*Tetrahedron: Asymmetry* Vol. 4, No. 5, pp. 1017-1026, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

# Enzyme Assisted Synthesis of Enantiomerically Pure δ-Lactones

**Bernhard Haase and Manfred P. Schneider***

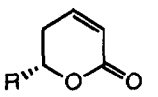
FB 9-Bergische Universität-GH-Wuppertal, D-5600 Wuppertal-1 Germany

(*Received* 15 *February* 1993; *accepted* 30 *March* 1993)

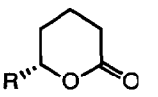
***Abstract***: Both enantiomeric series of a wide variety of optically pure 6-alkylated δ-lactones - saturated as well as unsaturated - were prepared *via* an enzyme mediated route. The key reaction step is the nucleophilic ring opening of enantiomerically pure alkyl-oxiranes, accessible via the corresponding β-hydroxythioethers which can be obtained enantiomerically pure *via* enzyme catalyzed kinetic resolutions.

## *1. Introduction*

Chiral 6-substituted 5,6-dihydro-2*H*-pyran-2-ones (α,β-unsaturated δ-lactones **1**) are key structural subunits of widely occurring natural products[1,2]. They display a wide variety of biological activities and have been reported as plant growth inhibitors, insect antifeedants, antifungal and antitumor agents[1].The short chain alkyl homologues are volatile and important aroma compounds in both foods and beverages. Together with their saturated analogues they constitute the flower bouquet of Tuberose flowers [Polianthes Tuberosal (Amaryllidaceae)][1]. Last but not least, these α,β-unsaturated δ-lactones are attractive precursors for the whole series of saturated analogues **2**.Saturated, chiral δ-lactones **2** have been identified as insect pheromones [1,3,4]. Due to their frequently low sensory threshold concentrations they represent key aroma constituents in various fruits and plants.



(*R*)-**1**



(*R*)-**2**

Interestingly enough - although natural products - these molecules are isolated from natural sources frequently not in enantiomerically pure form but as mixtures of enantiomers[4] in which the (*R*) - configurated compounds are usually dominating.

Since the physiological activities - odor or taste - are possibly dependent on the absolute configuration of these molecules, as a consequence the flavour notes of fruits can vary according to the region of growth, conditions of storage and degree of ripeness.

In spite of the importance of these molecules as aroma constituents there seems to exist no systematic study in which the relationship between organoleptic properties and their absolute configurations has been studied in detail, e.g. by a systematic determination of sensory threshold concentrations. Moreover there seem to be uncertainties regarding absolute configurations in a number of cases.The reason for this situation probably resides in the fact that enantiomerically pure δ-lactones of both absolute configurations are not easily accessible in multigram quantities. In view of a systematic study of organoleptic properties and detailed determinations of sensory threshold concentrations, it was our goal to synthesize both enantiomeric series of these molecules in good chemical yields and with high enantiomeric purities.

### 2. *Retrosynthetic Analysis*

In view of the importance of these molecules, synthetically useful precursors of these compounds are of considerable interest and numerous routes to them were developed in the past[5]. Enantiomerically pure, saturated δ - lactones can be corelated retrosynthetically with the corresponding δ -hydroxycarboxylic acids ( esters ). These, in turn, can be prepared by classical[6] or enzymatic[7] resolutions of their racemates or by selective chemical or microbial[8] reductions of the corresponding δ - keto carboxylic acids ( esters ) . ( Fig.1 ).

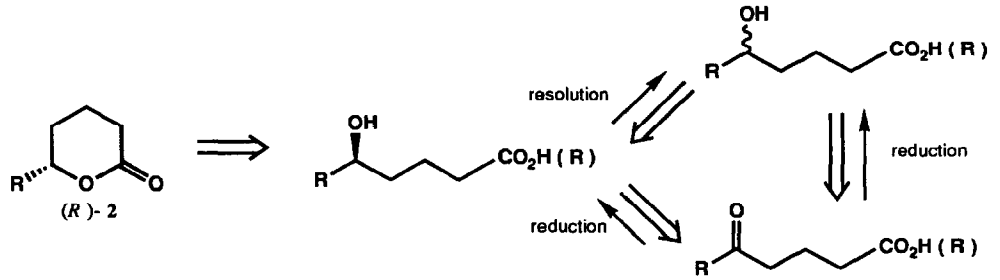



**Fig. 1.** Retrosynthetic analysis of enantiomerically pure δ - lactones ( *R* ) - **2**

Unfortunately , however , although useful in many cases the hitherto described methods frequently have drawbacks like low chemical or optical yields and sometimes only allow the production of one enantiomer. Morever, while saturated δ-lactones **2** are accessible *via* the coresponding δ-hydroxy-carboxylic acids ( esters ), their unsaturated analogues **1** are not. Both classes of compounds can, however, be made accessible conveniently using the retrosynthetic scheme shown in Fig 2.

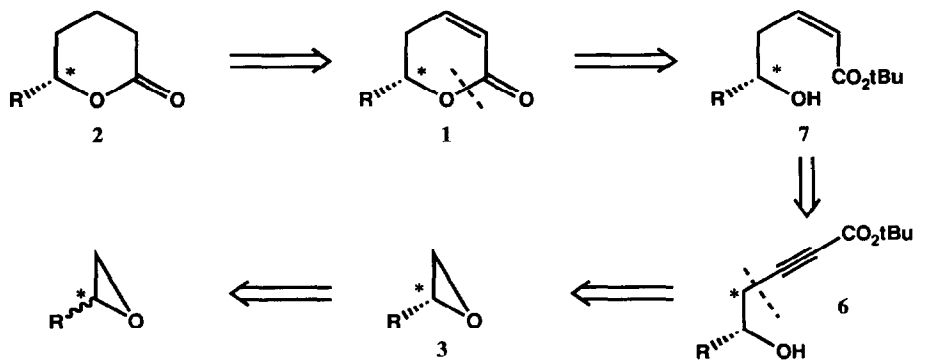



**Fig. 2.** Retrosynthetic analysis of both unsaturated and saturated δ - lactones ( *R* ) - **1** and **2**

Using this scheme ( Fig.2 ) all of the title compounds can be synthesized conveniently as outlined below[9,10].

