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BAKER'S YEAST REDUCTION OF ARYLALKYL AND ARYLALKENIL γ- AND δ-KETO ACIDS

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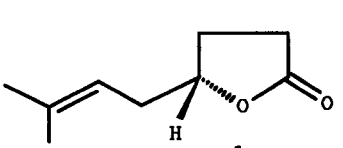
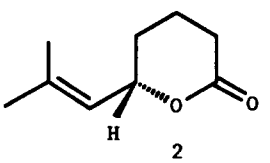
Abstract: γ- and δ-Lactones 5, 6, 13, 14, 15 and 16 were synthesized via baker's yeast reduction of the corresponding keto acids 3 ,4 and 9-12. The enantioselectivity of the reduction is strongly dependent on the nature of the keto acid: the δ-lactones were always obtained in an ee% higher than the γ-lactones and ranging from 70% to 100%.

A recent paper[1] on the synthesis of chiral γ- and δ-lactones 1 and 2 (Figure 1) from 7,7-dimethylbicyclo 3.2.0. hept-2-enone through enzyme-mediated procedures prompted us to report our approach to the same class of compounds. Our method is based on a straightforward baker's yeast mediated reduction of the corresponding γ- and δ-keto acids. The capacity of the microorganisms to enantioselectively reduce mid-chain aliphatic γ- and δ-keto acids is well known.[2,3a] The majority of the microorganisms tested, including baker's yeast, afforded carbinols with (R) absolute configuration in high enantiomeric purity. Only a few examples yielding the (S) enantiomer are reported.

Figure 1



1

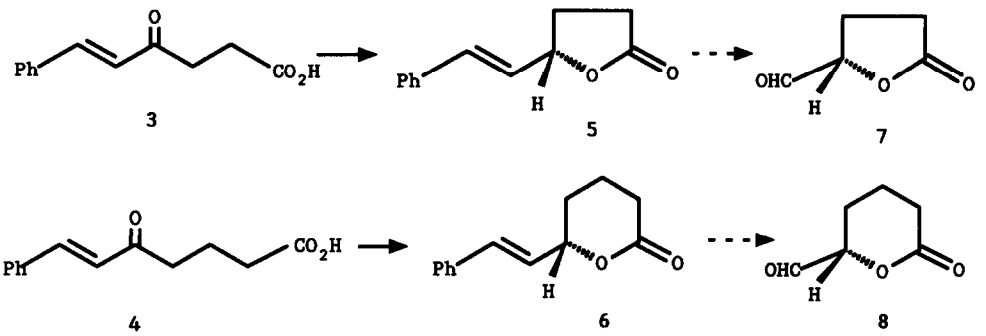


2

We first tested the ability of baker's yeast to reduce the carbonyl group of the unsaturated γ- and δ-keto acids 3 and 4, the aim being to obtain optically pure forms of

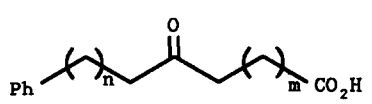
the stiryl lactones 5 and 6 (Scheme 1) of which the synthetic potential has recently been outlined.[4] In fact, these lactones possess a versatile functionality, the double bond, which can be manipulated to provide synthetically useful structures such as the aldehydes 7 and 8. Although 7 can be prepared from L-glutamic acid[5] the corresponding homologue 8 is not so readily accessible from chiral-pool components because its synthetic precursor, L-2-amino adipic acid, is a rare compound.

Scheme 1

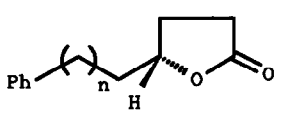


The keto acids 3 and 4, prepared respectively from levulinic and 4-acetyl butyric acids by base catalyzed condensation with benzaldehyde,[6] were readily reduced by yeast. Unfortunately, the lactones 5 and 6 could be isolated in good chemical yield after acidification and extractive work up the stereochemical results of the reductions were rather disappointing, the lactone enantiomeric excesses being only 10% and 70% respectively. The optical purity was determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ as the chiral shift reagent and by HPLC analysis on a chiral column.

