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The Enantioselective Synthesis of Simplified Southern-Half Fragments of Soraphen A

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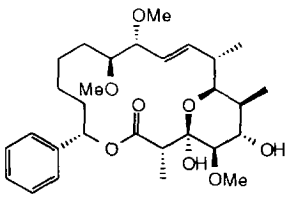
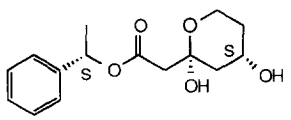
Abstract: The compound **2** comprises a southern-half subunit of the fungicidal macrolide soraphen A **1**. It was prepared by a Meinwald reaction of the enolate of ***S*-7** with the lactone ***S*-8**. Its enantiomer and diastereomers were synthesized in a similar manner. The lactone ***S*-8** and its enantiomer ***R*-8** were prepared by three different routes, including the enantioselective catalytic reduction of the β-keto ester **17**. These lactones are new and potentially useful as C-5 asymmetric building blocks.

Introduction. The macrolide soraphen A **1** was isolated recently from the myxobacterium *Sorangium cellulosum* by Hoefle et al.[1] On screening as a potential agrochemical, it was found to show potent activity against a range of plant pathogenic fungi.[2] Since then a number of semi-synthetic derivatives have been prepared,[3] and its total synthesis was recently completed.[4] In an attempt to mimic this fungicidal activity with molecular structures more simple than that of **1**, we were interested in the preparation of compound **2**,[5] which contains the hemiacetal and phenyl functionality found in the southern-half of the soraphen A molecule.



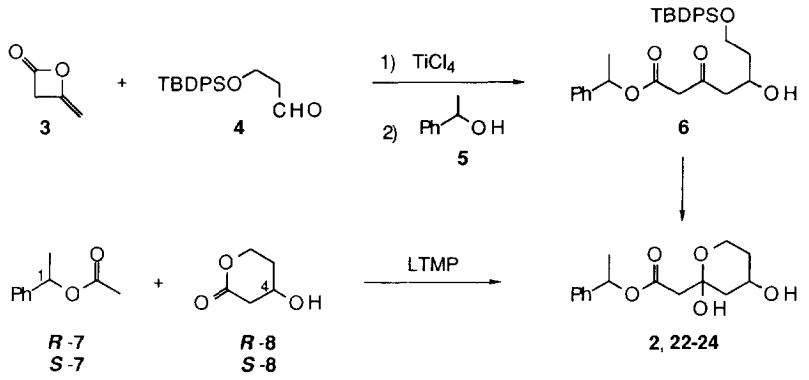
Soraphen A **1**



2

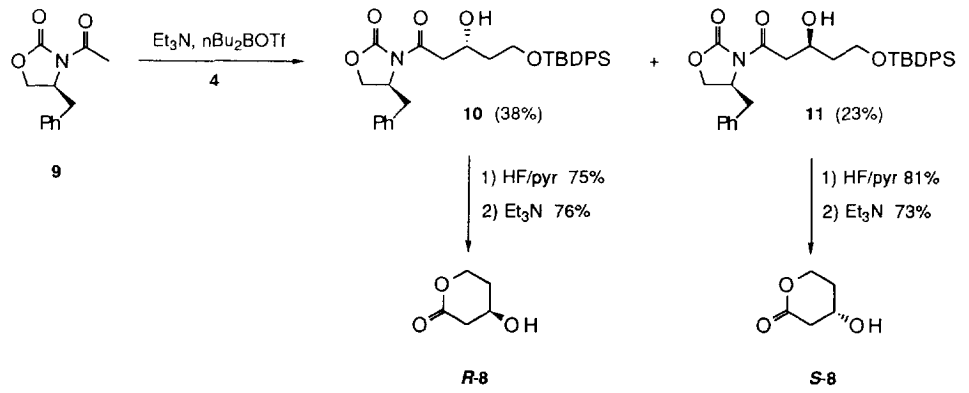
A rapid method for preparing the desired model compound **2** was previously found by elaborating a method described by Mukaiyama.[6] It involved a three component condensation of diketene **3**, a protected aldehyde **4** and an alcohol **5** mediated by $TiCl_4$ and yielded the desired product **2** as a racemate[5] (Scheme 1). Our attention was then turned to the preparation of the optically pure product. One approach to the enantiomers would involve the reaction of an ester enolate with the appropriate lactone (Meinwald reaction[7]), which we have shown to be a simple and direct route to such compounds.[8] For this purpose 4*S*-hydroxy-tetrahydropyran-2-one ***S*-8** was required. The only report of this lactone in the literature is its preparation as a racemate from the lead tetraacetate treatment of an acyclic tin compound.[9] Its enantiomers ***R*-** and ***S*-8** have never been described,

although their 4-O-silyl protected analogs have been reported.[10] We describe now three methods for the synthesis of ***R***- and ***S*-8**. Firstly by means of an aldol reaction using a chiral auxiliary. Secondly through the elaboration of the enzymatic hydrolysis product ***R*-13**, and finally using the Noyori hydrogenation of the β-keto ester **17**. The successful coupling of ***R***- and ***S*-8** with the enolates of ***R***- and ***S*-7** yielding the target compound **2**, its enantiomer **22**, and their diastereomers **23** and **24**, is further reported.