### 3. *Enzyme Mediated Synthesis of enantiomerically pure δ-lactones* (R)- *and* (S)- *1 a -e and 2 a - e .*

Based on the above retrosynthetic scheme ( Fig.2 ) the racemic alkyloxiranes ( ± ) - **3 a - e** -conveniently accessible commercially or by simple epoxidation of the corresponding 1-alkenes - were converted by regioselective ring opening using *t*-butylthiol into the corresponding racemic β-hydroxythioethers ( ± ) - **4 a-e**

(Fig. 3 )[9].Treatment of ( ± ) - **4a -e** with chloroacetic anhydride/pyridine in the presence of *N,N*-dimethyl-4-aminopyridine ( DMAP ) leads to the corresponding chloroacetates ( ± ) - **5a - e.** Enantioselective hydrolyses of ( ± ) - **5a - e** in presence of a lipase from *Pseudomonas sp.* (SAMII)[11] proceeded with very high enantioselectivities indeed. Thus 10-500 mmol of these substrates were emulsified in 20-500 ml phosphate buffer of pH 7.0 by stirring. The enzymatic hydrolysis was initiated by addition of 50-500mg of the crude lipase preparation while the pH of the reaction mixture was maintained at pH 7.0 by continous addition of 1 M NaOH (pH-stat. conditions). All reactions came to a complete standstill after 50% conversion in 15 to 35 hrs.

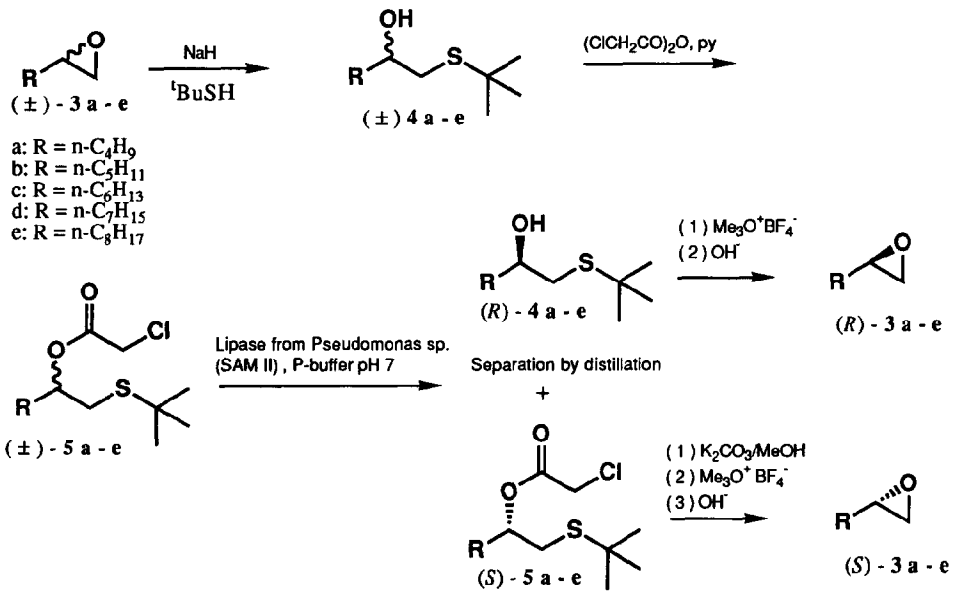



**Fig. 3.** Synthetic routes to enantiomerically pure 1,2-epoxyalkenes ( *R* ) - and ( *S* ) - **3 a - e**

The use of chloroacetates not only led to much more rapid enzymatic hydrolyses as compared to non activated esters[11], but due to the substantial differences in boiling points also allowed an extremely facile separation of the resulting products by simple vacuum destillation.Thus obtained are ( *R* ) - **4a - e** and ( *S* ) - **5a - e** in enantiomerically pure form. ( *S* ) - **5a-e** can be conveniently converted into the corresponding optically pure ( *S* ) - **4 a - e** by hydrolysis using $K_2CO_3$/MeOH. The high optical purities of ( *R* ) - **4 a- e** and ( *S* ) - **4 a - e** were confirmed by GC analysis of these compounds on a chiral support ( Cyclodex β I/P ).

*S* - Alkylation of the thus obtained, enantiomerically pure ( *R* ) - and ( *S* ) - **4 a - e** using Meerwein's salt ($Me_3O^+BF_4^-$), followed by treatment with aqueous NaOH[12] affords in a one pot reaction the enantiomerically pure oxiranes ( *R* ) - and ( *S* ) - **3 a - e** ( Fig. 3 ). The enantiomeric purities of ( *R* ) - and ( *S* ) - **3 a - e** were confirmed *via* chromatographic hplc analysis of the diastereomeric thiourea derivatives - resulting from the reaction of the corresponding β-hydroxyaminoalcohols, obtained by nucleophilic ring opening of the oxiranes with isopropylamine - with BGIT[13].

The thus obtained oxiranes ( *R* ) - and ( *S* ) - **3 a - e** of high enantiomeric purities are highly suitable building blocks for both enantiomeric series of unsaturated and saturated δ-lactones as outlined in Fig. 4.

