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# Synthesis of diastereo- and enantiomerically pure *anti*-3-methyl-1,4-pentanediol via lipase catalysed acylation

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**Abstract**—Racemic *trans*-4,5-dimethylhydrofuran-2(3H)-one was synthesised from 5-methyl-furan-2(3*H*)-one, (α-angelica lactone). The key reaction in the synthesis was the 1,4-conjugate addition of an organocuprate to 5-methylfuran-2(5*H*)-one (β-angelica lactone). Different types of organocuprates were tested with the highest *anti*:*syn* ratio of 99.4:0.6 being obtained by the use of a Gilman organocuprate reagent. The enantioselective acylation of racemic 3-methyl-pentan-1,4-diol, catalysed by a variety of lipases in organic media, was investigated. The highest enantioselectivity ($E$ >400) was obtained when Novozyme 435 was used as the catalyst at a water activity of $a_w \sim 0$. Thus, both enantiomers, (3*S*,4*R*)- and (3*R*,4*S*)-3-methyl-pentan-1,4-diol, were obtained in very high diastereomeric (>99% de) and enantiomeric purities (>99.8% and >97.4% ee, respectively).


## 1. Introduction

In the northern hemisphere some pine sawfly species are severe pests on pines.[1] The sex pheromones most of the pine sawfly species employ, are esters of *erythro*-(2*S*,3*S*,7*S*)- or *threo*-(2*S*,3*R*,7*R*)-3,7-dimethyl-2-pentadecanol (diprionol).[2,3] Lately, several structurally similar sex pheromone precursor alcohols have been identified in the females of other pine sawfly species.[4–6] In fact the structures identified to date are basically methyl-branched long-chain 3-methyl-2-alcohols. Our previous long-standing interest in the synthesis of structurally similar compounds led us to develop a synthetic route as shown in Scheme 1. Elaboration of D- or L-tartaric acid, after a few steps leads to *cis*-4,5-dimethylhydrofuran-2(3H)-one, a key intermediate in the synthesis of the *erythro* pine sawfly sex pheromone. However, the disadvantage of this method for the preparation of the other diastereomer of this pheromone, namely the *threo* compound, is evident in Scheme 1 in that the synthetic methodology requires at first the synthesis of the *erythro* compound, which subsequently leads to the *threo* compound.[7]

Our earlier work[7] prompted us to develop a new synthetic approach for the preparation of enantiomerically pure 3-methyl-pentane-1,4-diol, a potential precursor for the direct synthesis of *threo*-isomer of pine sawfly sex pheromones.

## 2. Results and discussion

Our previous experience from the synthetic studies of 3-methyl-2-pentanols (precursors of pine sawfly sex pheromones) and targeting racemic *anti*-3-methyl-pentane-1,4-diol led us to select α-angelica lactone **1** as the precursor. Thus, the commercially available and inexpensive lactone **1** was isomerised to β-angelica lactone **2** in the presence of triethylamine under reflux conditions (Scheme 2). After 40 min, the reaction mixture was cooled and compound **2** obtained in 50% isolated yield.[8]

However, gas chromatographic analysis showed that the thermodynamic equilibrium is achieved after a period of 17 h. Therefore, a better chemical yield of compound **2** can be obtained after prolonged reflux of the reaction mixture.

Our next target was to prepare stereochemically pure *trans*-4,5-dimethylhydrofuran-2(3H)-one **3**. The high

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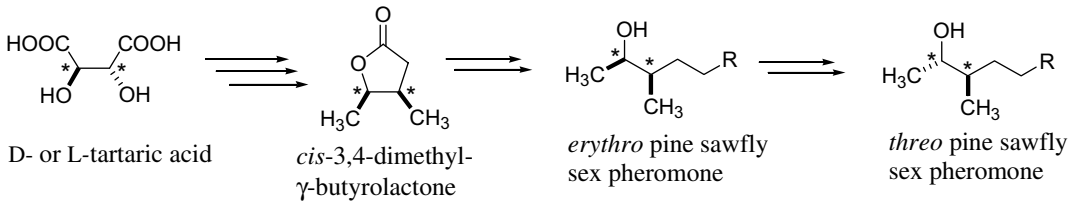
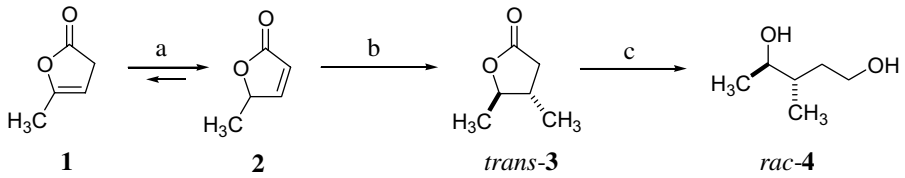



**Scheme 1.** Indirect synthesis of stereoisomerically pure *threo* pine sawfly sex pheromones through their diastereomer *erythro* compound.




