the reaction of substrate **2** with sodium dimethylmalonate at –20 °C in DMF as solvent had previously yielded the ester (+)-**3** with 93% *ee*.[8a] In THF as solvent the *ee* of the product was only 85%, although the reaction was faster than in DMF. Lowering the amount of catalyst from 1 mol-% to 0.1 mol-%, as is desirable for preparative applications, gave (+)-**3** with 82% *ee* (88% yield). Fortunately, a high degree of enantioselectivity is not required for the alkylation as the iodolactone (–)-**6** (see below), an intermediate in the route to wine lactone, can be obtained enantiomerically pure by simple recrystallization. In previous work, the alkylation of

[a] Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany
Fax: (internat.) +49-6221/544-205
E-mail: en4@ix.urz.uni-heidelberg.de

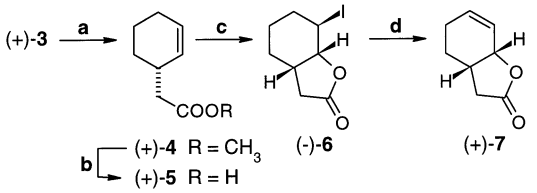
  1434–193X/00/0203–0419 $ 17.50+.50/0



Scheme 2. Reagents and conditions: (a) procedure 1: 0.1 mol-% of $[C_3H_5PdCl]_2$, 0.12 mol-% of **L1**, THF, $NaCH(COOCH_3)_2$, 5 °C (88%, 82% *ee*); procedure 2: 3.0 mol-% of $[C_3H_5PdCl]_2$, 9.0 mol-% of **L2**, THF, $LiCH(COOCH_3)_2$, room temp. (91%, 95% *ee*)

2 with lithium dimethylmalonate in THF as solvent was also carried out with the enantiomer of **L2** as ligand which induced formation of the product with 98% *ee*.[9] For the present work a sample of **L2** with an *ee* of only 92% was available; due to a nonlinear effect,[10] this nevertheless induced the formation of (+)-**3** with 95% *ee* (yield 91%) in the Pd-catalyzed reaction of acetate **2** with lithium dimethylmalonate.

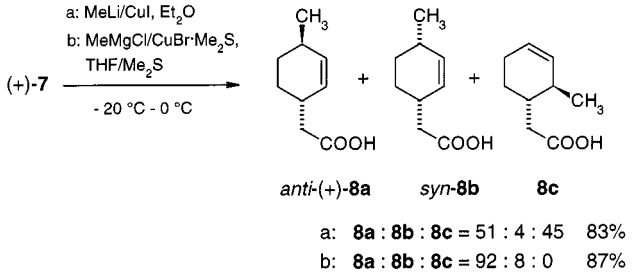
The alkylated malonate (+)-**3** was subjected to a Krapcho decarbomethoxylation (Scheme 3)[11] and the resulting ester was saponified. Subsequent iodolactonization gave (–)-**6**.[12] The enantiomeric purity of this compound could be raised to > 99.9% *ee* by recrystallization.[13] The yields of (–)-**6** were 66 and 82% when the *ee* of the starting material (+)-**5** was 82 and 95%, respectively. Elimination of HI from (–)-**6** by treatment with DBU gave the unsaturated lactone (+)-**7** in excellent yield.



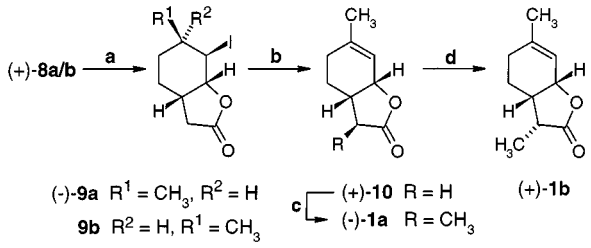
Scheme 3. Reagents and conditions: (a) NaCl, H_2O, DMSO, 160 °C (74%); (b) NaOH, 120 °C (95%); (c) KI, I_2, $NaHCO_3$, H_2O (82%, > 99.9% *ee*); (d) DBU, THF, reflux (82–91%)