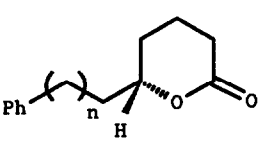
Figure 2



n=1 m=1 9
n=1 m=2 10
n=2 m=1 11
n=2 m=2 12



n=1 13
n=2 15



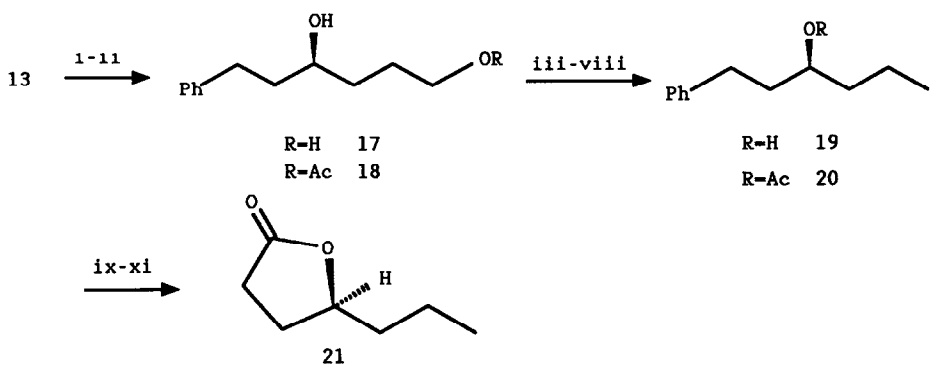
n=1 14
n=2 16

The absolute configuration (S) was established in both cases through a chemical correlation reported further on in the text. The modest enantioselectivity of the yeast

reduction of **3** and **4** is probably due to the presence of the conjugated double bond, in fact the yeast treatment of the keto acids **9** and **10**[7] afforded the γ- and δ-lactones **13** and **14** in very high enantiomeric purity (Figure 2).

The absolute configurations and the optical purities were determined through chemical correlation. Thus the lactones **13** and **14** were transformed into known aliphatic lactones[3] following the procedure reported for lactone **13** in Scheme 2. The correlation involved the transformation of the hydroxymethyl group of diol **17**, obtained in turn via the $LiAlH_4$ reduction of the lactone **13**, into a methyl group (e.g. **19**). Initially, we tried to obtain this transformation via the reduction of the corresponding primary bromo derivative. Accordingly, the diol **17** was treated in methylene chloride at room temperature with NBS-Ph_3P.[8] The reaction product, which can be isolated in 70% chemical yield, was the tetrahydrofuran derivative **22** with no evidence of other reaction-intermediates (Figure 3). The optical purity of derivative **22** was not determined, however the mechanism of this reaction will be further investigated. The desired conversion of **17** into **19** was achieved by the $LiAlH_4$ reduction of the primary tosylate derivative obtained, in turn, through the protective group manipulations illustrated in Scheme 2. The alcohol **19** was acetylated and the aromatic ring of **20** was oxidized with ruthenium trichloride-H_5IO_6,[9] yielding the (S)-heptanolide **21** in 92% ee. The absolute configuration and the optical purity of **21** were determined by glc analysis using a chiral capillary column,[10] and by comparison with an authentic sample.[3b] Thus, the absolute configuration of **13** is (R) and the enantioselectivity in the yeast reduction of γ-keto acid **9** is drammatically enhanced with respect to the unsaturated analog **3**. The absolute configuration of **3** was established by catalytic hydrogenation of the double bond affording the (R) lactone **13** in 10% ee.

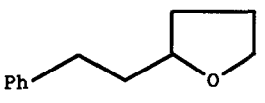
Scheme 2



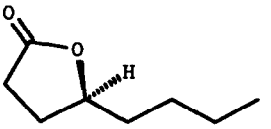
i) $LiAlH_4$-THF-reflux ii) $CH_2CHOCOCH_3$-lipase-PhH-4h-RT iii)dihydropyrane-PTSA-CH_2Cl_2 iv) NaOH-MeOH-reflux-4h v) PTSCl-Py-CH_2Cl_2 vi) $LiAlH_4$-THF-reflux vii) HCl-MeOH-H_2O-reflux-3h viii) Ac_2O-Py-16h ix) $RuCl_3H_2O$-H_5IO_6-CH_3CN-CCl_4-H_2O x) OH^- xi) H^+

The δ-lactone **14** was transformed into the γ-octanolide **23** (Figure 3) as reported for **13** in Scheme 2. However, in this case, the treatment of the 1,5-diol **24** with NBS-Ph_3P did not afford the ring closure product, as reported for **17**, but afforded, as expected, the primary bromo derivative. The tetrahydropyrane derivative can be obtained by treating the 5-hydroxy-1-bromo derivative with NaOH-MeOH.

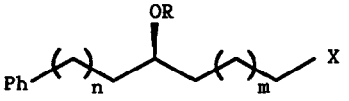
Figure 3



22



23



n=1 m=2 a
n=2 m=1 b
n=2 m=2 c

X=OH R=H 24 a,b,c
X=OAc R=H 25 a,b,c
X=H R=H 26 a,b,c
X=H R=Ac 27 a,b,c

Glc analysis on chiral column[10] of γ-octanolide **23** showed (S) absolute configuration and 100% ee. Thus, the yeast reduction of γ-keto acid **10** afforded the lactone **14** with (R) absolute configuration, as for the reduction of **9**, but in higher optical yield.

Catalytic hydrogenation of **6** led to the determination of its absolute configuration, affording **14** in (R) absolute configuration.