**Scheme 2.** Synthesis of racemic *anti*-3-methyl-pentane-1,4-diol, *rac*-**4**. Reagents and conditions: (a) $Et_3N$, $\Delta_x$; (b) CuI, $CH_3Li$, $Et_2O$, −78 °C; (c) $LiAlH_4$, $Et_2O$.

*anti*:*syn* ratio for compound *trans*-**3** was a crucial structural demand. For this purpose the 1,4-conjugate addition of organocuprates to β-angelica lactone **2** was studied. These results are summarised in Table 1.

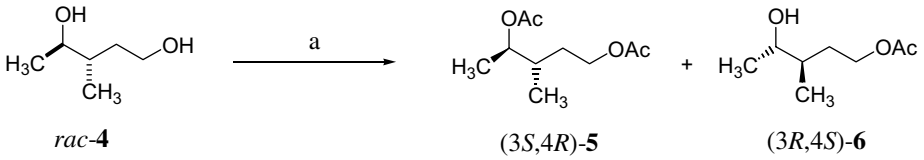
To achieve a high *anti*:*syn* ratio, the reaction of a sterically demanding mixed organocuprate was first screened. For this purpose, both reagents, $CH_3$(thienyl)CuLi and $CH_3$(phenyl)CuLi, were first tested (entries 1 and 2). These organocuprates, under the reaction conditions, did not react with substrate **2**. Next, we tried the cyano organocuprates taking into consideration that these cuprates,[9] at least in some cases, are more reactive than the corresponding simple organocuprates. It has been reported previously[9] that the cyanide ligand of a cyano organocuprate causes a build-up of negative charge in the complex and thus facilitates the alkyl group transfer. Herein, the reaction of the cyano cuprate $(CH_3)_2CuCNLi_2$ with **2** afforded a high *anti*:*syn* ratio of 99.1:0.9 (entry 3), however the product yield obtained was poor. Furthermore, the use of a mixed cyano cuprate of the formula $CH_3$(thienyl)$CuCNLi_2$ reverses the *anti*:*syn* ratio to 40:60 (entry 4). This interesting result was not within the range of this synthesis and thus not further investigated. To this end, we treated **2** with 2 equiv of a simple Gilman reagent $(CH_3)_2CuLi$ using slightly modified standard conditions to the ones used in the synthesis of the whisky lactone.[10] This reaction afforded an excellent stereoselectivity of an *anti*:*syn* ratio of 99.4:0.6, accompanied by a rather low 44% conversion (entry 5, Table 1). To improve the conversion, 1 equiv of trimethylsilyl chloride (TMSCl) was added to the previous reaction mixture. It is known that TMSCl enhances the reaction rate and the product yield of 1,4-conjugated organocuprate additions.[11–13] We also observed an improvement in the yield, but to our disappointment, the *anti*:*syn* ratio was decreased to a 76:24 ratio (entry 6). Finally, an increase in the amount of the organocuprate used $(CH_3)_2CuLi$ from 2 to 4 equiv[14] led to higher conversion (81%, entry 7, Table 1), accompanied by a slight decrease in the *anti*:*syn* selection of 97.4:2.6. The observed selectivity and conversion of this reaction, when taken together, exhibited the best case among the surveyed organocuprates and was used in the next step of the synthesis. Trace amounts (2.6%) of the diastereoisomer *cis*-3,4-dimethyl-γ-butyrolactone were easily removed by liquid chromatography (MPLC). Thus, under these experimental conditions, 1.12 g (48% yield) of the racemic lactone *trans*-**3** was isolated and fully characterised with an excellent diastereomeric and chemical purity. Reduction of *trans*-**3** with $LiAlH_4$ afforded the racemic 3-methylpentan-1,4-diol, *rac*-**4**, in near quantitative yield.