The methyl group at C-6 was introduced by reaction of (+)-**7** with a methyl copper compound (Scheme 4). This type of reaction was previously studied by Curran et al. and Grieco et al. with analogous five-membered bicyclic lactones.[14] It was reported that reactions with organocopper compounds prepared from organolithium compounds proceeded with low degrees of regioselectivity due to competing S_N2' and S_N2 reactions. High selectivity in favor of the S_N2'-mode was obtained with organocopper reagents "RCu/$MgBr_2$" derived from Grignard compounds, in combination with stoichiometric amounts of CuBr·Me_2S. Our own results with (+)-**7** corroborate these generalizations. Thus, reaction of (+)-**7** with a reagent prepared from methyllithium and CuBr in diethyl ether at –20 °C gave a mixture of regioisomers (+)-**8a/8b**:**8c** = 55:45 (^{1}H NMR) via S_N2' or S_N2 attack, respectively. The ratio of the stereoisomers **8a** and **8b** could not be determined directly because of overlapping signals in the ^{1}H NMR spectrum. Indirect assessment was carried out with the subsequently formed iodolactones **9** (see below). As anticipated, an organocopper compound prepared from MeMgCl and CuBr·Me_2S complex in a mixture of THF and Me_2S as solvent furnished exclusively the products of S_N2' attack; an *anti-syn* selectivity of (+)-**8a**:**8b** = 92:8 was obtained.

Iodolactonization under standard conditions gave a 92:8 mixture (GC) of the diastereomers (–)-**9a** and **9b** in 95% yield (Scheme 5). The major diastereomer (–)-**9a** was obtained in a pure form by recrystallization. Dehydrohalogenation with DBU gave the lactone (+)-**10** in excellent yield; the original 92:8 mixture of (–)-**9a** and **9b** gave rise to an inseparable mixture of (+)-**10** with **9b** which does not undergo the elimination.



Scheme 4. Regioselectivity in reactions with organocopper compounds



Scheme 5. Reagents and conditions: (a) KI, I_2, $NaHCO_3$, H_2O/THF, room temp. (95%, *dr* = 92:8; after recrystallization: 60%, *dr* > 99:1); (b) DBU, THF, reflux (92%); (c) LDA, MeI, THF, –78 °C (79–90%); (d) LDA, THF, then $H_2C(COOtBu)_2$, –78 °C (61–74%)

Finally, alkylation of (+)-**10** according to the procedure of Bartlett and Pizzo[5] gave (–)-**1a**. The epimeric lactone (+)-**1b** was prepared from (–)-**1a** by deprotonation and subsequent reprotonation (Scheme 5). The diastereoselectivity was strongly dependent on the acid used for protonation. Thus, after deprotonation with LDA treatment of the resultant lithium enolate with CH_3COOH gave a 3:1 ratio of (–)-**1a** and (+)-**1b**. In order to increase the likelihood of direct C-protonation relative to O-protonation, di-*tert*-butyl malonate[15] was used as the CH-acid; this procedure indeed furnished the *epi*-wine lactone (+)-**1b** with a diastereoselectivity of > 99:1.

Conclusion

In conclusion, our route based on the asymmetric allylic alkylation allows wine lactone and its C-3-epimer to be conveniently prepared. As the Pd-catalyzed allylic substitution can provide enantiomers with equal facility, the four stereoisomers with constitution **A** possessing a *cis*-configuration of the bicyclic ring system are accessible via this route in an enantiomerically pure form.

Experimental Section

General Methods: Reactions in dry solvents were carried out under an argon atmosphere. – Melting points and boiling points are uncorrected. – TLC: Machery-Nagel Polygram Sil G/UV precoated sheets, treatment with I_2 and/or aqueous $KMnO_4$ solution for visualization. – For flash chromatography ICN Kieselgel S (0.032–0.063 mm) was used. – ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer [300.13 MHz (^1H), 75.46 MHz (^{13}C), $CDCl_3$]. – Optical rotations were determined with a Perkin–Elmer 241 Polarimeter. – Gas chromatography was carried out on a Hewlett–Packard HP 5890 A instrument equipped with a Chrompack Permethyl β-CD (50 m × 0.25 mm) column. – CuBr·Me_2S was purchased from Fluka. CuI was purchased from Aldrich. – Ligand **L2** was liberated from **L2·BH3** directly prior to use by heating a solution of **L2·BH3** and 1.1 equiv. of DABCO in dry toluene (2 mL per mmol) at reflux for 3 h followed by removal of the solvent in vacuo.