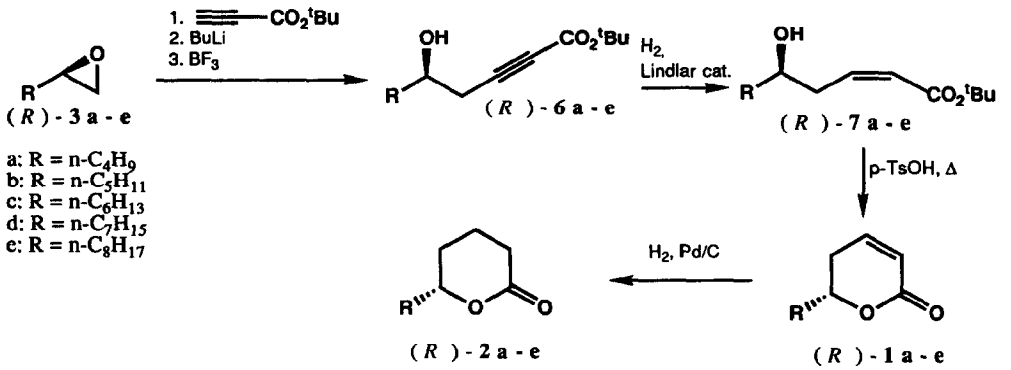



**Fig. 4.** Synthesis of enantiomerically pure δ - lactones ( *R* ) - **1 a - e** and ( *R* ) - **2 a - e**

Regioselective, boron trifluoride assisted ring opening of the oxirane moiety in ( *R* ) - and ( *S* )- **3 a - e** with the carbanion derived from *t*-propylpropiolate[14] leads to the corresponding ( *R* ) - and ( *S* ) - *t* - butyl-5-hydroxy-2-alkinates ( *R* )- and ( *S* ) - **6 a - e.**

Partial hydrogenation of ( *R* ) - and ( *S* ) - **6 a - e** in presence of Lindlar catalyst produced quantitatively the corresponding ( *R* ) - and ( *S* ) - *t* -butyl-5-hydroxy-2-alkenates ( *R* ) - and (S)- **7 a - e.**

Finally both enantiomeric series of these molecules can be converted into the saturated analogues ( *R* ) - and ( *S* ) - **2 a - e** by quantitative hydrogenation in presence of Pd - C (Engelhardt catalyst ). The high enantiomeric purities of ( *R* ) - and ( *S* ) - **2 a - e** were again confirmed by GC analyses on a chiral support.

### *3. Summary*

The above described method provides a rapid and facile access to a wide variety of both unsaturated and saturated δ-lactones. Using the above described enzyme assisted synthetic sequence both enantiomeric series of the title compounds with various substituents R were synthesized in high chemical and optical yields and in multigram quantities. They are now available for detailed studies regarding the relationship between absolute configurations and biological as well as sensory properties. Experiments of this nature are presently in progress.

### *Acknowledgements*

We are grateful to Boehringer Mannheim GmbH and the Fonds der Chemischen Industrie for support of this research.

## EXPERIMENTAL

General: NMR: Bruker WM 250 (all samples in $CDCl_3$), IR: Perkin-Elmer 397, optical rotations: Perkin-Elmer polarimeter 241 (all samples in $CHCl_3$, c = 1), chiral GC: Cyclodex β I/P , carrier $H_2$, Lipodex E, carrier He.

**( ± ) - *t* - Butyl - ( 2 - hydroxyhexyl ) - sulfide ( ± ) - 4 a:** 31.7g (351mmol) of *t*-butylthiol, dissolved in 120 ml anhydrous THF were cooled under an atmosphere of dry nitrogen to 0°C. To this solution 1.4 g ( 35mmol ) of NaH ( 60% in mineral oil ) were added and the mixture stirred at room temperature for 30 min. After cooling to 0 °C, 35.2 g ( 351mmol ) of 1,2-epoxyhexane ( ± ) - **3 a**, disssolved in 35ml of anhydrous

THF were added to this solution. The resulting mixture was stirred at room temperature for 1h and then for 2h under reflux. After cooling to roomtemperature the mixture was neutralized with 1N HCl and all solvents removed under reduced pressure. The residue was diluted with 40ml of water and extracted with 2 times 100ml $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, the solvent removed and the residue distilled under reduced pressure. 61.5g (92%) of ( ± ) - **4a** were obtained as colourless oil, bp $_{0.1}$ 75-78°C.

$^1$H-NMR: δ = 0.85 (pseudo t, 3H, C<u>H</u>$_3$-CH$_2$, $^3$J = 7.0 Hz), 1.01-1.55 (m, 6H, (CH$_2$)3), 1.27 (s, 9H, (CH$_3$)3), 2.42-2.73 (8 lines, AB-part of ABX-system, $\nu_A$ = 2.46, $\nu_B$ = 2.70, $|^2J_{AB}|$ = 12.8Hz, $|^3J_{AX}|$ = 8.3Hz, $|^3J_{BX}|$ = 3.9Hz, 2H, CH(OH)C<u>H</u>$_2$S), 2.58 (s, large, 1H, OH), 3.54-3.63 (m, X-part, 1H, C<u>H</u>(OH)).

$^{13}$C {$^1$H}-NMR: δ = 13.79 (<u>C</u>H$_3$-CH$_2$), 22.46, 27.67, 36.04 ((CH$_2$)3), 30.87 (C(<u>C</u>H$_3$)3), 36.33 (CH$_2$S), 42.05 (<u>C</u>(CH$_3$)3), 69.87 (CH(OH)).

IR (neat) [cm$^{-1}$]: 3440 (m, large, ν OH), 2960 (vs, ν CH3 in $^t$Bu), 2920 (vs, ν CH3), 2860 (s, ν CH$_2$), 1460 (m, δ CH$_2$), 1370 (m, δ CH3), 1160, 1020 (m, ν C-O), further signals 1120 w,.

GC: OV 1701, $R_t$ = 8.76min. (160°C), Cyclodex β I/P, $R_t$ = 24.60min. for (*R*), 23.16min. for (*S*) (110°C).

( ± ) - **4 b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to ( ± ) - **4 a** with the exception of signals caused by the different chain lengths of the alkyl residues[15]. The yields and GC retention times for ( ± ) - **4 b - e** are summarized in Table 1.