Our previous work[5,15] and that of others[16–18] have demonstrated an efficient lipase catalysed stereoselective

**Table 1.** Survey of 1,4-conjugate addition of organocuprates to β-angelica lactone **2**

| Entry | Organocuprate | Equivalents[a] | Conversion (%) | *anti*:*syn* |
|---|---|---|---|---|
| 1 | $CH_3$(thienyl)CuLi | 2 | None | — |
| 2 | $CH_3$(phenyl)CuLi | 2 | None | — |
| 3 | $(CH_3)_2CuCNLi_2$ | 2 | nd[b] | 99.1:0.9 |
| 4 | $CH_3$(thienyl)$CuCNLi_2$ | 2 | nd[b] | 40:60 |
| 5 | $(CH_3)_2CuLi$ | 2 | 44 | 99.4:0.6 |
| 6 | $(CH_3)_2CuLi$–TMSCl | 2:1 | ∼100 | 75.7:24.3 |
| 7 | $(CH_3)_2CuLi$ | 4 | 81 | 97.4:2.6 |

[a] Based on compound **2**.
[b] Not determined.




*rac*-**4** (3*S*,4*R*)-**5** (3*R*,4*S*)-**6**

**Scheme 3.** Lipase catalysed enantioselective acylation of racemic *anti*-3-methyl-1,4-pentandiol *rac*-**4**. Lipase, vinyl acetate, *t*-BuOMe with controlled $a_w$.

acylation of racemic secondary alcohols structurally similar to *rac*-**4**. Therefore the enantioselective resolution of *rac*-**4** was tested via an acylation reaction catalysed by lipase (Scheme 3). Vinyl acetate was used as the acyl donor in this enzymatic acylation reaction. The screening of a number of promising lipases for high enantiomeric preference is summarised in Table 2. Within a period of 1–40 h, all the lipases used in this study showed a strong preference for the acetylation of the primary hydroxyl group of the diol *rac*-**4**. The initial test was performed by the use of Amano PS at different initial water activities[19] $a_w$ (entries 1–4). At a higher $a_w$, entry 1, the reaction was very slow, probably due to the competing backward[20] hydrolysis of the produced ester. We[15] and others[21] have shown previously that small amounts of water in the reaction medium substantially increase the enzyme selectivity for secondary alcohols. When the $a_w$ was 0.12, entry 2, the reaction rate increased while the obtained *E*-value[22] was found as high as 140. Thus, we used dry conditions (4 Å molecular sieves were added to the reaction mixture), entry 3, to suppress further the undesired hydrolysis of the newly formed ester and increase the reaction rate. In fact, the reaction rate was doubled, although, the *E*-value decreased to 55.

Next we investigated the effect of two different immobilisations[24] of Amano PS lipase, namely the immobilisation on tyonite and diationite (entries 4 and 5, respectively). In these two cases, the reaction rate increased substantially and both gave high enantioselectivity (*E* >70). Lipase from *Pseudomonas fluorescens*, entry 6, gave a good *E*-value of 51 while SP 526, entry 7, gave a very low *E*-value of 9. To this end, Novozyme 435, entry 8, showed an excellent enantiomeric preference, resulting in a high enantioselectivity value of *E* >400. This lipase also acylated the primary hydroxyl group of *rac*-**4** at the highest rate (1.5 h) among the lipases surveyed in this work. At high conversion (*c* = 80%), entry 9, the reaction afforded the monoacetate enantiomer **6**, in good enantiomeric purity (>97% ee). In this case, the enantiomeric purity of the remaining substrate **6** was expected to be >99%. It is interesting to note here that in the presence of small quantities of water, the Amano PS lipase is shown to preferably catalyse the hydrolysis of the produced ester instead of acylating the remaining substrate.[20] This competing backwards reaction decreases the enantiomeric excess of the remaining substrate, in this case monoacetate **6**. To minimise this effect, the reaction must be interrupted at conversions lower than 60%. This significant observation[20] enables us to produce both enantiomers of diol-**4** in their enantiomerically pure forms.