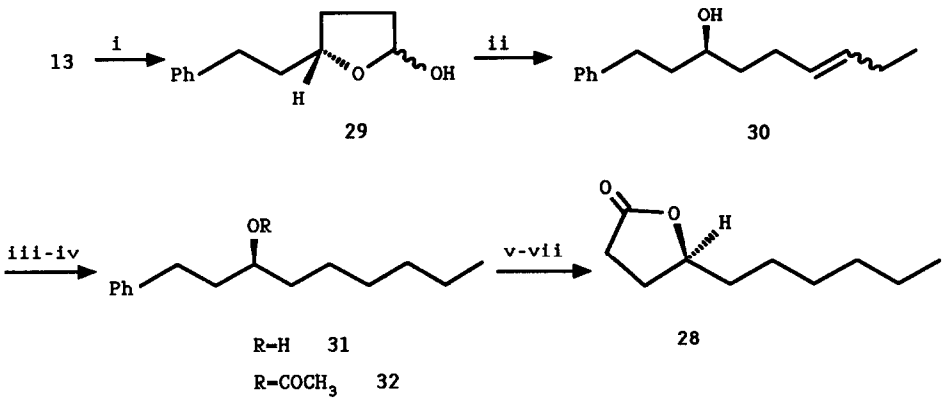
The lactone **13** was also correlated to the known lactone **28**,[11] according to the sequence reported in Scheme 3, and this confirmed the (R) configuration of **13** (**28**: 97% ee by glc analysis).

The unsaturated lactone **5**, obtained in low optical yield by yeast reduction, can be prepared by a simple manipulation of **13**. In fact, lactone **13** after benzylic bromination (NBS, CCl_4) and dehydrobromination (DBU) afforded lactone **5** in the same optical purity as the starting material and in good chemical yield. On other hand, the transformation of δ-lactone **14** into the unsaturated δ-lactone **6** using this procedure did not perform so well, the chemical yield being very low (30%).

Subsequently, the γ- and δ-keto acids **11** and **12** were reduced by baker's yeast to give lactones **15** and **16** (Figure 2). These were submitted to the usual correlation protocol which afforded the aliphatic δ-lactones **33** and **34**, respectively (Figure 4). The optical purities (40% for **33**,and 93% for **34**) and the absolute configuration ((S) in both cases) were determined by optical measurements and comparison with the $[\alpha]_D^{25}$ values reported in the literature[3a] (**33**: $[\alpha]_D^{25}$=-26.4° (c 1, THF); **34**: $[\alpha]_D^{25}$=-58.8° (c 1, THF)). Also in this case the δ-keto acid was reduced with higher enantioselectivity than

the γ one, as was observed for the reduction of **13** and **14**.

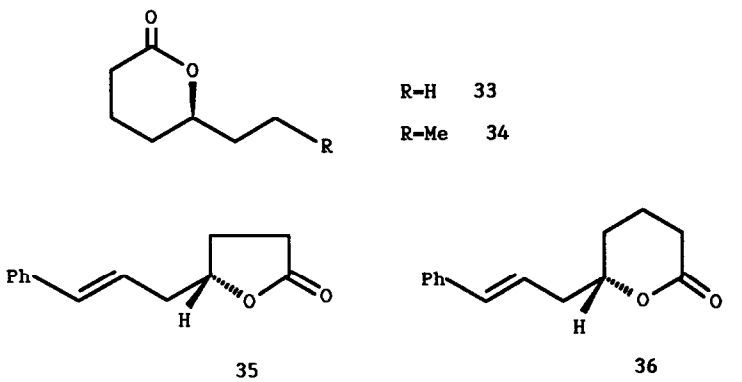
Scheme 3



i) DIBAL ii) $Ph_3PCHCH_2CH_3$-THF iii) H_2-Pd-C-MeOH-H_2O iv) Ac_2O-Et_3N-DMAP-CH_2Cl_2 v) $RuCl_3H_2O$-H_5IO_6-CH_3CN-CCl_4-H_2O vi) OH^- vii) H^+

The unsaturated lactones **35** and **36** can be obtained in good yield from **15** and **16**, respectively, by the benzylic bromination-dehydrobromination procedure.

Figure 4



These results confirm the validity of baker's yeast as a simple system for the production, through enantioselective carbonyl reduction, of quantities of materials with very high ee. At the same time, this further confirms that baker's yeast is very sensitive to structural limits, making the precise accetability of a substrate by the enzymic system(s) presiding over the carbonyl reduction unpredictable.