**Table 1.** Yields and GC retention times for ( ± ) - **4 a - e**

| compound | yield[a] (%) | $R_t$[b] (min.) | T(°C) | $R_t$(*R*)[c] | $R_t$(*S*)[c] | T | bp.(°C) |
|---|---|---|---|---|---|---|---|
| ( ± ) - **4 a** | 92 | 8.76 | 160 | 25.60 | 23.16 | 110 | 75-78/0.1 |
| ( ± ) - **4 b** | 90 | 9.63 | 170 | 34.06 | 32.19 | 115 | 69-73/0.001 |
| ( ± ) - **4 c** | 90 | 8.18 | 190 | 45.85 | 43.42 | 120 | 89-90/0.005 |
| ( ± ) - **4 d** | 93 | 8.23 | 200 | 59.89 | 56.94 | 125 | 99-102/0.001 |
| ( ± ) - **4 e** | 84 | 7.69 | 210 | 79.17 | 75.65 | 130 | 116-118/0.005 |

a) isolated b) OV 1701 c) Cyclodex β I/P

**( ± ) - *t*-butyl - ( -2 - ( chloroacetyl ) - hexyl ) - sulfide ( ± ) - 5 a**: 58.1g ( 305mmol ) of ( ± ) - **4 a** were dissolved under an atmosphere of dry nitrogen in 160ml anhydrous methylenechloride to which 26.1g ( 330mmol ) of anhydrous pyridine and 0.1g *N,N*-dimethyl-4-aminopyridine ( DMAP ) were added. The mixture was cooled to 0 °C and 56.4 g ( 330mmol) of chloroacetic anhydride in 150ml of anhydrous $CH_2Cl_2$ were added dropwise. Stirring was continued for 4 h at r.t. The resulting homogeneous solution was washed successively with 100 ml 1N HCl, 150ml $NaHCO_3$-solution and 150ml brine. The organic layer was separated and dried over $MgSO_4$. After removal of the solvent on a rotavapor the residue was distilled under reduced pressure leading to 74.9g (92%) of ( ± ) - **5 a** as colourless oil; bp $_{0.1}$ 105-107°C.

$^1$H-NMR: δ = 0.86 (pseudo t, 3H, CH$_3$-CH$_2$, $^3$J = 6.5 Hz), 1.02-1.78 (m, 6H, (CH$_2$)3), 1.28 (s, 9H, (CH$_3$)3), 2.59-2.75 (8 lines, AB-part of ABX-system, $\nu_A$ = 2.63, $\nu_B$ = 2.71, $|^2J_{AB}|$ = 13.1Hz, $|^3J_{AX}|$ = 6.7Hz, $|^3J_{BX}|$ = 6.0Hz, 2H, CH(OH)CH$_2$S), 4.04 (s, 2H, CH$_2$Cl), 4.91-4.99 (m, X-part, 1H, CHOC(O)).

$^{13}$C {$^1$H}-NMR: δ = 13.70 (CH$_3$-CH$_2$), 22.19, 27.08, 31.71 ((CH$_2$)3), 30.71 (C(CH$_3$)3), 32.57 (CH$_2$S), 40.86 (CH$_2$Cl), 42.29 (C(CH$_3$)3), 76.05 (CHOC(O)), 166.80 (C=O).

IR (neat) [cm$^{-1}$]: 2960 (vs, ν CH3 in $^t$Bu), 2920 (vs, ν CH3), 2860 (s, ν CH$_2$), 1750 (s, ν C=O), 1460 (m, δ CH$_2$), 1410 (w, δ CH3 in $^t$Bu), 1370 (m, δ CH3), 1280, 1180 (m,s, ν C-O-C), further signals 1300m, 1080m, 970m, 780m.

GC: OV 1701, $R_t$ = 23.52min. (160°C).

( ± ) - **5 b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to ( ± ) - **5 a** with the exception of signals caused by the different chain lengths of the alkyl residues[15]. The yields and GC retention times for ( ± ) - **5 b - e** are summarized in Table 2.

**Table 2.** Yields, boiling points and GC retention times for ( ± ) - **5 a - e**

| | yield (%)[a] | $R_t$[b] (min.) | T(°C) | bp.(°C) |
|---|---|---|---|---|
| ( ± ) - **5 a** | 92 | 23.52 | 160 | 105-107/0.1 |
| ( ± ) - **5 b** | 90 | 22.47 | 170 | 99-100/0.001 |
| ( ± ) - **5 c** | 86 | 18.42 | 190 | 120-122/0.005 |
| ( ± ) - **5 d** | 93 | 17.33 | 200 | 132-133/0.001 |
| ( ± ) - **5 e** | 76 | 15.68 | 210 | 149-150/0.005 |

a) isolated b) OV 1701

**(*R* ) -*t* -butyl -( 2-hydroxyalkyl )-sulfide (*R* ) - 4a - e and ( *S* ) -*t*- butyl-( 2- (chloro-acetyl)-alkyl ) - sulfide ( *S* ) - 5a - e.** General procedure: 200mmol of ( ± ) - **4a - e** were suspended in 300ml 0.1M phosphate buffer of pH 7.0. 250mg of the crude lipase from *Pseudomonas sp.* (SAM II) (Fluka AG) were added. The beginning enzymatic hydrolysis was indicated by a rapid decrease of the pH which was kept at pH 7.0 by continous addition of 1N NaOH from an autoburette (pH stat conditions). After 50% conversion the reactions came to a standstill (15-35h). The enzyme was removed by filtration and the suspension extracted with 3 times 50ml of methylenechloride. The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent on a rotavapor, followed by fractionation under reduced pressure yielded ( *R* ) - **4a - e** and ( *S* ) - **5a - e**. Reaction times and yields for the enzyme mediated synthesis of ( *R* ) - **4a - e** and ( *S* ) - **5a - e** are summarized in Table 3.