Scheme 1

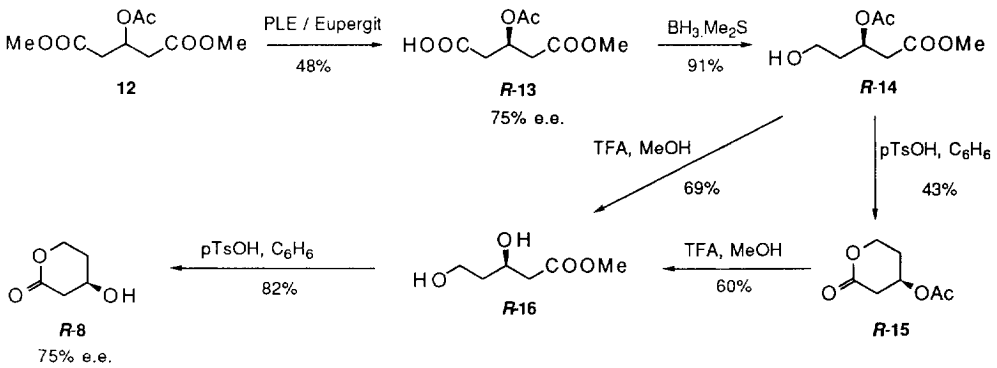
Results and discussion. In order to obtain pure samples for preliminary work, we prepared ***R***- and ***S*-8** according to Scheme 2. (4*S*)-Isopropyl-N-acetyl-oxazolidinone is known to afford only poor stereoselectivity in aldol reactions.[11] This proved also to be the case when the enolate of **9** was treated with the aldehyde **4**. The aldol products **10** and **11** were isolated in 61% combined yield. Although the reaction was unselective, it was possible to separate these two diastereomers completely by chromatography. Removal of the silyl groups[12] and subsequent mild basic treatment led to *R*- and *S*-**8** in good yield and > 95% e.e. The optical purity was determined by NMR integration using the (+)-TAE[13] shift reagent.



Scheme 2

An enantioselective approach to the lactone ***R*-8** was then developed starting from the enzymatic hydrolysis product ***R*-13** (Scheme 3). This acid or compounds similar to it have been obtained by esterase catalysed enantioselective hydrolysis of compounds similar to **12**. The enzymes used were chymotrypsin (e.e.=80%,[14] 64-93%,[15] 69%[16,17]), esterase 30000 (e.e.>98%[18]) and pig liver esterase (PLE) (e.e.=22%,[16] 90%,[19,20] 100%[21]). The same acid **13** or similar compounds with different protecting groups have also been prepared by -a) desymmetrisation of protected 3-hydroxy glutaric anhydrides by ring opening with chiral alcohols[10a,22] or amines,[23] or with alcohols using esterases[24] and -b) resolution of **13**.[25]

Because of the simple work-up and recovery of enzyme on a large scale, PLE bound on Eupergit[26] was used for this work (Scheme 3). The acid ***R*-13** was obtained in 48% yield and 75% e.e. by this method, which is less than that (90% e.e.) reported for native PLE by Santaniello[19] and Szantay.[20] The discrepancy may be due to the differences in the state of the enzyme or to differences in the reaction conditions to which the enzymatic reaction is known to be susceptible.[27] The e.e. was again determined by (+)-TAE induced NMR shift. A sample of racemic **13** needed for the e.e. determination was prepared by selective Me_3SiI hydrolysis[28] of the triester **12**. Borane reduction[29] of ***R*-13** afforded ***R*-14** in high yield. Lactonisation of ***R*-14** with Et_3N was accompanied by elimination of the acetate group to 5,6-dihydropyran-2-one. However acid catalysed cyclisation[30] led successfully to ***R*-15** in 43% yield. In view of the ready elimination of the acetate group under basic conditions, acid catalysed methanolysis was used to remove the acetate group of ***R*-15**. Ring opening accompanied the acetate cleavage and ***R*-16** was isolated in 60% yield. This compound was relactonised with Et_3N in acetone (59%) or in better yield (82%) with TsOH in benzene[30] to the desired compound ***R*-8**. The synthesis could be shortened and improved by treating ***R*-14** with acidic methanol. A mixture (8:2) of ***R*-16** and ***R*-8** was isolated in 69% yield. Treatment of this mixture with TsOH in benzene[30] led to ***R*-8** in 82% yield. Aqueous work-up was avoided in the last two steps to aid isolation of these water soluble and volatile compounds. The e.e. of ***R*-8** was 75%, identical to that of the product of enzymatic hydrolysis ***R*-13**, demonstrating that the conversion of ***R*-13** to ***R*-8** takes place without measurable racemisation.