Acknowledgment: We wish to thank Rosanna Bernardi for her contribution in the GLC analysis and CNR for financial support through Piano Finalizzato Chimica Fine II.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker AC-250 or a Bruker CXP-300 instrument in the FT mode or with a Varian EM-390 with tetramethylsilane as internal standard. Optical rotations were measured in a 1 dm cell of 1 ml capacity by using a Jasco DIP-181 polarimeter. Silica gel $60F_{254}$ plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merck) for flash chromatography or 70-230 mesh silica gel (Merck) for chromatography. HPLC analyses were performed on a Merck Hitachi L-6200 with a Chiracel OD (Daicel) column and a UV (245 nm) detector using a Hewlett-Packard 3396A integrator. GLC analyses were performed on a Hewlett-Packard 5890 instrument with a capillary chiral Megadex 1 column using a Hewlwtt-Packard 5895A integrator. The keto acids **3-4** and **9-12** were synthesized according to literature procedures (see ref. 6 and 7).

Yeast Reduction.General Procedure. A suspension of 2.5 kg of baker's yeast and 2.0 kg of D-glucose in 7.5 l of tap water was stirred for 30 min at 32°C. A solution of keto acids (150 mmol) in 150 ml of 1M NaOH was then added. After 16h at room temperature 1.0 kg of Celite was added and the reaction mixture was filtered washing, the Celite pad with 2.0 l of AcOEt. The filtrate was adjusted to pH 4 with 2N HCl and extracted twice with 2 l portions of AcOEt. The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude material was chromatographed on 350 g of silica gel with n-hexane/AcOEt 8/2 as eluent, giving the lactones **5-6** and **13-16** in 70-80% yield.

Lactone **5**: ^{1}H NMR ($CDCl_3$, 250MHz) δ: 2.00-2.20 (1H, m), 2.40-2.70 (3H, m), 5.06-5.20 (1H, m), 6.20 (1H, dd, J=15.00, 7.50Hz), 6.70 (1H, d, J=15.00Hz), 7.20-7.50 (5H, m). ee 10% (^{1}H NMR in the presence of Eu(hfc)$_3$ and HPLC with Chiracel OD column using n-hexane/iPrOH 9/1 as eluent flow 0.6 ml/min). Anal.Calcd. for $C_{12}H_{12}O_2$: C,76.57; H,6.44. Found: C,76.60; H,6.40.

Lactone **6**: ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.70-1.82 (1H, m), 1.88-2.12 (3H, m), 2.46-2.70 (2H, m), 4.94-5.04 (1H, m), 6.19 (1H, dd, J=15.50, 6.00Hz), 6.65 (1H, d, J=15.50Hz), 7.20-7.40 (5H, m). ee 70% (determined as reported for **5**). Anal.Calcd. for $C_{13}H_{14}O_2$: C,77.20; H,6.99. Found: C,77.22; H,6.98.

Lactone **13**: ^{1}H NMR ($CDCl_3$, 250MHz) δ: 1.80-2.14 (3H, m), 2.24-2.38 (1H, m), 2.49-2.58 (2H, m), 2.64-2.90 (2H, m), 4.42-4.52 (1H, m), 7.10-7.34 (5H, m). $[\alpha]_D^{25}$=+71.3° (c 1.03, $CHCl_3$). Anal.Calcd. for $C_{12}H_{14}O_2$: C,75.76; H,7.43. Found: C,75.70; H,7.45.

Lactone **14**: ^{1}H NMR ($CDCl_3$, 250MHz) δ: 1.48-2.12 (6H, m), 2.38-2.42 (4H, m), 4.20-4.33 (1H, m), 7.10-7.34 (5H, m). $[\alpha]_D^{25}$=+81.9° (c 1.04, $CHCl_3$). Anal.Calcd. for $C_{13}H_{16}O_2$: C,76.44; H,7.91. Found: C,76.47; H,7.95.

Lactone **15**: ^{1}H NMR ($CDCl_3$, 250MHz) δ: 1.60-1.94 (5H, m), 2.25-2.40 (1H, m), 2.48-2.58 (2H, m), 2.60-2.70 (2H, m), 4.45-4.56 (1H, m), 7.15-7.32 (5H, m). $[\alpha]_D^{25}$=+21.7° (c 1.04, $CHCl_3$). Anal.Calcd. for $C_{13}H_{16}O_2$: C,76.44; H,7.91. Found: C,76.46; H,7.88.

Lactone **16**: ^{1}H NMR ($CDCL_3$, 250MHz) δ: 1.40-2.00 (8H, m), 2.33-2.70 (4H, m), 4.22-4.36 (1H, m), 7.12-7.34 (5H, m). $[\alpha]_D^{25}$=+21.7° (c 1.04, $CHCl_3$). Anal.Calcd.for $C_{14}H_{18}O_2$: C,77.03; H,8.33. Found: C,77.00; H,8.37.