Dimethyl (+)-(*R*)-2-(Cyclohex-2-enyl)malonate [(+)-3]. – Procedure 1: A solution of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (11 mg, 30 μmol) and **L1** (43 mg, 73 μmol) in dry THF (30 mL) was stirred at room temperature for 20 min under an argon atmosphere, then cooled to 5 °C, and (±)-2-cyclohexen-1-yl acetate (8.4 g, 60 mmol) was added to give solution A. – Sodium hydride (2.16 g, 90.0 mmol, 95%) was suspended in dry THF (150 mL) and malonic acid dimethyl ester (15.8 g, 120 mmol) was added. Upon stirring at room temperature a clear, colorless solution resulted which was added to solution A. After stirring for 7 d at 5 °C satd. NH_4Cl solution (100 mL) was added and the mixture was extracted with diethyl ether. The organic layer was washed with water, dried over Na_2SO_4, and the solvents removed in vacuo. Flash chromatography on silica gel (35 × 5 cm) using petroleum ether/ethyl acetate 97:3 as eluent gave (+)-**3** (11.2 g, 88%) as a colorless oil. An *ee* of 82% was determined by GC analysis on a Chrompack Permethyl β-CD column at 110 °C, t_R[(–)-(*S*)-**3**] = 36.9 min, t_R[(+)-(*R*)-**3**] = 37.9 min. – $[\alpha]_D^{20}$ = +38.5 (*c* = 3.4, $CHCl_3$). – ref.[16]: $[\alpha]_D^{22}$ = –15.6 (*c* = 2.6, $CHCl_3$, 50% *ee*). – ^1H NMR ($CDCl_3$): δ = 1.27–1.36 (m, 1 H, CH_2), 1.48–1.65 (m, 1 H, CH_2), 1.68–1.73 (m, 2 H, CH_2), 1.93–2.00 (m, 2 H, CH_2), 2.85 (m_c, 1 H, C=CCH), 3.24 [d, *J* = 9.5 Hz, 1 H, $CH(COOCH_3)_2$], 3.68 (s, 6 H, OCH_3), 5.47 (dd, *J* = 10.1 Hz, *J* = 2.0 Hz, 1 H, HC=C*H*CH), 5.72 (m_c, 1 H, *H*C=CHCH). – ^{13}C NMR: δ = 20.8 (t, CH_2), 24.8 (t, CH_2), 26.6 (t, CH_2), 35.3 (d, C=C–CH), 52.2 (q, OCH_3), 56.8 [d, $CH(COOCH_3)_2$], 127.3 (d, C=C–CH), 129.5 (d, C=C-CH), 168.6 (s, C=O).

Procedure 2: A solution of **L2**, obtained by deprotection from **L2·BH3** (162 mg, 0.45 mmol) (see General Methods), and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (27 mg, 74 μmol) in dry THF (3 mL) was stirred at room temperature for 20 min under an argon atmosphere; then (±)-2-cyclohexen-1-yl-acetate (0.70 g, 4.99 mmol) was added to give solution A. – A 1.6 M solution of *n*BuLi (5.0 mL, 8.0 mmol) in *n*-hexane was added dropwise to a solution of malonic acid dimethyl ester (1.32 g, 10.0 mmol) in dry THF (15 mL) at –40 °C. After removal of the cooling bath, the reaction mixture was stirred at room temperature for 10 min. The resultant suspension was then added to solution A. After stirring for 1 h at room temperature satd. NH_4Cl solution (30 mL) was added and the mixture was extracted with diethyl ether. The organic layer was washed with water, dried over Na_2SO_4 and the solvents were removed in vacuo to give an oil which was subjected to flash chromatography on silica gel (35 × 5 cm) using petroleum ether/ethyl acetate (97:3) as eluent. Malonate (+)-**3** (0.96 g, 91%) was obtained as a colorless oil. The *ee* of 95% was determined by GC analysis as described above.