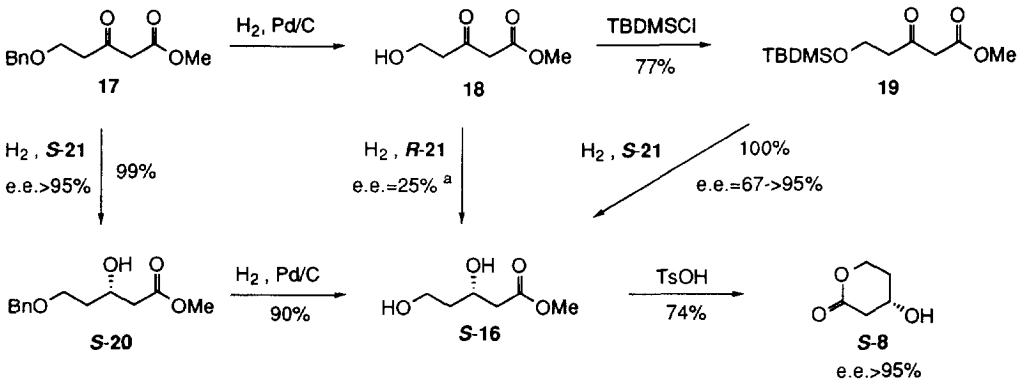


Scheme 3

In view of the fact that the target lactone ***R*-8** was easily prepared from the dihydroxy ester ***R*-16** as shown in Scheme 3, another simpler route to ***R*-** and ***S*-8** was found involving the enantioselective reduction of the β-keto ester **17** to ***R*-** or ***S*-16**[31] (Scheme 4). Apart from this catalytic route, compounds similar to **16** (Scheme 3) have also been prepared by reduction of 5-hydroxy-3-oxopentanoate esters with baker's yeast.[10b,c]

Enantioselective hydrogenation of β-keto ester **17**[32] with $[Ru_2Cl_4[(R)$ or (S) BINAP$]_2]$ Et_3N (***R***-or ***S*-21**) afforded the hydroxy ester ***S*-20** with >95% e.e.,[31] which was then hydrogenolysed to ***S*-16** in high yield using Pd/C as a catalyst. Afterwards the desired lactone ***S*-8** was obtained in good yield and with excellent e.e. from ***S*-16** by treatment with TsOH in refluxing benzene.[30] Its enantiomer ***R*-8** was prepared analogously.

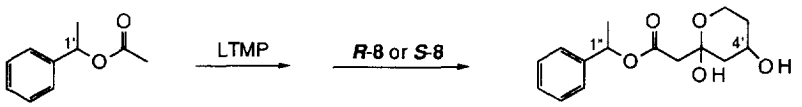
The β-keto esters **18** and **19** were less suitable as precursors. ***S*-16** of only 25% e.e. was obtained from **18**, probably due to competition between the ester and the hydroxy group for the directing of the ketone reduction. ***S*-16** was also obtained directly from **19** after hydrogenation with ***R***- or ***S*-21**. As only one equivalent of H_2 was taken up, it is clear that the silyl group was cleaved by Lewis acid and not by hydrogenolysis. The high stereoselectivity indicates that reduction of the ketone largely preceded silyl cleavage.



a: This hydrogenation was performed in the enantiomeric series and yielded R-16.

Scheme 4

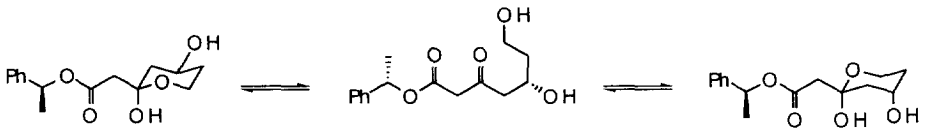
Having found a rapid and useful method for the synthesis of the desired lactones ***R***- and ***S*-8** in high yield and excellent e.e., we turned to the preparation of the four enantiomers (**2**, **22-24**) of the target compound **2**. This was simply done under typical Meinwald conditions whereby ***R***- and ***S*-8** were treated with the enolates of the chiral esters ***R***- and ***S*-7**. The enolates were prepared using LTMP rather than LDA,[8b] and three equivalents were used to allow for deprotonation of the 4-hydroxy groups of ***R***- and ***S*-8**. The desired products (**2**, **22-24**) were obtained in good yield (Scheme 5). These compounds exist as a mixture of equilibrating hemiacetal-hydroxyketone tautomers **A-C** (Scheme 6) as is usual for this type of compound.[5,8]