**Table 3.** Yields and reaction times for enzymatic mediated hydrolysis of ( ± ) - **4 a - e**

| Substrate | Reaction time (h) | Products | Yield[a] | E[16] | [%ee] | $[\alpha]_D^{20}$ | (*S*-Enantiomer) |
|---|---|---|---|---|---|---|---|
| ( ± ) - **4 a** | 15 | ( *R* ) - **4 a** | 46% | >100 | >99 | –29.6 | (+23.6) |
| | | ( *S* ) - **5 a** | 40% | | >99 | –38.7 | |
| ( ± ) - **4 b** | 20 | ( *R* ) - **4 b** | 44% | >100 | >99 | –25.0 | (+19.0) |
| | | ( *S* ) - **5 b** | 36% | | >99 | –35.2 | |
| ( ± ) - **4 c** | 22 | ( *R* ) - **4 c** | 42% | >100 | 98 | –21.5 | (+21.6) |
| | | ( *S* ) - **5 c** | 36% | | 98 | –34.9 | |
| ( ± ) - **4 d** | 25 | ( *R* ) - **4 d** | 40% | >100 | 96 | –20.0 | (+18.2) |
| | | ( *S* ) - **5 d** | 34% | | >99 | –30.1 | |
| ( ± ) - **4 e** | 35 | ( *R* ) - **4 e** | 38% | >100 | >99 | –19.0 | (+14.6) |
| | | ( *S* ) - **5 e** | 34% | | >99 | –28.0 | |

a) isolated

**Hydrolysis of ( *S* ) -*t*- butyl - ( 2-( chloroacetyl )-hexyl )-sulfide ( *S* ) - 4 a :** 16.1g (60mmol) of ( *S* ) - **5a** were dissolved in 60 ml of MeOH, 20ml of saturated methanolic $K_2CO_3$-solution containing 1% $H_2O$ was added and the mixture stirred for 12h at roomtemperature. The solvent was evaporated under reduced pressure. To the residue 20ml of water and 40ml of $CH_2Cl_2$ were added.The layers were separated and the aqueous layer was extracted with 3 times 20ml $CH_2Cl_2$. The organic layers were combined, washed with brine, and dried over $MgSO_4$. After evaporation of the solvent the residue was distilled (Kugelrohr) under reduced pressure to yield 11.3g ( 99% ) of ( *S* ) -*t*- butyl - ( 2 - hydroxyhexyl ) - sulfide ( *S* ) - **4a.** ( *S* ) - **4b - e** were prepared using exactly the same procedure ( yields 98-99% ).

**( *R* ) - 1,2 - Epoxyhexane ( *R* ) - 3a:** To a solution of 9.5g (50mmol) of ( *R* ) - **4 a** in 150ml of anhydrous $CH_2Cl_2$ 8.5g ( 57mmol ) of trimethyloxonium tetrafluoroborate was added rapidly under an atmosphere of dry nitrogen. The mixture was stirred for 2h at room temperature. After addition of 110 ml NaOH ( 10%vv ) solution stirring was continued for another 2.5h. The layers were separated and the aqueous phase extracted with 2 times 20ml $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, $CH_2Cl_2$ was evaporated and the residue fractionated under atmospheric pressure. One obtained 3.7g (74%) of ( *R* ) - **3a** as colourless liquid, bp.1013 115-118°C.

$^1$H-NMR: δ = 0.88 (pseudo t, 3H, C(6)$H_3$, $^3J$ = 7.0Hz), 1.22-1.51 (m, 6H, C(5)$H_2$-C(3)$H_2$), 2.41-2.72 (8 lines, AB-part of ABX-system, $\nu_A$ = 2.43Hz, $\nu_B$ = 2.72Hz, $^2J_{AB}$ = 5.0Hz, $^2J_{AX}$ = 2.7Hz, $^2J_{BX}$ = 4.1Hz, C(1)$H_2$), 2.83-2.90 (m, 1H, X-part, C(2)H).

$^{13}$C {$^1$H}-NMR: δ = 13.78 (C6), 22.33 (C5), 27.92 (C4), 32.00 (C3), 46.89 (C1), 52.17 (C2).

IR (neat) [$cm^{-1}$]: 3040 (m, ν CH, oxiran), 2960, 2930 (vs, ν $CH_3$), 2860 (vs, ν $CH_2$), 1460 (s, δ $CH_2$), 1410 (m, $\delta_{as}$ $CH_3$), 1380 (m, $\delta_s$ $CH_3$), 1260, 1130, (m, ν C-O-C), further signals 960m, 920m, 840s, 750m.

( *R* ) - and ( *S* ) - **3b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to ( *R* ) - **3a** with the exception of signals caused by the different chain lengths of the alkyl residues[15]. The yields and the boiling points are summarized in Table 4.

**Table 4.** Yields, boiling points and chiroptical properties of ( *R* ) - and ( *S* )- **4 a - e**

| Product | Yield [%][a)] | bp. (°C) | pressure (mbar) | [%ee] | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|
| ( *R* ) - **3 a** | 74 | 115-118 | 1013 | 98 | +9.1 |
| ( *S* ) - **3 a** | 69 | 115-118 | 1013 | >99 | –9.0 |
| ( *R* ) - **3 b** | 66 | 50-52 | 20 | >99 | +9.8 |
| ( *S* ) - **3 b** | 70 | 50-55 | 20 | >99 | –9.5 |
| ( *R* ) - **3 c** | 75 | 58-61 | 20 | 95 | +9.8 |
| ( *S* ) - **3 c** | 77 | 60-62 | 20 | >98 | –8.3 |
| ( *R* ) - **3 d** | 67 | 76-78 | 20 | 96 | +8.1 |
| ( *S* ) - **3 d** | 67 | 77-79 | 20 | 97 | –8.6 |
| ( *R* ) - **3 e** | 74 | 94-96 | 20 | 98 | +7.4 |
| ( *S* ) - **3 e** | 72 | 94-96 | 20 | >99 | –8.1 |