Methyl (+)-(*S*)-(Cyclohex-2-enyl)acetate [(+)-4]: A mixture of NaCl (3.30 g, 56.7 mmol), water (13 mL, 0.7 mol), (+)-**3** (10.9 g, 52.0 mmol, *ee* = 82%) and DMSO (80 mL) was heated at 160 °C for 24 h. After cooling, the mixture was diluted with water (300 mL) and extracted with diethyl ether. The organic layer was dried over Na_2SO_4. The solvent was then removed and the residue was purified by flash chromatography on silica gel (40 × 3.5 cm) using petroleum ether/ethyl acetate (97:3) as eluent to give (+)-**4** (5.9 g, 74%) as a colorless liquid. – $[\alpha]_D^{20}$ = +50.9 (*c* = 4.0, $CHCl_3$). – ^1H NMR ($CDCl_3$): δ =1.18–1.29 (m, 1 H, CH_2), 1.45–1.61 (m, 1 H, CH_2), 1.63–1.71 (m, 1 H, CH_2), 1.72–1.83 (m, 1 H, CH_2), 1.91–1.98 (m, 2 H, CH_2), 2.22 (dd, *J* = 14.8 Hz, *J* = 8.1 Hz, 1 H, CH_2C=O), 2.29 (dd, *J* = 14.8 Hz, *J* = 6.8 Hz, 1 H, CH_2C=O), 2.50–2.60 (m, 1 H, HC=CHC*H*), 3.64 (s, 3 H, OCH_3), 5.50 (dd, *J* = 10.1 Hz, *J* = 2.0 Hz, 1 H, HC=C*H*CH), 5.65–5.71 (m, 1 H, *H*C=CHCH). – ^{13}C NMR: δ = 20.7 (t, CH_2), 25.8 (t, CH_2), 28.6 (t, CH_2), 32.0 (d, HC=CH*C*H), 40.4 (t, *C*HC=O), 51.1 (q, OCH_3), 127.9 (d, HC=*C*HCH), 129.8 (d, H*C*=CHCH), 172.9 (s, C=O). – $C_9H_{14}O_2$ (154.209): calcd. C 70.09, H 9.15; found C 70.16, H 9.21.

(+)-(*S*)-Cyclohex-2-enylacetic Acid [(+)-5]: An emulsion of (+)-**4** (5.4 g, 35 mmol, 82% *ee*) in 1 N NaOH (50 mL) was vigorously stirred and heated at reflux for 1 h. After cooling to room temperature, the solution was acidified with 6 N HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield (+)-**5** (4.7 g, 95%) as a slightly yellow oil. – $[\alpha]_D^{27}$ = +54.2 (*c* = 2.9, $CHCl_3$, 82% *ee*). – ref.[17]: $[\alpha]_D^{27}$ = +65.0 (*c* = 2.7, $CHCl_3$, 84% *ee*). – ^1H NMR ($CDCl_3$): δ = 1.22–1.34 (m, 1 H, CH_2), 1.47–1.61 (m, 1 H, CH_2), 1.63–1.74 (m, 1 H, CH_2), 1.79–1.89 (m, 1 H, CH_2), 1.93–2.09 (m, 2 H, CH_2), 2.27 (dd, *J* = 15.3 Hz, *J* = 8.1 Hz, 1 H, CH_2C=O), 2.35 (dd, *J* = 15.3 Hz, *J* = 8.1 Hz, 1 H, CH_2C=O), 2.58 (m, 1 H, HC=CHC*H*), 5.54 (dd, *J* = 10.1 Hz, *J* = 2.0 Hz, 1 H, HC=C*H*CH), 5.67–5.74 (m, 1 H, *H*C=CHCH), 11.4 (br. s, 1 H, COOH). – ^{13}C NMR: δ = 20.7 (t, CH_2), 24.8 (t, CH_2), 28.5 (t, CH_2), 31.8 (d, HC=CH*C*H), 40.4 (t, *C*H_2C=O), 123.2 (d, HC=*C*HCH), 129.6 (d, H*C*=CHCH), 179.3 (s, COOH).

(–)-(3a*S*,7*R*,7a*R*)-Hexahydro-7-iodo-benzo[*b*]furan-2-one [(–)-6]: A solution of iodine (16.2 g, 63.6 mmol) and KI (32.3 g, 195 mmol) in water (60 mL) was added to a solution of (+)-**5** (4.50 g, 32.3 mmol, 82% *ee*) and $NaHCO_3$ in water (170 mL). The resulting mixture was stirred for 5 h at room temperature. A satd. aqueous $Na_2S_2O_3$ solution was then added until the reaction mixture became colorless. The mixture was extracted four times with diethyl ether, the organic layer was dried over Na_2SO_4 and concentrated in vacuo to give (–)-**6** (7.92 g, 92%, 82% *ee*). Recrystallization from ethyl acetate/diethyl ether yielded enantiomerically pure (–)-**6** (5.64 g, 66%, > 99.9% *ee*)[18] as colorless crystals. – M.p. 95–96 °C, ref.[13]: m.p. 96–96.5 °C. An *ee* of > 99.9% was determined by GC analysis on a Chrompack Permethyl β-CD column at 155 °C, t_R[(+)-**6**] = 29.2 min, t_R[(–)-**6**] = 30.4 min. – $[\alpha]_D^{20}$ = –53.4 (*c* = 3.6, CH_3OH). – ref.[13]: $[\alpha]_D^{22}$ = –56.6 (*c* = 0.4, CH_3OH, > 99.9%