***R*-7**
***S*-7**

2	75%	1"*S*	4'*S*
22	75%	1"*R*	4'*R*
23	71%	1"*R*	4'*S*
24	44%	1"*S*	4'*R*

Scheme 5



2A 2B 2C

Scheme 6

Conclusion. The compounds (**2**, **22-24**) were tested for biological activity and showed disappointingly neither fungicidal activity[33] nor inhibiton of acetyl coenzyme A carboxylase[34] at concentrations up to 300 times the IC_{50} of **1**. However, although our goal of achiving fungicidal activity with simple molecules was not met, the enantiomerically pure C-5 lactones ***R***- and ***S*-8** have been prepared for the first time. These lactones are useful C5 asymmetric synthons.

EXPERIMENTAL

General. Solvents (Fluka or Merck "puriss") were used without further distillation. THF was freshly distilled from sodium/benzophenone under argon. Glassware was dried with a flame and cooled under nitrogen. NMR spectra were recorded with tetramethylsilane as internal standard on a Varian Unity 500 (500 MHz ^1H), a Bruker ACF 250 (250 MHz ^1H), or a Brücker AM 400 (400 MHz ^1H) spectrometer. Chemical shifts are given in ppm. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Mass spectra (MS) were recorded with electron impact (EI, 8 keV), or field desorption (FD). Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter at 23 ± 2 °C. Flash chromatography was performed by use of Merck silica gel 60 (230-400 mesh). $PdCl_2$ (0.5%) in HCl (aq.) was used as a spray reagent for tlc.

(4'*S*)-Benzyl-3'-((3*R*) and (3*S*)-hydroxy-5-tert.butyldiphenylsilyloxy-pentanoyl)-oxazolidin-2'-one (10) and (11). Under argon, triethylamine (9.32 ml, 68.85 mmol) and a solution of dibutylboryl trifluormethanesulfonate (1M in CH_2Cl_2, 61.3 ml, 61.3 mmol) was added successively to a solution of **9**[35] (12.2 g, 55.7 mmol) in CH_2Cl_2 (150 ml) at -78°C. After 1 *h*. at this temperature the mixture was warmed to 0°C, stirred 15 min, cooled again to -78°C, then the aldehyde **4**[5,36] (19.12 g, 61.3 mmol) was added. The mixture was stirred 90 min at -78°C and then 90 min at 0°C. 370 ml of a 1M sodium acetate solution in 90% MeOH/H_2O was then added. After 5 min, 30% H_2O_2 (30 ml) was slowly added. The mixture was stirred 15 min at 10-15°C and H_2O (500 ml) and hexane (300 ml) was successively added. The organic layer was washed with $NaHCO_3$ (satd.) and NaCl (satd.), dried over Na_2SO_4 and concentrated to give 30.66 g of material. Chromatography (EtOAc / hexane 1:4) of 1 g of the crude product yielded 380 mg (38%) of the diastereomer **10** and 232 mg (23%) of the diastereomer **11**. Chromatography on a larger scale, led to more mixed fractions.

Diastereomer **10**: ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.06 (s, tBu); 1.81 (m, 2H-4); 2.79 (dd, J=13, 10Hz, C<u>H</u>-Ph); 3.09 (dd, J=17, 4Hz, H-2); 3.18 (dd, J=17, 8Hz, H-2); 3.32 (dd, J=13, 3Hz, C<u>H</u>-Ph); 3.43 (d, J=4Hz, HO); 3.89 (m, 2H-5); 4.21 (m, 2H-5'); 4.44 (m, H-3); 4.70 (m, H-4'); 7.20-7.46 (m, H-arom); 7.66-7.72 (m, H-arom). MS (EI): 532 $[M+H]^+$, 276 $[M\text{-}TBDPSO]^+$.

Diastereomer **11**: ^{1}H- NMR (400 MHz; $CDCl_3$): δ = 1.06 (s, tBu); 1.81 (m, 2H-4); 2.79 (dd, J=13, 10Hz, C<u>H</u>-Ph); 3.10 (dd, J=18, 3Hz, H-2); 3.17 (dd, J=18, 9Hz, H-2); 3.32 (dd, J=13, 3Hz, C<u>H</u>-Ph); 3.45 (d, J=4Hz, HO); 3.89 (m, 2H-5); 4.21 (m, 2H-5'); 4.48 (m, H-3); 4.70 (m, H-4'); 7.20-7.47 (m, H-arom); 7.66-7.71 (m, H-arom). MS (EI): 532 $[M+H]^+$, 277 $[M+H\text{-TBDPSO}]^+$.