Diol **17**. A solution of the lactone **13** (20 g, 105.3 mmol) in 30 ml of dry THF was added to a boiling THF (100 ml) suspension of $LiAlH_4$ (7 g, 184.4 mmol) under nitrogen. After refluxing for 4h, the reaction mixture was quenched by sequential addition of AcOEt, a saturated solution of potassium sodium tartrate and water. The organic layer was separated, dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude product was purified by chromatography (AcOEt/n-hexane 65/35) to give diol **17** in 78% yield. ^{1}H NMR ($CDCl_3/D_2O$, 90MHz) δ: 1.50-1.95 (6H, m), 2.55-2.85 (2H, m),

3.50-3.78 (3H, m), 7.10-7.33 (5H, m). $[\alpha]_D^{25}$=+7.5° (c 1.00, $CHCl_3$). Anal.Calcd. for $C_{12}H_{18}O_2$: C,74.19; H,9.36. Found: C,74.16; H,9.30.

Acetyl derivative 18. The diol 17 (14g, 72.2mmol) in 150 ml of benzene-n-hexane (1:1) was treated with vinyl acetate (13.4ml, 216.6mmol) and 3g of lipase from Candida cylindracea (Fluka) at room temperature. After 3h stirring, the reaction mixture was filtered and the solvent evaporated under reduced pressure. The crude product was purified by chromatography (n-hexane/AcOEt 8/2) to give 18 in 83% yield. ^1H NMR ($CDCl_3$, 250MHz) δ: 1.48-1.85 (7H, m), 2.03 (3H, s), 2.61-2.87 (2H, m), 3.60-3.70 (1H, m), 4.09 (2H, t, J=6.00Hz), 7.18-7.31 (5H, m). $[\alpha]_D^{25}$=+6.0° (c 1.00, $CHCl_3$). Anal.Calcd.for $C_{14}H_{20}O_3$: C,71.16; H,8.55. Found: C,71.12; H,8.58.

Alcohol 19. A solution of acetyl derivative 18 (14g, 59.3mmol) in methylene chloride (80 ml) was treated with dihydropyrane (5.9ml, 65.23mmol) and p-toluensulfonic acid (1g) at 0°C. After 3h, 3% $NaHCO_3$ aqueous solution (20ml) was added and the organic phase was separated, dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude product was dissolved in MeOH (50ml), treated with sodium hydroxide (4.0g, 100mmol) and refluxed for 4h. The reaction mixture was concentrated, diluted with ice-water and extracted with methylene chloride (2x100ml). The organic extracts were dried over sodium sulfate and the solvent evaporated under reduced pressure. A solution of the crude product was treated with p-toluensulfonyl chloride (19g, 100mmol) at 0°C. The reaction mixture was warmed at room temperature and, after 16h, was poured into ice-water then extracted with methylene chloride (3x100ml). The organic layers was washed with 3% HCl, water, 3% $NaHCO_3$, water and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The crude product was dissolved in THF (30ml) and added to $LiAlH_4$ (5g, 131.6mmol) in boiling THF (100ml). After 10h, the reaction mixture was treated, in sequence, with AcOEt, methanol and potassium sodium tartrate. The solvent was evaporated under reduced pressure. The residue dissolved in 100 ml of MeOH/H_2O (1:1) was treated with conc. HCl (5ml) and refluxed for 3 h. The reaction mixture was concentrated, cooled and extracted with methylene chloride (2x100ml). The organic extract was dried and the solvent evaporated under reduced pressure. The crude product was purified by chromatography (n-hexane/AcOEt 9/1) to give the compound 19 in 39% yield. ^1H NMR ($CDCl_3/D_2O$, 250MHz) δ:0.91 (3H, t, J=5.50Hz), 1.28-1.53, (4H, m), 1.65-1.85 (2H, m), 2.60-2.87 (2H, m), 3.58-3.69 (1H, m), 7.15-7.32 (5H, m). $[\alpha]_D^{25}$=+12.8° (c 1.00, $CHCl_3$). Anal.Calcd.for $C_{12}H_{18}O$: C,80.85; H,10.20. Found: C,80.88; H,10.21.

Acetyl derivative 20. A solution of alcohol 19 (3g, 16.9mmol) in pyridine (4ml) was treated with Ac_2O (4ml, 42.4mmol) at room temperature. After 16 h, the reaction mixture was evaporated under reduced pressure and the crude product purified by distillation (b.p. 80°C/14mmHg) to give 20 in 90% yield. ^1H NMR ($CDCl_3$, 300MHz) δ: 0.91 (3H, t, J=7.50Hz), 1.24-1.42 (2H, m), 1.49-1.53 (2H, m), 1.82.1.93 (2H, m), 2.03 (3H, s), 2.54-2.71 (2H, m), 4.90-5.00 (1H, m), 7.13-7.30 (5H, m). $[\alpha]_D^{25}$=-16.5° (c 1.00, $CHCl_3$). Anal.Calcd for $C_{14}H_{20}O_2$: C,76.33; H,9.17. Found: C,76.28; H,9.12.