### 2.1. Confirmation of the absolute configuration

To establish the absolute configuration and to confirm which of the enantiomers, (3*R*,4*S*) or (3*S*,4*R*), of diol-**4** reacts faster in the lipase catalysed acylation sequence, diester 3-methyl-pentane-1,4-diylacetate **5** was reduced with $LiAlH_4$ to the corresponding diol, followed by monosilylation[25] of the primary hydroxyl group to give compound **7** (Scheme 4). The specific rotation of $[\alpha]_D^{20} = -5.8$ (*c* 1.88, $CHCl_3$) was identical (within experimental error) to that of $[\alpha]_D^{20} = +6$ (*c* 0.11, $CHCl_3$), which had previously been reported[25] for the (3*R*,4*S*)-**7** enantiomer, with an opposite sign of specific rotation. We therefore conclude that the (3*S*,4*R*)-**4** enantiomer reacts faster to give diacetate (3*S*,4*R*)-**5**, leaving (3*R*,4*S*)-**4** as the remaining substrate. This result is also in

**Table 2.** Lipase catalysed acylation of racemic *anti*-3-methyl-1,4-pentandiol, *rac*-**4**[f]

| Entry | Enzyme | $a_w$ | Time (h) | Conversion[a] (%) | *E*[b] | Monoacetate ee[c] (%) | Diacetate ee[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | Amano PS | 0.32 | 296 | 7 | nc[e] | 55 | nd[d] |
| 2 | Amano PS | 0.12 | 269 | 42 | 140 | 71 | 97 |
| 3 | Amano PS | ~0 | 120 | 42 | 55 | 67 | 93 |
| 4 | Amano PS on tyonite | ~0 | 17 | 44 | 74 | 76 | 94 |
| 5 | Amano PS on diationite | ~0 | 17 | 44 | 72 | 74 | 94 |
| 6 | Amano PS fluorescens | ~0 | 67 | 43 | 51 | 71 | 92 |
| 7 | SP 526 | ~0 | 217 | 47 | 9 | 59 | 66 |
| 8 | Novozyme 435 | ~0 | 3.5 | 42 | >400 | 71 | >99 |
| 9 | Novozyme 435 | ~0 | 72 | 80 | nc[e] | >97 | 80 |

[a] Calculated according to the equation $c = ee_s/(ee_s + ee_p)$.[23]

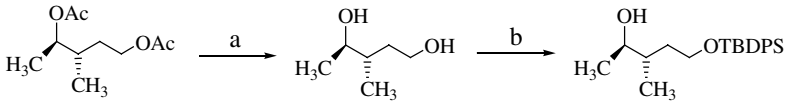
[b] Calculated according to the equation $E = \ln[(1 - ee_s)/(1 + ee_s/ee_p)]/\ln[(1 + ee_s)/(1 + ee_s/ee_p)]$.[22]

[c] Measured by GC on a β-dex 120 chiral column.

[d] Not determined.

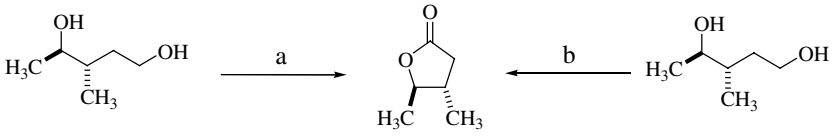
[e] Not calculated.

[f] General procedure: The substrate dissolved in *t*-BuOMe was stored for 24 h in a vessel containing LiCl satd solution or MgCl satd solution or 4 Å molecular sieves were added into the reaction vessel, depending on the water desired activity. The enzyme was added and the reaction was started by addition of vinyl acetate.




(3*S*,4*R*)-**5** (3*S*,4*R*)-**4** (3*S*,4*R*)-**7**

**Scheme 4.** Elaboration of the diacetate (3*S*,4*R*)-**5** to establish the absolute configuration. Reagents: (a) $LiAlH_4$, $Et_2O$; (b) TBDPSCl, imidazole, DMF.




*rac*-**4** *trans*-**3** *rac*-**4**

**Scheme 5.** The synthesis of *cis*- or *trans*-4,5-dimethylhydrofuran-2(3H)-one. Reagents: (a) $Ag_2CO_3$/Celite; (b) HLADH, $NAD^+$.

agreement with the empirical rules, recently published, for the stereoselectivity of a lipase towards secondary alcohols containing two neighbouring stereocentres.[26]

Furthermore, we investigated an alternative route to obtain both enantiomers of lactone *trans*-**3**. Previous work has shown that of a variety of lactones can be formed stereoselectively through HLADH (horse liver alcohol dehydrogenase) catalysed oxidation of diols[27,28] (Scheme 5). Thus, the racemic *anti*-3-methyl-1,4-pentandiol *rac*-**4** was enzymatically oxidised by HLADH/$NAD^+$ in a 100 mM glycine/NaOH buffer at pH 9. After 3 h the conversion reached 44 ± 5% (according to NMR and GC data) and, after termination of the reaction, gave the lactone, *trans*-**3**, which was analysed on a chiral GC-column. Unfortunately, both enantiomers were formed in nearly equal amounts, meaning that this method was not useful here. However this reaction proved to be a good alternative route for ring closure of diol *rac*-**4** to lactone *trans*-**3** when left to completion compared to the $Ag_2CO_3$/Celite method.