(4*R*)-Hydroxy-tetrahydro-pyran-2-one (*R*-8). a) The imide **10** (570 mg, 1.07 mmol) was dissolved in (HF/pyr/THF) (6 ml) and stirred 3 h. at RT. After extraction with ethyl acetate the organic layer was washed with HCl (1M), $NaHCO_3$ (satd.), and NaCl (satd.) and then dried over Na_2SO_4. Chromatography (EtOAc / hexane 3:1) yielded 236 mg (75%) of (4'*S*)-benzyl-3'-((3*R*),5-dihydroxy-pentanoyl)-oxazolidin-2'-one. ^{1}H-NMR (400 MHz; $CDCl_3$): δ = 1.79 (m, 2H-5); 2.45 (t, J=5Hz, HO-5); 2.81 (dd, J=13, 10Hz, C<u>H</u>-Ph); 3.12 (dd, J=17, 8Hz, H-2); 3.17 (dd, J=17, 4Hz, H-2); 3.29 (dd, J=13, 3Hz, C<u>H</u>-Ph); 3.45 (d, J=2.5Hz, HO-3); 3.88 (q, J=5Hz, 2H-4); 4.23 (m, 2H-5'); 4.34-4.43 (m, H-3); 4.72 (m, H-4'); 7.19-7.39 (m, H-arom). MS (EI): 294 $[M+H]^+$, 276 $[M+H\text{-}H_2O]^+$.

b) Triethylamine (2.65 ml, 19 mmol) was added to a solution of (4'*S*)-benzyl-3'-((3*R*),5-dihydroxy-pentanoyl)-oxazolidin-2'-one (930 mg, 3.17 mmol) in CH_2Cl_2 (15 ml). The mixture was stirred 48 h. at RT and toluene (10 ml) was added. Concentration and chromatography (EtOAc 100%) yielded 281 mg (76%) of ***R*-8** with a e.e. >95%. ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.91 (m, Heq-4); 1.98 (s, HO); 2.14 (ddd, J=17.5, 8, 4Hz, Hax-4); 2.60 (dd, J=17, 5Hz, H-2); 2.84 (dd, J=17, 5Hz, H-2); 4.30 (ddd, J=11.5, 6.5, 4.5Hz, Heq-5); 4.37 (m, H-3); 4.59 (ddd, J=11.5, 8, 4Hz, Hax-5). IR: 1725 cm^{-1} (C=O); 3430 cm^{-1} (OH). MS (FD): 117 $[M+H]^+$, 98 $[M\text{-}H_2O]^+$. $[\alpha]_D^{20}$ = -4.7 ($CHCl_3$, c=1).

(4*S*)-Hydroxy-tetrahydro-pyran-2-one (*S*-8). a) The imide **11** (1.99 g, 3.75 mmol) was treated analogous to **10** in the procedure described above for the preparation of ***R*-8**. Chromatography (EtOAc 100%) yielded 892 mg (81%) of (4'*S*)-benzyl-3'-((3*S*),5-dihydroxy-pentanoyl)-oxazolidin-2'-one. ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.81 (m, 2H-5); 2.43 (m, HO-5); 2.80 (dd, J=13, 10Hz, C<u>H</u>-Ph); 3.07 (dd, J=18, 9Hz, H-2); 3.24 (dd, J=18, 3Hz, H-2); 3.32 (dd, J=13, 3Hz, C<u>H</u>-Ph); 3.39 (m, HO-3); 3.90 (t, J=5Hz, 2H-4); 4.23 (m, 2H-5'); 4.43 (m, H-3); 4.70 (m, H-4'); 7.20-7.39 (m, H-arom). MS (EI): 294 $[M+H]^+$, 276 $[M\text{-HO}]^+$.

b) (4'*S*)-Benzyl-3'-((3*S*),5-dihydroxy-pentanoyl)-oxazolidin-2'-one (865 mg, 2.95 mmol) was treated with Et_3N as described above for the preparation of ***R*-8** yielding 248 mg (73%) of *S*-**8** with a e.e. >95%. $[\alpha]_D$ = +3.5 ($CHCl_3$, c=1).

The e.e. of the lactones ***R*-** and *S*-**8** was determined from the integral of the H-C_2 signal in the ^{1}H-NMR at 2.84 ppm which was shifted on addition of (+) trifluoroanthranyl ethanol (TAE) to 2.41 for the lactone ***R*-8** and to 2.46 for the lactone *S*-8.

(3*R*)-Acetoxy-pentanedioic acid monomethyl ester (*R*-13). 15 g of PLE on Eupergit was added to an emulsion of **12** (105.5 g, 484 mmol) in 2.6 L of pH 7 phosphate buffer . The pH was maintained between 6.98 and 7.01 by addition of 1M NaOH. After addition of 484 ml of 1M NaOH the mixture was filtered and extracted with EtOAc (6 x 800 ml). The aqueous layer was acidified with 1N HCl, extracted with EtOAc (3 x 600 ml) and dried over Na_2SO_4. Concentration yielded 47.1 g (48%) of ***R*-13** with 75% e.e. $[\alpha]_D^{20}$ = +5.9 ($CHCl_3$, c=1); $[\alpha]_D^{20}$ = +5.4 ($CHCl_3$, c=5.5).