ee). – ^{1}H NMR ($CDCl_3$): δ = 1.23–1.36 (m, 1 H, CH_2), 1.50–1.97 (m, 5 H, CH_2), 2.27 (dd, *J* = 16.9 Hz, *J* = 3.4 Hz, 1 H, CH_2C=O), 2.57 (dd, *J* = 16.9 Hz, *J* = 6.8 Hz, 1 H, CH_2C=O), 2.73–2.83 (m, 1 H, C*H*CH_2C=O), 4.59–4.61 (m, 1 H, CHI), 4.67–4.69 (m, 1 H, CHO). – ^{13}C NMR: δ = 20.3 (t, CH_2), 26.3 (t, CH_2), 27.4 (d, CHI), 30.4 (t, CH_2), 32.4 (d, *C*HCH_2C=O), 36.8 (t, *C*H_2C=O), 82.8 (d, CHO), 175.8 (s, C=O).

(+)-(3a*S*,7a*R*)-3a,4,5,7a-Tetrahydrobenzo[*b*]furan-2-one [(+)-7]: A solution of (–)-**6** (2.93 g, 11.0 mmol, > 99.9% *ee*) and DBU (2.01 g, 13.2 mmol) in dry THF (20 mL) was heated at reflux for 3 h. After cooling, 6 N HCl (40 mL) was added and the mixture was extracted repeatedly with ethyl acetate. The organic layer was dried and concentrated in vacuo. Recrystallization of the residue from ethyl acetate/*n*-hexane gave (+)-**7** (2.15 g, 82%) as colorless plates. – M.p. 51–52 °C. – $[\alpha]_D^{20}$ = +103.6 (*c* = 3.3, $CHCl_3$). – ref.[19]: $[\alpha]_D^{27}$ = +104.7 (*c* = 1.0, $CHCl_3$, > 95% *ee*). – ^{1}H NMR ($CDCl_3$): δ = 1.37–1.49 (m, 1 H, CH_2), 1.66–1.76 (m, 1 H, CH_2), 1.92–2.17 (m, 2 H, CH_2), 2.28 (dd, *J* = 17.0 Hz, *J* = 3.8 Hz, 1 H, CH_2C=O), 2.48–2.59 (m, 1 H, C*H*CH_2C=O), 2.68 (dd, *J* = 17.0 Hz, *J* = 8.1 Hz, 1 H, CH_2C=O), 4.76 (m, 1 H, CHO), 5.80–5.86 (m, 1 H, HC=C*H*CH), 6.00–6.16 (m, 1 H, *H*C=CHCH). – ^{13}C NMR: δ = 22.6 (t, CH_2), 23.4 (t, CH_2), 33.4 (d, *C*H-CH_2C=O), 35.0 (t, *C*H_2C=O), 75.4 (d, CHO), 123.1 (d, HC=*C*HCH), 134.0 (d, H*C*=CHCH), 176.4 (s, C=O).

(+)-(2*S*,4*R*)- and (2*S*,4*S*)-(4-Methylcyclohex-2-enyl)acetic Acid [(+)-8a, 8b]: Under an argon atmosphere, a stirred suspension of CuBr·Me_2S (5.20 g, 25.3 mmol) in a mixture of THF (50 mL) and Me_2S (20 mL) was cooled to –20 °C and a solution of CH_3MgCl (8.5 mL, 26 mmol, 3 M in THF) was added dropwise. After stirring for 1 h a solution of (+)-**7** (1.38 g, 10.0 mmol, > 99.9% *ee*) in THF (8 mL) was added dropwise to the reaction mixture. The resulting yellow suspension was allowed to warm to –10 °C and was stirred for a further 12 h. Then 1 N NaOH (100 mL) was added, the mixture stirred for 2 h and extracted with diethyl ether (50 mL). The organic layer was discarded and the aqueous layer was acidified with 6 N HCl. After re-extraction with diethyl ether (3 × 200 mL) the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (30 × 4 cm) using petroleum ether/ethyl acetate 9:1 as eluent gave a 92:8 mixture of (+)-**8a** and **8b** (1.74 g, 87%) as a colorless oil. – $[\alpha]_D^{20}$ = +130 (*c* = 3.8, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.00–1.28 (m, 2 H, CH_2), 1.77–1.91 (m, 2 H, CH_2), 2.12 (m_c, 1 H, C*H*CH_3), 2.25 (dd, *J* = 15.3 Hz, *J* = 8.0 Hz, 1 H, CH_2C=O), 2.33 (dd, *J* = 15.3 Hz, *J* = 7.0 Hz, 1 H, CH_2C=O), 2.54 (m_c, 1 H, C*H*CH_2C=O), 5.45–5.49 (m, 1 H, H_3CCHCH=C*H*), 5.52–5.56 (m, 1 H, H_3CCHCH=), 10.8 (s, 1 H, COOH). – ^{13}C NMR δ = 21.4 (q, CH_3), 28.6 (t, CH_2CH_2), 30.2 (d, *C*HCH_3), 30.6 (t, CH_2CH_2), 128.7 (d, H_3CCHCH=*C*H), 134.5 (d, H_3CCH–*C*H=), 178.8 (s, COOH).