a) isolated

**( *R* ) -*t* - butyl -5- hydroxy -2- nonionate ( *R* ) - 6a:** 3.8g (30mmol) of *t*-butylpropiolate, dissolved in 60 ml anhydrous THF were cooled under an atmosphere of dry nitrogen to -78°C. 18.8ml (30mmol) of n-butyllithium ( 15% w/v in n-hexane ) were added dropwise and the mixture was stirred for 15min. 3.0g ( 30mmol ) ( *R* ) - **3a** in 30ml of anhydrous THF were added to this mixture, followed by rapid addition of 3.9ml borontrifluoride-diethyletherate. After stirring for 1.5 h 23ml 10% aqueous $KH_2PO_4$-solution was added and the mixture allowed to warm up to room temperature. The organic layer was separated and the aqueous layer was extracted with 3 times 30ml ether/n-pentane ( 1:1 v/v ). The combined organic layers were dried over $MgSO_4$, the solvent removed and the residue worked up by flash chromatography over 50g of silica gel ( EtOAc/n-hexane 1:4 ). After evaporation of the solvents the residue was distilled on a Kugelrohr apparatus. Obtained are 4.7g ( 70% ) of ( *R* ) - **4a** as colourless oil, bp.0.001 115°C.

$^1$H-NMR: δ = 0.86 (pseudo t, 3H, $C\underline{H}_3CH_2$, $^3J$ = 6.8Hz), 1.18-1.69 (m, 6H, $(CH_2)_3$), 1.44 (s, 9H, $(CH_3)_3$), 2.34-2.52 (m, 2H, CH(OH)$C\underline{H}_2$), 2.72 (s, large, 1H, OH), 3.71-3.81 (m, 1H, $C\underline{H}$(OH)).

$^{13}$C {$^1$H}-NMR: δ = 13.76 ($\underline{C}H_3CH_2$), 22.30, 27.35, 27.46 ($(CH_2)_3$), 27.73 ($C(\underline{C}H_3)_3$), 35.88 ($\underline{C}H_2C{\equiv}C$), 69.27 ($\underline{C}(CH_3)_3$), 75.90 (CH(OH)), 83.07 (C≡$\underline{C}$-C(O)O), 83.72 ($\underline{C}$≡C-C(O)O), 152.69 (C(O)O).

IR (neat) [$cm^{-1}$]: 3440 (m, large, ν OH), 2960 (s, ν $CH_3$ in $^tBu$), 2940 (ws, ν $CH_3$), 2870 (s, ν $CH_2$), 2240 (s, ν C≡C), 1700 (vs, ν C=O), 1460 (m, δ $CH_2$), 1390 (m, δ $CH_3$ in $^tBu$), 1370 (s, δ $CH_3$), 1270, 1070 (s, ν C-O-C), 1160, 1030 (s, ν C-O-C), further signals 840m, 750m.

(*R*) - and (*S*) - **6b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to (*R*) - **6a** with the exception of signals caused by the different chain lengths of the alkyl residues[15]. The yields and the boiling points are summarized in Table 5

**Table 5.** Yields, boiling points and chiroptical properties of (*R*) - and (*S*)- **6 a - e**

| product | Yield [%][a)] | bp. [°C]0.001 | [%ee] | $[\alpha]_D^{20}$ |
|---|---|---|---|---|
| (*R*) - **6 a** | 70 | 115 | >99 | −6.8 |
| (*S*) - **6 a** | 68 | 115 | >99 | +7.5 |
| (*R*) - **6 b** | 67 | 130 | >99 | −6.5 |
| (*S*) - **6 b** | 68 | 130 | >99 | +5.1 |
| (*R*) - **6 c** | 69 | 145 | 98 | −3.2 |
| (*S*) - **6 c** | 70 | 145 | 98 | +6.5 |
| (*R*) - **6 d** | 72 | 150 | 96 | −5.2 |
| (*S*) - **6 d** | 73 | 150 | >99 | +4.0 |
| (*R*) - **6 e** | 63 | 160 | >99 | −5.0 |
| (*S*) - **6 e** | 61 | 160 | >99 | +3.6 |

a) isolated

**(*R*) - *t* - butyl -5- hydroxy -2- noneonate (*R*) - 7a:** 3.4g (15mmol) of (*R*) - **6a** were dissolved in 80 ml of EtOAc and hydrogenated at atmospheric pressure in presence of 500mg Lindlar catalyst poisoned with 10 µl of quinoline. After take-up of 336ml $H_2$ (15mmol) the mixture was filtered, the solvent evaporated and the residue distilled under reduced pressure using a Kugelrohr apparatus. Obtained were 3.2g (93%) (*R*) - **7a** as colourless oil bp.0.001 100°C.

$^1$H-NMR: δ = 0.89 (pseudo t, 3H, C<u>H</u>$_3$-$CH_2$, $^3J$ = 7.0 Hz), 1.17-1.72 (m, 6H, $(CH_2)_3$), 1.47 (s, 9H, $(CH_3)_3$), 2.30-2.44 (s, large, OH), 2.71-2.77 (m, 2H, C<u>H</u>$_2$CH=CH, X-part), 3.67-3.77 (m, 1H, C<u>H</u>(OH)), 5.80-5.86 (6 lines, A-part of $ABX_2$-system, $\nu_A$ = 5.83, $|^3J_{AB}|$ = 11.6Hz, $|^4J_{AX}|$ = 1.4Hz, 1H, $CH_2$CH=C<u>H</u>), 6.20-6.31 (6 lines, B-part of $ABX_2$-system, $\nu_B$ = 6.26, $|^3J_{BX}|$ = 7.8Hz, $CH_2$C<u>H</u>=CH)

$^{13}$C {$^1$H}-NMR: δ = 13.90 (<u>C</u>H$_3$-$CH_2$), 22.56, 27.70, 36.24 ($(CH_2)_3$), 28.04 (C(<u>C</u>H$_3$)$_3$), 37.13 (<u>C</u>H$_2$CH=CH), 71.17 (<u>C</u>(CH$_3$)$_3$), 80.48 (CH(OH)), 123.62 (CH=<u>C</u>H-C(O)O), 144.34 (<u>C</u>H=CH-C(O)O), 166.37 (C(O)O).