Lactone 21. Compound 20 (2g, 9.09mmol) dissolved in acetonitrile (18.1ml) carbon tetrachloride (18.1ml) and water (30.3ml) was treated with periodic acid (29.2g, 129.0mmol). The reaction mixture was stirred 10 min (until both phases became clear) and then ruthenium trichloride hydrate (37.8mg, 0.18mmol) was added. After stirring for 3h, the reaction mixture was cooled to 0°C and ethyl ether (60ml) was added with vigorous stirring for 10 min. The organic phase was separated, washed twice with water then dried and the solvent evaporated under reduced pressure. The crude 4-acetyloxy eptanoic acid was dissolved in MeOH (78ml) and treated with 1N NaOH solution (39ml). The reaction mixture was stirred at room temperature for 6 h, then acidified to pH 4 with 2N HCl. The solvent was concentrated until 1/3 volume and 2N HCl was added until pH 1. The reaction mixture was stirred for 1 h and extracted with Et_2O, dried and filtered. The product was purified by bulb to bulb distillation under vacuo to give lactone 21 in 60% yield. ee 92% (glc analyses: Megadex column $T_{initial}$=110°C/3min /3°C/min/ T_{final}=180°C).

Correlation of lactones 14, 15 and 16. The correlation of lactones 14, 15 and 16 were carried out in the same way as described for γ-lactone 13: 14 was transformed into the δ-lactone 23, 15 and 16 into the δ-lactones 35 and 36 respectively.

Intermediate product characterizations:

Diol **24a**. ^{1}H NMR ($CDCl_3$, 90MHz) δ: 1.4-1.9 (8H, m), 2.6-2.9 (2H, m), 3.5-3.7 (3H, m), 7.1-7.3 (5H, m). $[\alpha]_D^{25}$=+9.3° (c 1.00, $CHCl_3$).

Acetyl derivative **25a**. ^{1}H NMR ($CDCl_3/D_2O$, 90MHz) δ: 1.4-1.9 (8H, m), 2.0 (3H, s), 2.6-2.9 (2H, m), 3.5-3.7 (1H, m), 4.0-4.2 (2H, m), 7.2-7.3 (5H, m). $[\alpha]_D^{25}$=+8.6° (c 1.00, $CHCl_3$).

Alcohol **26a**. ^{1}H NMR ($CDCl_3/D_2O$, 90MHz) δ: 0.9 (3H, t, J=6.0Hz), 1.2-1.9 (8H, m), 2.5-2.9 (2H, m), 3.5-3.7 (1H, m), 7.1-7.3 (5H, m). $[\alpha]_D^{25}$=+14.0° (c 1.00, $CHCl_3$).

Acetyl derivative **27a**. ^{1}H NMR ($CDCl_3$, 90MHz) δ:0.9 (3H, t, J=6.0Hz), 1.2-2.0 (8H, m), 2.1 (3H, s), 2.4-2.7 (2H, m), 5.0 (1H, q, J=6.0Hz), 7.1-7.3 (5H, m). $[\alpha]_D^{25}$=-13.2° (c 1.00, $CHCl_3$).

Diol **24b**. ^{1}H NMR ($CDCl_3/D_2O$, 250MHz) δ: 1.40-1.80 (8H, m), 2.60 (2H, t, J=7.50Hz), 3.50-3.68 (3H, m), 7.10-7.30 (5H, m). $[\alpha]_D^{25}$=-1.4° (c 1.00, $CHCl_3$).

Acetyl derivative **25b**. ^{1}H NMR ($CDCl_3/D_2O$, 250MHz) δ: 1.35-1.85 (8H, m), 2.03 (3H, s), 2.63 (2H, t, J=7.50Hz), 3.57-3.68 (1H, m), 4.07 (2H, t, J=6.50Hz), 7.14-7.31 (5H, m). $[\alpha]_D^{25}$=-1.5° (c 1.00, $CHCl_3$).

Alcohol **26b**. ^{1}H MNR ($CDCl_3/D_2O$, 250MHz) δ: 0.91 (3H, t, J=7.25Hz), 1.30-1.85(8H, m), 2.63 (2H, t, J=7.50Hz), 3.57-3.68 (1H, m), 7.15-7.32 (5H, m). $[\alpha]_D^{25}$=0° (c 1.00, $CHCl_3$).

Acetyl derivative **27b**. ^{1}H NMR ($CDCl_3$, 250MHz) δ: 0.88 (3H, t, J=7.00Hz), 1.20-1.70 (8H, m), 2.02 (3H, s), 2.58-2.64 (2H, m), 4.88-4.97 (1H, m), 7.13-7.32 (5H, m). $[\alpha]_D^{25}$=-4.7° (c 1.00, $CHCl_3$).