(–)-(3a*S*,6*R*,7*R*,7a*R*)-3a,4,5,6,7,7a-Hexahydro-7-iodo-6-methylbenzofuran-2(3*H*)-one [(–)-9a]: A solution of iodine (5.55 g, 21.9 mmol) and KI (10.8 g, 65.1 mmol) in water (30 mL) was added to a well stirred mixture of (+)-**8a/8b** (1.64 g, 10.6 mmol, > 99.9% *ee*), prepared as described above, THF (30 mL), $NaHCO_3$ (2.7 g, 32.1 g) and water (30 mL). After stirring for 2 h at room temperature, saturated aqueous $Na_2S_2O_3$ solution was added to remove the unreacted iodine. The mixture was extracted with diethyl ether (4 × 150 mL), the organic layer dried over Na_2SO_4 and concentrated in vacuo to give a 92:8 mixture (GC) of (–)-**9a** and **9b** (2.83 g, 95%) as a yellow solid. Recrystallization from ethyl acetate/*n*-hexane gave pure *trans*-isomer (–)-**9a** (1.78 g, 60%) as colorless crystals. – M.p. 89–91 °C. – $[\alpha]_D^{20}$ = –12.2 (*c* = 3.0, $CHCl_3$, > 99.9% *ee*). – ^{1}H NMR ($CDCl_3$): δ = 0.90–0.94 (m, 1 H, C*H*CH_3), 0.93 (s, 3 H, CH_3), 1.20–1.39 (m, 3 H, CH_2), 1.77–1.84 (m, 1 H, CH_2), 2.22 (d, *J* = 16.7 Hz, 1 H, CH_2C=O), 2.64 (dd, *J* = 16.7 Hz, *J* = 6.4 Hz, 1 H, CH_2C=O), 2.81 (dd, *J* = 11.2, *J* = 4.3 Hz, 1 H, C*H*CH_2C=O), 4.71 (m_c, 1 H, CHI), 4.81–4.83 (m, 1 H, CHO). – ^{13}C NMR: δ = 23.5 (q, CH_3), 27.6 (t, CH_2), 28.1 (t, CH_2), 30.3 (d, *C*HCH_3), 31.0 (d, *C*HCH_2C=O), 38.7 (t, *C*H_2C=O), 41.7 (d, CHI), 83.8 (d, CHO), 176.1 (s, C=O). – $C_9H_{13}IO_2$ (280.10): calcd. C 38.59, H 4.68, I 45.31; found C 38.65, H 4.72, I 45.56.

(+)-(3a*S*,7a*R*)-2,3,3a,4,5,7a-Hexahydro-6-methylbenzofuran-2(3*H*)-one [(+)-10]: A solution of (–)-**9a** (1.78 g, 6.40 mmol, > 99.9% *ee*) and DBU (1.26 g, 8.20 mmol) in THF (20 mL) was heated to reflux for 2 h. After cooling, 6 N HCl (50 mL) was added and the mixture was extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give (+)-**10** (0.89 g, 92%) as colorless crystals. – M.p. 45–47 ° C. – $[\alpha]_D^{20}$ = +63.2 (*c* = 3.03, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.42–1.53 (m, 1 H, CH_2), 1.67–1.76 (m, 1 H, CH_2), 1.74 (s, CH_3), 1.96–2.0 (m, 2 H, CH_2CH_2), 2.28 (dd, *J* = 17.2 Hz, *J* = 3.5 Hz, 1H, CH_2C=O), 2.43–2.48 (m, 1 H, C*H*CH_2C=O), 2.68 (dd, *J* = 17.2, *J* = 8.0 Hz, 1 H, CH_2C=O), 4.75–4.78 (m, 1 H, CHO), 5.57–5.60 (m, 1 H, =CH). – ^{13}C NMR: δ = 23.7 (q, CH_3), 23.9 (t, CH_2), 27.8 (t, CH_2), 32.9 (d, *C*HCH_2C=O), 35.3 (t, *C*H_2C=O), 76.7 (d, CHO) 117.6 (s, =*C*CH_3), 142.9 (d, HC=), 176.7 (s, C=O).