## 3. Conclusion

In conclusion, we have developed a new method for the synthesis of both enantiomers of *anti*-3-methyl-1,4-pentandiol in very high diastereomeric and enantiomeric purities. These enantiomerically pure building blocks, after short chemical elaboration, can lead to the direct synthesis of the pure *threo*-isomers of the pine sawfly sex pheromones.

## 4. Experimental

Commercially available chemicals were used without further purification unless otherwise stated. All dried solvents were stored over molecular sieves (4 Å) under argon. $Et_2O$ was dried by distillation from $LiAlH_4$. Vinyl acetate and *t*-BuOMe were dried with molecular sieves (3 Å) before use. The purity of 5-methylfuran-2(3*H*)one (α-Angelica lactone), **1**, was determined by $^1H$ NMR before use. Amano PS, Amano PS on diationite and Amano PS on tyonite-200-P were obtained from Amano Pharmaceutical Co. Ltd. Novozyme 435 and SP 526 were obtained from Novo Nordisk and Amano PS fluorescens from Biochemica Fluka. Nuclear magnetic resonance spectra were recorded on a Brucker DMX 250 spectrometer with $CDCl_3$ as solvent and TMS as internal reference. Optical rotations were measured using a Perkin–Elmer 241. Mass spectra were taken on a Saturn 2000 instrument coupled to a Varian 3800 GC instrument. Preparative liquid chromatography (LC) was performed on straight phase silica gel (Merck 60, 230–400 Mesh) employing a gradient of eluent.

### 4.1. 5-Methyl-2(5*H*)-furanone (β-angelica lactone), 2

α-Angelica lactone (70 g, 0.714 mol) was added to 0.625 mL triethylamine. The mixture was heated under reflux and after 40 min the mixture was allowed to reach room temperature. Upon distillation, 34.7 g (49.5%) of β-angelica lactone bp 82 °C/10 mmHg was obtained. $^1H$, $^{13}C$ NMR and MS spectral data were similar to published data.[29,30] IR spectral data were also similar to published data.[31,32]

### 4.2. *trans*-4,5-Dimethylhydrofuran-2(3*H*)-one, 3

General procedure exemplified with the cuprate $(CH_3)_2CuLi$: A mixture of CuI (2 or 4 equiv) in distilled dry $Et_2O$ (13 vol) was cooled to 0 °C and $CH_3Li$ (4 or 8 equiv) was added under argon. After 40 min, the mixture was cooled to −78 °C and β-angelica lactone (1 equiv in dry $Et_2O$) was added dropwise. TMSCl (1 equiv) was then slowly added in some reactions. The reaction was stirred at −78 °C for 1–2 days. Saturated ammonium chloride was slowly added and the reaction temperature left to reach room temperature. After separation of the organic phase, the water phase was continuously extracted with $Et_2O$ followed by $CH_2Cl_2$ (3 vol × 20). The combined organic phase was washed with saturated NaCl solution (6 vol × 2), dried over $MgSO_4$ and the solvent evaporated. After LC, product **3** was obtained chemically pure in >99% de. $^1H$, $^{13}C$ NMR and MS spectral data were similar to published data.[33,35] Also IR spectral data were identical to published data.[34]

### 4.3. Racemic-3-methyl-1,4-pentanediol, *rac*-4

An excess of $LiAlH_4$ was added under argon to dry $Et_2O$ and lactone **3** dissolved in $Et_2O$ was added dropwise. After 0.5 h, the excess of hydride was destroyed by a small amount of water. LC (10–100% ethyl acetate in cyclohexane), evaporation of the solvent and bulb to bulb distillation (75–80 °C/2.8 mbar, lit.[36] 134 °C/20 Torr) gave 1.08 g of diol **4** (yield 89%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.93 (d, 3H, $J = 6.8$); 1.19 (d, 3H, $J = 6.3$); 1.67 (m, 3H); 2.04 (s, 2H, OH); 3.66 (m, 2H); 3.77 (m, 1H). $^{13}$C NMR (250 MHz): 16.4, 20.5, 36.1, 38.1, 60.3, 71.7. IR: 3356, 2966, 2931, 1065, 909, 734. Mass spectrum, *m*/*z* (relative intensity): 119 ($M^+$, 2%), 101 (11), 85 (82), 67 (13), 56 (100), 41 (79).