Diol **24c**. ^{1}H NMR ($CDCl_3/D_2O$, 250MHz) δ: 1.33-1.85 (10H, m), 2.61 (2H, t, J=7.50Hz), 3.50-3.62 (3H, m), 7.10-7.30 (5H, m). $[\alpha]_D^{25}$=-2.1° (c 1.00, $CHCl_3$).

Acetyl derivative **25c**. ^{1}H NMR ($CDCl_3/D_2O$, 250MHz) δ: 1.35-1.85 (10H, m), 2.03 (3H, s), 2.63 (2H, t, J=7.50Hz), 3.55-3.64 (1H, m), 4.05 (2H, t, J=6.50Hz), 7.11-7.29 (5H, m). $[\alpha]_D^{25}$=-0.3° (c 1.00, $CHCl_3$).

Alcohol **26c**. ^{1}H NMR ($CDCl_3/D_2O$, 300MHz) δ: 0.90 (3H, t, J=7.50Hz), 1.25-1.85 (10H, m), 2.63 (2H, t, J=5.00Hz), 3.56-3.62 (1H, m), 7.13-7.29 (5H, m). $[\alpha]_D^{25}$=+1.3° (c 1.00, $CHCl_3$).

Acetyl derivative **27c**. ^{1}H NMR ($CDCl_3$, 250MHz) δ: 0.88 (3H, t, J=7.00Hz), 1.18-1.35 (4H, m), 1.45-1.70 (6H, m), 2.01 (3H, s), 2.55-2.64 (2H, m), 4.85-4.95 (1H, m), 7.12-7.40 (5H, m). $[\alpha]_D^{25}$=-4.4° (c 1.00, $CHCl_3$).

Lactol **29**. A solution of lactone **13** (4.00g, 0.021mmol) in dry methylene chloride (200ml) at -78°C and under nitrogen was treated with a solution of DIBAL (31.6ml, 1M in n-hexane). After stirring for 1 h, the reaction mixture was quenched with 10% NaOH aqueous solution and extracted with methylene chloride. The organic extracts were washed with water, brine, dried over sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the product was purified by flash chromatography (n-hexane/AcOEt 7/3). The lactol **29** was obtained, as diastereoisomeric mixture, in 94% yield. ^{1}H NMR ($CDCl_3/D_2O$, 250MHz) δ: 1 62-2.12 (6H, m), 2.60-2.80 (2H, m), 3.95-4.30 (1H, m), 5.48-5.60 (1H, m), 7.13-7.32 (5H, m).

Unsaturated alcohol **30**. Propyltriphenylphosphonium bromide (8.67g, 22.5mmol) dissolved in dry THF (220ml) under nitrogen was treated with a solution of n-BuLi (13.2ml, 1.5M in n-hexane) After stirring for 2 h at room temperature, the reaction mixture was cooled at -78°C and a solution of lactol **29** (1.73g, 19.0mmol) in dry THF (5ml) was added. The temperature was raised to room temperature. After stirring for 30 min at this temperature, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with AcOEt. The organic extracts were dried, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane/AcOEt 8/2) to give the product **30** in 89% yield (Z/E mixture). ^{1}H NMR ($CDCl_3/D_2O$, 250MHz) δ: 0.98 (3H, t, J=7.50Hz), 1.46-1.62 (2H, m), 1.71.1.82 (2H, m), 1.93-2.23 (4H, m), 2.60-2.88 (2H, m), 3.60-3.70 (1H, m), 5.28-5.56 (2H, m), 7.15-7.35 (5H, m)

Acetate **32**. Unsaturated alcohol **30** (1.20g, 5.45mmol) in 200 ml of $MeOH/H_2O$ (3:1) was hydrogenated in the presence of catalytic amounts of 10% Pd/C. After 20 h, the reaction

mixture was filtered and the solvent evaporated under reduced pressure to give the crude alcohol **31**. **31**: ^{1}H NMR ($CDCl_3/D_2O$, 90MHz) δ: 0.9 (3H, t, J=8.0Hz), 1.2-1.9 (12H, m), 2.6-2.8 (2H, m), 3.5-3.7 (1H, m), 7.1-7.3 (5H, m). A solution of the crude alcohol **31** in dry methylene chloride (32ml) was treated with Et_3N (1.69ml, 12.0mmol), Ac_2O (1.03ml, 10.9mmol) and a catalytic amount of DMAP. After stirring at room temperature for 1 h, the reaction mixture was washed with water, 5% aqueous HCl and water. The organic layer was dried over sodium sulfate , filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane/AcOEt 95/5) to give the acetate **32** in 95% yield. ^{1}H NMR ($CDCl_3$, 250MHz) δ: 0.87 (3H, t, J=6.75Hz), 1.20-1.30 (10H, m), 1.50-1.61 (2H, m), 1.80-1.92 (2H, m), 2.04 (3H, s), 2.52-2.72 (2H, m), 4.88-4.98 (1H, m), 7.13-7.32 (5H, m). $[\alpha]_D^{25}$=-10.4° (c 1.07, $CHCl_3$). Anal.Calcd.for $C_{17}H_{26}O_2$: C,77.82; H,10.01. Found: C,77.87; H,10.03.