IR (neat) [$cm^{-1}$]: 3440 (m, large, ν OH), 3040 (vw, ν C=CH), 2960 (s, ν $CH_3$ in $^tBu$), 2940 (vs, ν $CH_3$), 2870 (s, ν $CH_2$), 1710 (vs, ν C=O), 1640 (m, ν C=C), 1460 (m, δ $CH_2$), 1410 (m, δ $CH_3$ in $^tBu$), 1370 (m, δ $CH_3$), 1250, 1040 (vs,s, ν C-O), 1150, 1080 (m,s ν C-O), 850, 820 (m, δ C=CH), 750 (w, δ $(CH_2)_n$).

(*R*) - and (*S*) - **7b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to (*R*) - **7a** with the exception of signals caused by the different chain lengths of the alkyl residues[15]. The yields and the boiling points are summarized in Table 6.

**Table 6.** Yields, boiling points and chiroptical properties of ( *R* ) - and ( *S* )- **7 a - e**

| Product | Yield [%][a)] | bp. (°C)0.001 | [%ee] | $[\alpha]_D^{20}$ |
|---|---|---|---|---|
| ( *R* ) - **7 a** | 93 | 100 | >99 | +11.1 |
| ( *S* ) - **7 a** | 92 | 100 | >99 | −10.1 |
| ( *R* ) - **7 b** | 92 | 110 | >99 | +9.2 |
| ( *S* ) - **7 b** | 92 | 110 | >99 | −10.5 |
| ( *R* ) - **7 c** | 92 | 130 | 98 | +8.9 |
| ( *S* ) - **7 c** | 91 | 130 | 98 | −8.2 |
| ( *R* ) - **7 d** | 93 | 140 | 96 | +6.0 |
| ( *S* ) - **7 d** | 92 | 140 | >99 | −6.6 |
| ( *R* ) - **7 e** | 94 | 145 | >99 | +7.1 |
| ( *S* ) - **7 e** | 91 | 145 | >99 | −8.4 |

a) isolated

**6 - Butyl -5,6 - dihydro -2*H*- pyran-2-one ( *R* ) - 1a:** 2.7g (12mmol) of ( *R* ) - **7a** are dissolved in 30ml of water-saturated toluene to which 0.24g (1.2mmol) of p-toluenesulfonic acid was added. The mixture was heated under reflux for 1.5h and than cooled to room temperature. After washing with 10ml of sodium bicarbonate solution, drying over $MgSO_4$, evaporation of the organic solvent and distillation under reduced pressure on a Kugelrohr apparatus 1.9g ( 97% ) of ( *R* ) - **1a** were obtained, bp.0.001 80°C.

$^1$H-NMR: δ = 0.87 (pseudo t, 3H, C(10)H$_3$, $^3$J = 5.7 Hz), 0.95-1.88 (m, 6H, C(7-9)H$_2$), 2.19-2.40 (m, 2H, C(5$_{ax}$H, 5$_{eq}$H), $|^2J_{5eq,5ax}|$ = 17Hz), 4.38 (m, 1H, C(6)H, $|^3J_{6,5eq}|$ = 5.1Hz, $|^3J_{6,5ax}|$ = 11.1Hz), 5.96 (m, 1H, C(3)H, $|^4J_{3,5ax}|$ = 1.4Hz, $|^4J_{3,5eq}|$ = 2.2Hz, 6.85 (m, 1H, C(4)H, $|^3J_{4,5ax}|$ = 3.6Hz, $|^3J_{4,5eq}|$ = 5.1Hz, $|^3J_{4,3}|$ = 9.7Hz).

$^{13}$C {$^1$H}-NMR: δ = 13.68 (C10), 22.21 (C9), 26.69 (C8), 29.15 (C5), 34.31 (C7), 77.81 (C6), 121.10 (C3), 144.99 (C4), 164.41 (C2).

IR (neat) [cm$^{-1}$]: 3050 (vw, ν C=CH), 2930 (vs, ν CH$_3$), 2870 (s, ν CH$_2$), 1720 (vs, ν C=O), 1630 (wv, large, ν C=C), 1470 (m, δ CH$_2$), 1390 (m, δ CH$_3$), 1250, 1030 (s,m, ν C-O), 820 (m, δ C=CH).

( *R* ) - and ( *S* ) - **1b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to ( *R* ) - **1a** with the exception of signals caused by the different chain lenghts of the alkyl residues[15]. The yields and GC retention times for ( *R*) - and ( *S* ) - **1b - e** are summarized in Table 7.

**Table 7.** Yields, GC retention times and chiroptical properties of ( *R* ) - and ( *S* )- **1 a - e**

| | yield (%)[a)] | $R_t$[b)] (min.) | T(°C) | bp.(°C)/0.001 | [%ee] | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|
| ( *R* ) - **1 a** | 97 | 20.61 | 120 | 80 | >99 | −128.8 |
| ( *S* ) - **1 a** | 95 | 19.10 | 120 | 80 | >99 | +129.2 |
| ( *R* ) - **1 b** | 89 | 31.51 | 120 | 100 | >99 | −114.5 |
| ( *S* ) - **1 b** | 94 | 29.88 | 130 | 100 | >99 | +111.6 |
| ( *R* ) - **1 c** | 93 | 41.33 | 125 | 120 | 98 | −125.4 |
| ( *S* ) - **1 c** | 92 | 39.56 | 125 | 120 | 98 | +109.3 |
| ( *R* ) - **1 d** | 90 | 54.38 | 130 | 135 | 96 | −78.0 |
| ( *S* ) - **1 d** | 92 | 52.62 | 130 | 135 | >99 | +69.5 |
| ( *R* ) - **1 e** | 90 | 69.13 | 135 | 145 | >99 | −86.6 |
| ( *S* ) - **1 e** | 92 | 67.35 | 135 | 145 | >99 | +82.1 |

a) isolated b)Lipodex E

**( *R* ) - 6 - Butyl - oxan -2- one ( ( *R* ) - δ - Nonalactone ) ( *R* ) - 2a:** 1.5g (10mmol) of ( *R* )- **1a** were dissolved in 100ml of EtOAc and hydrogenated under atmospheric pressure in presence of 200mg Pd-C