The e.e. of **13** was determined from integral of the methoxy signal in the ^{1}H-NMR which was shifted on addition of (+) TAE to 3.45 for ***R*-13** and to 3.44 for ***S*-13**.

(*RS*)-3-Acetoxy-pentanedioic acid monomethyl ester (13). Under argon, NaI (529.11 mg, 3.53 mmol) and Me_3SiCl (0.45 ml, 3.53 mmol) was successively added to a solution of **12** (700 mg, 3.21 mmol) in CH_3CN (3 ml). The mixture was refluxed for 48 h. and cooled to RT, then H_2O (5 ml) was added. The mixture was extracted with Et_2O and washed with H_2O, $Na_2S_2O_3$ (10%) and $NaHCO_3$ (15%). The bicarbonate extract was acidified with HCl (2M), extracted with EtOAc and the organic layer dried over Na_2SO_4. Concentration yielded 187.5 mg (29%) of ***RS*-13**.

(3*R*)-Acetoxy-5-hydroxy-pentanoic acid methyl ester (*R*-14). Under argon, BH_3Me_2S (3.62 ml, 38.12 mmol) was slowly added to a solution of ***R*-13** (7.07 g, 34.65 mmol) in dry THF (35 ml). After 20 h. at RT methanol (18 ml) was added. After stirring an additional hour and concentration the residue was dissolved in EtOAc (20 ml), washed with H_2O, $NaHCO_3$ (satd.), NaCl (satd.), and dried over K_2CO_3. After evaporation of the solvent ***R*-14** (5.97 g, 91%) was obtained. ^{1}H NMR (400 MHz; $CDCl_3$); δ= 1.76 (m, H-4); 1.890 (m, H-4); 2.08 (s, Ac); 2.28 (dd, J=7.5, 5Hz, HO); 2.61 (dd, J=15, 5Hz, H-2); 2.70 (dd, J=7.5, 15Hz, H-2); 3.58 (m, H-5); 3.69 (m, H-5, OCH_3); 5.42 (m, H-3). IR: 1735 cm^{-1} (C=O); 3520 cm^{-1} (OH). MS (EI): 191 $[M+H]^+$, 173 $[M-HO]^+$. $[\alpha]_D^{20}$ = +17.8 ($CHCl_3$, c=1).

(4*R*)-Acetoxy-tetrahydro-pyran-2-one (*R*-15). In a flask equipped with a "Dean-Stark" apparatus, a mixture of hydroxy ester ***R*-14** (5.8 g, 30.53 mmol) and p-toluene sulfonic acid (85.6 mg, 0.46 mmol) in benzene (800 ml) was refluxed for 3 h.. The mixture was allowed to cool to RT, then washed with $NaHCO_3$ (satd. 80 ml), and NaCl (satd. 80 ml) and dried over Na_2SO_4. Chromatography (Et_2O 100%) yielded 2.04 g (43%) of ***R*-15**. ^{1}HNMR (400 MHz; $CDCl_3$): δ = 2.02 (m, Heq-5); 2.10 (s, CH_3); 2.21 (m, Hax-5); 2.71 (dd, J=17, 5Hz, H-3); 2.88 (dd, J=17, 5Hz, H-3); 4.39 (ddd, J=11.5, 6.5, 4.5Hz, Heq-6); 4.50 (ddd, J=11.5, 8, 4Hz, Hax-6); 5.25 (m, H-4). IR: 1740 cm^{-1} (C=O). MS (FD): 159 $[M+H]^+$, 98 $[M-AcOH]^+$. $[\alpha]_D^{20}$ = -3.4 ($CHCl_3$, c=1).

(3*R*),5-Dihydroxy-pentanoic acid methyl ester (*R*-16). I) A solution of the lactone **15** (102 mg, 0.645 mmol) and trifluoroacetic acid (TFA) (80 µl) in 2 ml of MeOH was left 20 h. at RT. The mixture was diluted with benzene (10 ml) and the solvent evapored. Chromatography (EtOAc 100%) yielded 57 mg (60%) of ***R*-16**.

II) A solution of (3*R*)-acetoxy-5-hydroxy-pentanoic acid methyl ester ***R*-14** (7.4 g, 38.94 mmol) and TFA (6 ml) in MeOH (54 ml) was stirred 45 h. at 50 °C. After dilution with methanol (100 ml), half of the solvent was removed unter reduced pressure, then the residue was diluted again with 100 ml of benzene. Concentration followed by chromatography on silica gel (EtOAc 100%) yielded 3.74 g (69%) of a 8:2 mixture of ***R*-16** and ***R*-8**. ^{1}HNMR (***R*-16** signals) (500 MHz; $CDCl_3$): δ = 1.74 (m, 2H-4); 2.57 (d, J=6Hz, 2H-2); 3.74 (s, OCH_3); 3.87 (m, 2H-5); 4.30 (m, H-3). IR: 1730 cm^{-1} (C=O); 3460 cm^{-1} (OH).