(–)-(3*S*,3a*S*,7a*R*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one [(–)-1a]: Under an argon atmosphere, a solution of diisopropylamine (0.66 g, 6.50 mmol) in THF (20 mL) was cooled to –78 °C and slowly treated with a solution of *n*-butyl lithium (4.10 mL, 6.50 mmol, 1.6 M in *n*-hexane). After stirring for 30 min at –78 °C, a solution of (+)-**10** (0.72 g, 4.70 mmol, > 99.9% *ee*) in THF (5 mL) was added to the reaction mixture over a period of 5 min. Stirring was continued for 30 min at –78 °C and then methyl iodide (3.90 g, 27.5 mmol) was added. After stirring for a further 1.5 h satd. NH_4Cl solution (40 mL) was added, the resultant mixture was allowed to warm to room temperature and was then extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (25 × 5 cm) using petroleum ether/ethyl acetate (9:1) as eluent to yield (–)-**1a** (0.63 g, 79%) as colorless crystals. – M.p. 48–50 °C. – An *ee* of > 99.9% was determined by GC analysis on a Chrompack Permethyl β-CD column at 115 C; t_R[(+)-**1a**] = 52.3 min, t_R[(–)-**1a**] = 54.5 min. – $[\alpha]_D^{20}$ = –13.1 (*c* = 3.0, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 7.2 Hz, 3 H, HCC*H*$_3$), 1.70 (s, 3 H, HC=CC*H*$_3$), 1.72–2.01 (m, 4 H, CH_2), 2.19–2.28 (m, 1 H, C*H*CH–CH_3), 2.34–2.44 (m, 1 H, C*H*CH_3), 4.85–4.88 (m, 1 H, CHO), 5.47 (m, 1 H, C=CH). – ^{13}C NMR: δ = 13.8 (q, HC*C*H_3), 22.1 (t, CH_2), 23.4 (q, C=CCH_3), 25.7 (t, CH_2), 37.6 (d, *C*HCH_3), 40.1 (d, *C*HCHCH_3), 75.2 (d, CHO), 118.6 (d, =CH), 140.5 (s, H_3CC=), 179.5 (s, C=O). – $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found C 72.13, H 8.45.

(+)-(3*R*,3a*S*,7a*R*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one [(+)-1b]: Under an argon atmosphere, a solution of *n*-butyl lithium (1.40 mL, 2.20 mmol, 1.6 M in *n*-hexane) was added slowly to a cooled (–78 °C) solution of diisopropylamine (0.27 g, 2.70 mmol) in THF (30 mL). After stirring for 30 min at –78 °C a solution of (–)-**1a** (0.30 g, 1.80 mmol) in THF (5 mL) was dropwise added over a period of 5 min and the mixture was stirred for 30 min. Di-*tert*-butylmalonate (0.58 g, 2.7 mmol) was then added and the mixture stirred for a further 40 min at –78 °C. After this time satd. NH_4Cl solution (30 mL) was added. The mixture was allowed to warm to room temperature and was then extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (25 × 5 cm)

using petroleum ether/ethyl acetate (95:5) as eluent gave (+)-**1b** (0.18 g, 61%) as colorless crystals. – M.p. 57–59 °C. – $[\alpha]_D^{20}$ = +112 (*c* = 3.0, $CHCl_3$, > 99.9% *ee*). – ^1H NMR ($CDCl_3$): δ = 1.12–1.17 (m, 1 H, CH_2), 1.15 (d, *J* = 7.2 Hz, 3 H, HCCH_3), 1.64–1.69 (m, 1 H, CH_2), 1.76 (s, 3 H, HC=CCH_3), 1.95–1.99 (m, 2 H, CH_2), 2.28–2.35 (m, 1 H, C*H*CHCH_3), 2.86 (dq, *J* = 7.5 Hz, *J* = 7.2 Hz, 1 H, *H*CCH_3), 4.59–4.62 (m, 1 H, CHO), 5.63–5.65 (m, 1 H, C=CH). – ^{13}C NMR: δ = 9.2 (q, HC*C*H$_3$), 19.6 (t, CH_2), 23.7 (q, C=C*C*H$_3$), 28.9 (t, CH_2), 37.8 (d, *C*HCHCH$_3$), 40.2 (d, *C*HCH$_3$), 74.6 (d, CHO), 117.0 (d, =CH), 144.0 (s, H_3C–*C*=), 178.8 (s, C=O). – $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found C 72.28, H 8.50.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 247) and the Fonds der Chemischen Industrie. We thank Mrs. Olena Tverskoy for skillful technical assistance.