(Engelhardt catalyst). After uptake of 224ml (10mmol) $H_2$ the mixture was filtered, the solvent removed and the residue distilled on a Kugelrohr apparatus. Obtained were 1.4g ( 95% ) of ( *R* ) - **2a** as a colourless oil, bp.0.001 75°C.

$^1$H-NMR: δ = 0.86 (pseudo t, 3H, C(10)H$_3$, $^3$J = 6.7Hz.), 1.24-1.78 (m, 6H, C(9-7)H$_2$), 1.80-2.12 (m, 4H, C(4)H$_2$C(5)H$_2$), 2.32-2.60 (m, 2H, C(3)H$_2$), 4.18-4.27 (m, 1H, C(6)H).

$^{13}$C {$^1$H}-NMR: δ = 13.75 (C10), 18.30 (C4), 22.31 (C9), 26.86 (C8), 27.60 (C5), 29.28 (C3), 35.33 (C7), 80.44 (C6), 171.88 (C2).

IR (neat) [cm$^{-1}$]: 2960 (vs, ν CH$_3$), 2880 (s, ν CH$_2$), 1740 (vs, ν C=O), 1470 (m, δ CH$_2$), 1380 (w, δ CH$_3$), 1240, 1030 (m, ν C-O), 730 (m, δ (CH$_2$)$_n$), further signals 1340w, 1190m, 1170m, 1120w, 930m.

( *R* ) - and ( *S* ) - **2b - e** were prepared using exactly the same procedure. The spectroscopic data of these compounds were very similar to ( *R* ) - **2a** with the exception of signals caused by the different chain lengths of the alkyl residues[15]. The yields and GC retention times for (*R*)- and ( *S* ) - **2b - e** are summarized in Table 8.

**Table 8** Yields, GC retention times and chiroptical properties of ( *R* ) - and ( *S* )- **1 a - e**

| | yield (%)[a] | R$_t$[b] (min.) | T(°C) | bp.(°C)/0.001 | [%ee] | [α]$_D^{20}$ |
|---|---|---|---|---|---|---|
| ( *R* ) - **2 a** | 98 | 24.51 | 115 | 75 | >99 | +50.6 |
| ( *S* ) - **2 a** | 96 | 23.34 | 115 | 75 | >99 | –52.5 |
| ( *R* ) - **2 b** | 91 | 38.99 | 115 | 95 | >99 | +47.2 |
| ( *S* ) - **2 b** | 92 | 37.48 | 115 | 95 | >99 | –47.9 |
| ( *R* ) - **2 c** | 93 | 50.22 | 120 | 105 | 98 | +43.7 |
| ( *S* ) - **2 c** | 92 | 48.34 | 120 | 105 | 98 | –42.4 |
| ( *R* ) - **2 d** | 94 | 63.77 | 125 | 130 | 96 | +35.3 |
| ( *S* ) - **2 d** | 91 | 62.20 | 125 | 130 | >99 | –37.2 |
| ( *R* ) - **2 e** | 89 | 83.40 | 130 | 140 | >99 | +38.4 |
| ( *S* ) - **2 e** | 90 | 81.83 | 130 | 140 | >99 | –35.9 |

a) isolated b) Lipodex E

## REFERENCES:


1. Davies-Coleman, M.T. and Rivett, D.E.A., *Fortschr. Chem. Org. Naturst.* 1989, **55**, 1-35
2. G. Ohloff, *Fortschr. Chem. Org. Naturst.* 1978, **35**, 431-527
3. W. Albrecht, M. Schwarz, J. Heidlas, and R. Tressl ., *J. Org. Chem.* 1992, **57**, 1954-1956
4. J.M. Brand *Fortschr. Chem. Org. Naturst.* 1979, **37** , 1-190
5. K. Mori, T. Otsuka and M. Oda, *Tetrahedron* 1984, **40**, 2929
6. G. Kramer, O. Fröhlich and P. Schreier in *Bioflavour '87*, p. 89 ff, Ed. Schreier, P.W. de Gruyter, Berlin 1988
7. M. Huffer and P. Schreier, *Tetrahedron: Asymmetry* , 1991, **2**, 1157-1164
8. M. Utake, H. Watabu and A. Takeda, *J. Org. Chem.*, 1987, **52**, 4363-4368
9. U. Goergens and M.P. Schneider, *Tetrahedron: Asymmetry* , 1992, **3**, 1149-1152
10. U. Goergens and M.P. Schneider, *Tetrahedron: Asymmetry* , 1992, **3** , 831-832
11. K. Laumen and M.P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1988, 598-600
12. U. Goergens and M.P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1991, 1065 and patent application PTC / EPO 91 . 01770
13. M. Lobell and M.P. Schneider, *J. Chromatogr.*, 1993, **633**, 287-294
14. T. Hoyer, A. Kjaer and J. Lykkesfeldt, *Collect. Czech. Chommun.*, 1991, **56**, 1042
15. A complete set of spectroscopic and chiroptical data is available from the authors upon request.
16. C.S.Chen, Y.Fujimoto,G.Girdaukas, and C.J.Sih, *J.Am.Chem.Soc.*, 1982, **104** , 7294