### 4.4. Enantioselective acylation of racemic *trans*-3-methyl-1,4-pentanediol, 4. General procedure

To control the water activity, the substrate was dissolved in *t*-BuOMe and stored for 24 h in a vessel containing a saturated solution of LiCl. Pure solvent (*t*-BuOMe) and vinyl acetate were stored in the same way but in separate vessels. This procedure gives an initial water activity of 0.11–0.12. To achieve an initial water activity of 0.32 a saturated solution of $MgCl_2$ was used and dry conditions ($a_w \sim 0$) obtained by adding 4 Å molecular sieves to the reaction mixture under argon.

Substrate **4** (70 mg, 0.59 mmol), the enzyme (Table 2) and *t*-BuOMe (1 mL) were added to the reaction bottle. The reaction was started under magnetic stirring by addition of vinyl acetate (0.31 g, 3.7 mmol). The bottle was kept closed with a septum during the reaction. Stirring was kept at 500 rpm. The conversion was followed on GC and the reaction was stopped at ~40% conversion. The reaction was filtered through a Pasteur pipette containing cotton wool and absorbed on 3–4 g silica gel followed by LC (10–100% ethyl acetate in cyclohexane). The mono- and diesters (3*R*,4*S*)-**6** and (3*S*,4*R*)-**5**, respectively, were obtained chemically pure (>99%) and completely separated from each other according to GC.

The conversion of diol *rac*-**4** to the mono- and diacetates, **6** and **5** respectively, were measured on GC (VA-1, fused silica capillary column 30 m × 0.25 mm, $d_f = 0.25$ μm, carrier gas He, pressure 13 psi, 70 °C for 4 min then 8 °C/min up to 300 °C). Retention time (min) for 3-methylpentane-1,4-diol *rac*-**4**: 9.45, 3-methylpentane-1,4-diyl acetate: 12.37, 4-hydroxy-3-methylpentyl acetate: 14.78. The actual conversions were calculated from the ee values obtained (Table 2).

The absolute configuration of the faster reacting enantiomer of *rac*-**4** was determined on the product, 3-methylpentane-1,4-diyl acetate, obtained from an enzymatic reaction using Novozyme 435 according to the general procedure at 33% conversion. The obtained diacetate was reduced (as above for lactone **3**) to the corresponding diol, which was purified by LC (10–100% ethyl acetate in cyclohexane) and distilled bulb to bulb. The pure diol was then mono silylated with *tert*-butyldiphenylsilyl chloride according to a published method[25] and the specific rotation of this product $\{[\alpha]_D^{20} = -5.8$ ($c$ 1.88, $CHCl_3$)$\}$ found to be of the opposite sign and of the same amplitude as the literature value for a stereoisomer with a (3*R*,4*S*)-configuration $\{[\alpha]_D^{20} = +6$ ($c$ 0.11, $CHCl_3$)$\}$.[25]

The enantiomeric excess (ee) of the mono- and diacetates, (3*R*,4*S*)-**6** and (3*S*,4*R*)-**5** respectively, were determined on GC (β-dex 120, β-cyclodextrin capillary column, premethylated β-CD, 30 m × 0.250 mm, carrier gas He, pressure 12 psi, 80 °C for 2 min then 1 °C/min up to 140 °C). Retention time (min) for the enantiomers of 3-methylpentane-1,4-diyl acetate **5**: 45.49; 45.80 and for 4-hydroxy-3-methylpentyl acetate **6**: 44.85; 46.47.

### 4.5. (3*S*,4*R*)-3-Methylpentane-1,4-diyl diacetate, (3*S*,4*R*)-5

99.8% ee (GC, β-dex 120). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.86 (d, 3H, $J = 6.8$ Hz); 1.10 (d, 3H, $J = 6.4$ Hz); 1.34 (m, 1H); 1.71 (m, 2H); 1.97 (S, 3H); 1.98 (s, 3H); 4.05 (m, 2H); 4.73 (m, 1H). $^{13}$C NMR (250 MHz): $\delta$ 14.6, 16.2, 20.8, 21.1, 31.0, 34.3, 62.4, 73.8, 170.4, 170.9. IR: 2961, 2932, 1740, 1371, 1244, 1042. Mass spectrum, *m*/*e* (relative intensity): 202 ($M^+$, 1%), 143 (9), 115 (6), 99 (14), 83 (35), 72 (17), 56 (20), 43 (100). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0. Found: C, 59.4; H, 9.1.