(4*S*)-Hydroxy-tetrahydro-pyran-2-one (*S*-8). In a flask with a "Dean-Stark" apparatus, ***S*-16** (4 g, 27 mmol) and p-toluene sulfonic acid (5 mg, 0.026 mmol) in benzene (300 ml) was refluxed for 3 h.. The mixture was cooled to RT and filtered. Concentration followed by chromatography (EtOAc 100%) yielded 2.3 g

(74%) of ***S*-8** with 95% e.e. $[\alpha]_D$ = +3.37 ($CHCl_3$, c=0.95). ***R*-8** was prepared analogously, but using ***R*-16** instead of ***S*-16**.

3-Oxo-5-tert.butyldimethylsilyloxy-pentanoic acid methyl ester (19). To a solution of **18**[32b] (1.1 g, 7.53 mmol) in DMF (10 ml) was added imidazole (512.9 mg, 7.53 mmol) and tert.butyl-dimethysilyl chloride (1.14 g, 7.53 mmol). The mixture was stirred 1h. at RT, then water was added. The reaction mixture was extracted with EtOAc, washed with HCl (1M), H_2O and dried over $MgSO_4$. Chromatography (EtOAc/hex 1:4) yielded 1.5 g (77%) of **19**. ^{1}HNMR (250 MHz; $CDCl_3$): δ = 0.00 (s, $(CH_3)_2Si$); 0.82 (s, t.BuSi); 2.68 (t, J=7Hz, 2H-4); 3.45 (s, 2H-2); 3.70 (s, OCH_3); 3.85 (t, J=7Hz, 2H-5).

(3*S*)-Hydroxy-5-benzyloxy-pentanoic acid methyl ester (*S*-20). **17** (5.75 g, 24.36 mmol) and $[Ru_2Cl_4$ ((*S*)BINAP)$_2]Et_3N$ (***S*-21**) (20 mg) were dissolved in dry MeOH (20 ml) under nitrogen. After replacement of the nitrogen by hydrogen the reaction mixture was stirred 50 h. at RT under 40 bars H_2. Filtration of the mixture on silica, followed by solvent evaporation afforded 5.74 g (99%) of ***S*-20**. ^{1}H-NMR (400 MHz; $CDCl_3$): δ = 1.80 (m, 2H-2); 2.52 (d, J=7Hz, 2H-4); 3.35 (d, J=3Hz, OH); 3.66 (m, 2H-1); 3.71 (s, OCH_3); 4.25 (m, H-3); 4.52 (s, C<u>H</u>$_2$-Ph); 7.27-7.37 (m, H-arom).
The enantiomer ***R*-20** was prepared by the same method using ***R*-21** instead of ***S*-21**.
The e.e. of **20** was determined by ^{1}H NMR, using (+) TAE as shift reagent. The methoxy peak at 3.71 ppm was shifted to 3.52 ppm (***R*-20**) or 3.53 ppm (***S*-20**).

(3*S*)-5-Dihydroxy-pentanoic acid methyl ester (*S*-16). I. **19** (630 mg, 2.42 mmol) and ***S*-21** (21.3 mg) were dissolved in dry MeOH (20 ml) under nitrogen. After replacement of the nitrogen by hydrogen the reaction mixture was stirred 22 h. at 30 °C under 40 bars H_2. Filtration of the mixture on silica followed by solvent evaporation afforded quantitatively crude ***S*-16**. The crude product was used in the next step. The e.e. was determined on the lactone **8** prepared without racemisation as shown above.
II. ***S*-20** (5 g, 21 mmol), 10% Pd/C (500 mg) and 5 drops Et_3N were stirred 20 h. in 50 ml THF under H_2 at RT. The reaction mixture was filtered on hyflo and chromatographed (EtOAc 100%) yielding 3.1 g (90%) of ***S*-16**.
The enantiomer ***R*-16** was prepared by these two methods, using ***R*-21** and ***R*-20**.