γ-Lactone **28**. Lactone **28** was obtained from **32** as already reported for the transformation of compound **20** into **21**. The crude product was purified by Kugerlohr distillation (135-140°C/15mmHg) to give the γ-lactone **30** in 65% overall yield. ^{1}H NMR ($CDCl_3$, 250MHz) δ: 0.88 (3H, t, J=7.50Hz), 1.23-1.94 (11H, m), 2.25-2.40 (1H, m), 2.49-2.58 (2H, m), 4.43-4.55 (1H, m). $[\alpha]_D^{25}$=-36.9° (c 1.03, MeOH); $[\alpha]_D^{25}$=-33.8° (c 1.05, $CHCl_3$). The 97% ee was determined by glc analysis on chiral column as reported for lactone **21**. Anal.Calcdfor $C_{10}H_{18}O_2$: C,70.55; H,10.68. Found: C,70.53; H,10.63.

Benzylic bromination-dehydrobromination. General Procedure. A solution of saturated lactone (1.58mmol) in CCl_4 (8ml) was treated with NBS (2.37mmol) and a catalytic amount of $PhCO_3H$. The reaction mixture was refluxed for 1 h, then filtered and the solvent evaporated under reduced pressure. The crude bromo derivative was dissolved in $CHCl_3$ (15.8ml) and treated with DBU (1.9mmol). After refluxing for 3 h, the reaction mixture was cooled and treated with 2N HCl until pH 5. The organic layer was washed with water and brine, then dried over sodium sulfate and the solvent evaporated under reduced presure. The product was purified by chromatography n-hexane/AcOEt 8/2.

Lactone **5**. 84% yield. $[\alpha]_D^{25}$=+2.9° (1.04, $CHCl_3$). 95%ee. Anal.Calcd.for $C_{12}H_{12}O_2$: C,76.57; H,6.44. Found: C,76.55; H,6.41.

Lactone **6**. 30% yield. $[\alpha]_D^{25}$=+0.6° (c 1.01, $CHCl_3$). 99%ee. Anal.Calcd.for $C_{13}H_{14}O_2$: C,77.20; H,6.99. Found: C,77.23; H,7.02.

Lactone **35**. 80% yield. ^{1}H MNR ($CDCl_3$, 250MHz) δ: 1.88-2.03 (1H, m), 2.25-2.40 (1H, m), 2.48-2.71 (4H, m), 4.58-4.68 (1H, m), 6.19 (1H, dt, J=15.75, 7.00Hz), 6.50 (1H, dt, J=15.75, 1.35Hz), 7.15-7.40 (5H, m). Anal.Calcd.for $C_{13}H_{14}O_2$: C,77.20; H,6.99. Found: C,77.25; H,6.95.

Lactone **36** . 82% yield. ^{1}H NMR ($CDCl_3$, 250MHz) δ: 1.50-1.68 (1H, m), 1.74-2.02 (3H, m), 2.40-2.70 (4H, m), 4.35-4.46 (1H, m), 6.23 (1H, dt, J=15.75, 7.00Hz), 6.49 (1H, d, J=15.75Hz), 7.19-7.39 (5H, m). $[\alpha]_D^{25}$=-0.5° (c 0.84, $CHCl_3$). Anal.Calcd.for $C_{14}H_{16}O_2$: C,77.75; H,7.46. Found: C,77.70; H,7.44.

Tetrahydrofuran derivative **20**. A solution of diol **17** (500mg, 2.58mmol) in methylene chloride (26ml) was treated with Ph_3P (1.49g, 5.52mmol) and NBS (1.01g, 5.52mmol). After stirring for 48 h at room temperature the solvent was evaporated under reduced pressure. The crude mixture was taken up with Et_2O, filtered and the solvent evaporated under reduced pressure. The product was purified by flash chromatography (n-hexane-AcOEt 9/1) to give **22** in 70% yield. ^{1}H NMR ($CDCl_3$, 250MHz) δ: 1.40-1.54 (1H, m), 1.69-2.05 (5H, m), 2.59-2.63 (2H, m), 3.68-3.94 (3H, m), 7.13-7.38 (5H, m). $[\alpha]_D^{25}$=+4.2° (c 1.06, $CHCl_3$). Anal.Calcd.for $C_{12}H_{16}O$: C,81.77; H,9.17. Found: C,81.74, H,9.17.

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