### 4.6. (3*R*,4*S*)-4-Hydroxy-3-methylpentyl acetate, (3*R*,4*S*)-6

97.4% ee (GC, β-dex 120). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.92 (d, 3H, $J = 6.7$ Hz); 1.16 (d, 3H, $J = 6.3$ Hz); 1.45 (m, 1H); 1.61 (m, 1H); 1.86 (m, 1H); 1.97 (s, 1H, OH); 2.05 (s, 3H); 3.66 (m, 1H); 4.12 (m, 2H). $^{13}$C NMR (250 MHz): $\delta$ 14.8, 19.7, 21.0, 31.2, 37.0, 63.0, 71.4, 171.3. IR: 3422, 2970, 2932, 1740, 1457, 1368, 1248, 1098, 1051. Mass spectrum, *m*/*e* (relative intensity): 161 ($M^+$, 6%), 143 (1), 115 (6), 101 (69), 83 (92), 61 (16), 56 (68), 43 (100). Anal. Calcd for $C_8H_{16}O_3$: C, 60.0; H, 10.1. Found: C, 57.2; H, 9.9.

### 4.7. (3*S*,4*R*)-3-Methyl-1,4-pentanediol

Reduction (as above for lactone **3**) of the diacetate (3*S*,4*R*)-**5** (from entry 8 Table 2) gave the title compound nearly quantitatively and with >99.8% ee (GC, β-dex 120). $[\alpha]_D^{25} = -15.2 \pm 0.7$ ($c$ 0.67, $CHCl_3$).

### 4.8. (3*R*,4*S*)-3-Methyl-1,4-pentanediol

Reduction (as above for lactone **3**) of the mono acetate (3*R*,4*S*)-**6** (from entry 9 Table 2) gave the title compound nearly quantitatively and with >97.4% ee (GC, β-dex 120). $[\alpha]_D^{25} + 16.2 \pm 0.5$ ($c$ 1.19, $CHCl_3$).

### 4.9. General methods for the formation of *trans*-4,5-dimethylhydrofuran-2(3*H*)-one

*Method 1*: Following a known procedure used for other lactones,[28] the *anti* diol **4** (21 mg, 0.18 mmol) was added to a solution of $NAD^+$ (240 mg, 0,36 mmol) in

a glycine/NaOH buffer at pH 9. The reaction was started by the addition of HLADH (Horse liver alcohol dehydrogenase, 3 mg). The pH was periodically checked and adjusted by the addition of 15% NaOH. After 2–3 h, the reaction had reached 40–45% conversion and was then stopped by the addition of an excess of brine followed by heating to 40 °C. After continuous extraction of the water phase with diethyl ether, the produced lactone was obtained in high yield.

*Method 2*:[37] Formation of $Ag_2CO_3$–Celite: Celite (6.0 g) and silver(I)nitrate (6.0 g) in water (40 mL) was stirred and $Na_2CO_3{\cdot}10H_20$ (6.0 g) in water (60 mL) added dropwise over a period of 0.5 h. The reaction vessel was kept in the dark during this time. The solid was washed with water to give the $Ag_2CO_3$–Celite, which was then dried in vacuum for 4 h. Diol **4** (9.9 mg, 0.08 mmol) and $Ag_2CO_3$–Celite (0.96 g, 1.5 mmol $Ag_2CO_3$) in $CHCl_3$ (3.4 mL) were heated under reflux for 5 h, after which filtration and evaporation of the solvent gave the *trans*-lactone in low yield.[38]

The enantiomeric excess (ee) of the *trans*-4,5-dimethylhydrofuran-2(3*H*)-one was detected on GC (HP-Chiral, β-cyclodextrin-containing capillary column, 20% premethylated, 30 m × 0.250 mm, carrier gas He, pressure 15 psi, oven temp 140°). Retention time (min) for the enantiomers of *trans*-4,5-dimethylhydrofuran-2(3H)-one: 13.6 (4*S*,5*R*); 15.0 (4*R*,5*S*).

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