[1] I. A. Southwell, *Tetrahedron Lett.* **1975**, *24*, 1885–1888.
[2] [2a] B. Bonnländer, B. Baderschneider, M. Messerere, P. Winterhalter, *J. Agric. Food Chem.* **1998**, *46*, 1474–1478. – [2b] H. Guth, *J. Agric. Food Chem.* **1997**, *45*, 3022–3026.
[3] H. Guth, *Helv. Chim. Acta,* **1996**, *79*, 1559–1571.
[4] [4a] T. Jagella, W. Grosch, *Z. Lebensm.-Unters. Forsch. A.* **1999**, *209*, 16–21. – [4b] A. Hinterholzer, P. Schieberle, *Flavour Fragrance J.* **1998**, *13*, 49–55.
[5] P. A. Bartlett, C. F. Pizzo, *J. Org. Chem.* **1981**, *46*, 3896–3900.
[6] [6a] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron Asymmetry* **1992**, *3*, 1089–1122. – [6b] T. Hayashi, in: *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), VCH, Weinheim, **1993**, pp 325–365. – [6c] T. Lübbers, P. Metz in Houben-Weyl E21, *Stereoselective Synthesis* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), **1995**, pp. 2371–2473 and 5643–5676. – [6d] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422. – [6e] G. Helmchen, *J. Organomet. Chem.* **1999**, *576*, 203–214.
[7] 2-Cyclohen-1-yl chloride or bromide as substrates gave markedly lower enantioselectivity than the acetate.
[8] [8a] S. Kudis, G. Helmchen, *Angew. Chem.* **1998**, *110*, 3210–3212; *Angew. Chem. Int. Ed.* **1998**, *37*, 3047–3050. – [8b] P. Sennhenn, B. Gabler, G. Helmchen, *Tetrahedron Lett.* **1994**, *35*, 8595–8598. – [8c] G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.* **1997**, *69*, 513–518. – [8d] S. Kudis, G. Helmchen, *Tetrahedron* **1998**, 10449–10456. – [8e] S. Schleich, G. Helmchen, *Eur. J. Org. Chem.* **1999**, in press.
[9] G. Knühl, P. Sennhenn, G. Helmchen, *J. Chem. Soc., Chem. Commun.* **1995**, 1845–1846.
[10] G. Helmchen, A. Geiser, unpublished results.
[11] [11a] A. P. Krapcho, *Synthesis* **1982**, 805–822. – [11b] A. P. Krapcho, *Synthesis* **1982**, 893–914.
[12] Alternatively, malonate (+)-**3** was saponified and the resultant carboxylic acid decarboxylated by heating. This procedure caused formation of substantial amounts of side products and purification of the iodolactone was difficult.
[13] The facility of purification of the iodolactone was independently found by us (ref.[7b]) and by the Scheffold group: T. Troxler, R. Scheffold, *Helv. Chim. Acta* **1994**, *77*, 1193–1202.
[14] [14a] D. P. Curran, M.-H. Chen, D. Leszcweski, R. L. Elliot, D. M. Rakiewiecz, *J. Org. Chem.* **1986**, *51*, 1612–1614. – [14b] P. A. Grieco, C. V. Srinivasan, *J. Org. Chem.* **1981**, *46*, 2591–2593.
[15] The choice of this CH-acid was based on previous work of our group: R. Wierzchowski, Dissertation, Universität Würzburg, **1985**.
[16] A. Togni, *Tetrahedron: Asymmetry* **1991**, *2*, 683–690.
[17] G. Buono, G. Pfeiffer, A. Mortreux, F. Petit, *J. Chem. Soc., Chem. Commun.* **1980**, 937–939.
[18] Using the same procedure (+)-**5** of 95% *ee* gave enantiomerically pure (–)-**6** after recrystallization (yield: 82%).
[19] E. Nagano, K. Mori, *Biosci. Biotech. Biochem.* **1992**, *10*, 1589–1591.

Received September 16, 1999
[O99530]