(4'*S*)-(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid (1"*R*)-phenyl-ethyl ester (23). Under argon, n-Buli (1.6M in hexane, 1.02 ml, 1.63 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (0.28 ml, 1.63 mmol) in dry THF (3 ml) at 0 °C. After 45 min, the mixture was cooled to -78 °C and a solution of (1'*R*)-phenylethyl acetate ***R*-7** (267.4 mg, 1.63 mmol) in dry THF (1 ml) was added slowly. After 45 min at -78 °C, a solution of ***S*-8** (63 mg, 0.54 mmol) in dry THF (0.7 ml) was added slowly. After 3 h. the reaction was quenched with NH_4Cl (satd. 1 ml) and allowed to warm to RT. The product was extracted with EtOAc and the organic layer was washed with H_2O, and dried over Na_2SO_4. Chromatography (EtOAc / hexane 4:1) yielded 107.6 mg (71%) of **23** as a 2.5 : 1 mixture of diastereomeric tautomers **23A** and **23C**. Diastereomer **23A**: ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.31 (ddd, J=12.5, 12.5, 2.5Hz, Hax-3'); 1.44 (d, J=5Hz, HO-4'); 1.50 (m, Hax-5'); 1.56 (m, Me); 1.90 (dddd, J=12, 4, 4, 2Hz, Heq-5'); 2.15 (ddd, J=12.5, 5, 2.5Hz, Heq-3'); 2.64 (d, J=15Hz, H-2); 2.72 (d, J=15Hz, H-2); 3.67 (m, Heq-6'); 3.89 (ddd, J=13, 11, 3Hz, Hax-6'); 4.15 (m, H-4'); 4.78 (d, J=2.5Hz, HO-2'); 5.96 (q, J=7.5Hz, C<u>H</u>-Ph); 7.28-7.39 (m, H-arom). IR: 1710 cm^{-1} (C=O); 3460 cm^{-1} (HO).

Diastereomer **23C**: ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.56 (m, Me); 1.68 (m, Heq-5', Hax-3'); 1.81 (m, Heq-5'); 1.99 (ddd, J=14, 2.5, 2.5Hz, Heq-3'); 2.57 (d, J=15Hz, H-2); 2.65 (d, J=15Hz, H-2); 3.67 (m, Heq-6'); 3.82 (d, J=10Hz, HO-4'); 4.15 (m, H-4'); 4.28 (ddd, J=12.5, 12.5, 3Hz, Hax-6'); 5.35 (d, J=2.5Hz, HO-2'); 5.95 (q, J=7.5Hz, C<u>H</u>-Ph); 7.28-7.39 (m, H-arom). IR: 1710 cm^{-1} (C=O); 3460 cm^{-1} (HO).

(4'*R*)-(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid (1"*R*)-phenyl-ethyl ester (22). Prepared analogously to **23**. Yield : 75%. Ratio **22A** : **22C** = 3 : 1.
Diastereomer **22A**: ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.31 (ddd, J=12.5, 12.5, 2.5Hz, Hax-3'); 1.45 (d, J=5Hz, HO-4'); 1.51 (m, Hax-5'); 1.57 (d, J=7.5Hz, Me); 1.91 (dddd, J=12, 4, 4, 2Hz, Heq-5'); 2.12 (ddd, J=12.5, 5, 2.5Hz, Heq-3'); 2.57 (d, J=15Hz, H-2); 2.71 (d, J=15Hz, H-2); 3.74 (ddd, J=11, 5, 2Hz, Heq-6'); 3.94 (ddd, J=12.5, 11, 3Hz, Hax-6'); 4.15 (m, H-4'); 4.89 (d, J=2.5Hz, HO-2'); 5.95 (q, J=7.5Hz, C<u>H</u>-Ph); 7.27-7.39 (m, H-arom). IR: 1715 cm^{-1} (C=O); 3460 cm^{-1} (HO).
Diastereomer **22C**: ^{1}HNMR (400 MHz; $CDCl_3$): δ = 1.57 (d, J=7.5Hz, Me); 1.68 (m, Heq-5', Hax-3'); 1.79 (m, Hax-5'); 2.01 (ddd, J=14, 2.5, 2.5Hz, Heq-3'); 2.57 (d, J=15Hz, H-2); 2.71 (d, J=15Hz, H-2); 3.60 (m, Heq-6'); 3.79 (d, J=10Hz, HO-4'); 4.10-4.26 (m, H-4', Hax-6'); 5.27 (d, J=2.5Hz, HO-2'); 5.96 (q, J=7.5Hz, C<u>H</u>-Ph); 7.27-7.39 (m, H-arom). IR: 1715 cm^{-1} (C=O); 3460 cm^{-1} (HO).

(4'*S*)-(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid (1"*S*)-phenyl-ethyl ester (2). Prepared according to **23**. Yield : 75%. Ratio **2A** : **2C** = 2.7 : 1. The ^{1}HNMR and IR of **2A** and **2C** are identical to those of **22A** and **22C** respectively.

(4'*R*)-(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid (1"*S*)-phenyl-ethyl ester (24). Prepared according to **23**. Yield : 44%. Ratio **24A** : **24C** = 2.7 : 1. The ^{1}HNMR and IR of **23A** and **23C** are identical to those of **23A** and **23C** respectively.

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