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Isolation of Racemic 2,4-Pentanediol and 2,5-Hexanediol from Commercial Mixtures of Racemic and Meso Isomers by way of Cyclic Sulfites.

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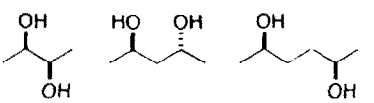
Abstract. Enantiomerically pure diols with C_2 symmetry such as 2,3-butanediol, **1**, 2,4-pentanediol, **2**, and 2,5-hexanediol, **3**, are useful chiral auxiliaries, but they are expensive because chemists lack good synthetic routes that eliminate both the meso isomer and one enantiomer. Enzymic resolutions efficiently separate the enantiomer, but do not remove the meso isomer. To simplify enzymic resolutions of **2** and **3**, we developed simple methods to isolate the racemic isomer from commercial mixtures of racemic and meso isomers. For **2**, the meso isomer selectively reacted with $SOCl_2$ to give a cyclic sulfite that was removed by column chromatography to leave (±)-**2**, 92% de, 1.4 g, 55% yield. For **3**, both meso and racemic isomers reacted with $SOCl_2$ to give cyclic sulfites, but the sulfite derived from the meso isomer rearranged to *trans*-2,5-dimethyltetrahydrofuran under acidic conditions. Hydrolysis of the remaining sulfite gave (±)-**3**, 84% de, 1.1 g, 37% yield. Resolution of (±)-**2** and (±)-**3** using lipase from *Pseudomonas cepacia* yielded (2R,4R)-**2**-diacetate, 78% ee, >97% de, 40% of theory and (2R,5R)-**3**-diacetate, 94% ee, >97% de, 47% of theory. Previously reported acetylations of **2** and **3** by lipase from *Candida antarctica* (CAL) or by lipase from *Pseudomonas* sp. (Amano lipase AK) are more enantioselective and thus, the best route to enantiomerically and diastereomerically pure **2** and **3** is removal of the meso isomer by way of cyclic sulfites followed by resolution with CAL or Amano lipase AK

Organic chemists use enantiomerically-pure diols, especially diols with C_2-symmetry such as **1-3**, as chiral auxiliaries.[1] Symmetrical diols are believed to be more enantioselective than unsymmetrical diols because symmetry eliminates competing transition states that might favor the other enantiomer.[2] Examples where chemists used **1** or **2** as chiral auxiliaries include: Lewis acid-catalyzed opening of acetals[1,3,4] β-elimination of acetals,[4] cyclopropanation,[5] Diels-Alder reactions,[6] and Grignard reactions.[7] Diols **1-3** have also been converted to other chiral auxiliaries such as diethers,[8] bis(phospholanes),[9] and diamines.[10]

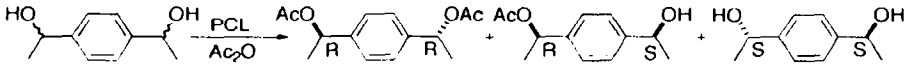


(2R,4R)-**1** (2R,4R)-**2** (2R,5R)-**3**

Synthetically useful routes to enantiomerically and diastereomerically pure **1-3** avoid not only the other enantiomer, but also the meso isomer. For example, asymmetric hydrogenation of 2,4-pentanedione using Ru-BINAP catalyst gave (R,R)-**2** contaminated with only 1% of the meso isomer, but hydrogenation of the 2,3-butanedione was not useful because it gave (S,S)-**1** contaminated with 26% of the meso isomer.[11] Current routes to both enantiomerically and diastereomerically pure diols **1-3** include: fermentation of sugars to give (R,R)-**1**,[12,13] chemical synthesis of **1** from diethyl tartrate in five steps (34% overall yield),[14] microbial reduction of the 2,4-pentanedione or 2,5-hexanedione to give (S,S)-**2**[15] or (S,S)-**3**[16] in >95% ee, selective alkylation of derivatives of 1,3-propandiol or 1,4-butanediol to give **2** or **3**,[17] and classical resolution of **2** or **3** by fractional crystallization of diastereomeric derivatives.[18] Another approach to **3** was asymmetric hydrogenation of β-ketobutyrate followed by dimerization of the resulting β-hydroxybutyric acid by electrochemical oxidation (40-50% overall yield).[9b]

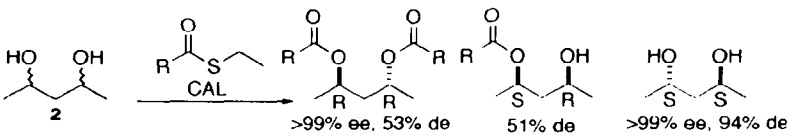
When lipase-catalyzed reactions are highly enantioselective, they can separate all three stereoisomers in a mixture of meso and racemic isomers. For example, Wallace *et al.* separated the three stereoisomers of α,α'-dimethyl-1,4-benzenedimethanol using an enantioselective acetylation catalyzed by lipase from *Pseudomonas*

cepacia (PCL), eq 1.[20] This lipase favored the (R)-stereocenter, so the (R,R)-isomer was diacetylated, the (R,S)-isomer was monoacetylated, and the (S,S)-isomer did not react.



(1)

Unfortunately, lipases are usually not sufficiently enantioselective to separate the three stereoisomers in diols **1-3** in a single step. Only for **3** could enantiomerically and almost diastereomerically pure material be prepared in a single resolution starting from the mixture of racemic and meso isomers: (S,S)-**3**, >99% ee, 97% de; diester of (R,R)-**3**, >99% ee, 98% de.[21] In most cases, lipases efficiently separate the enantiomers from each other, but not from the meso isomer. For example, Mattson *et al.* reported the resolution of a commercial mixture of *meso* and (±)-**2** using lipase from *Candida antarctica* (CAL), eq 2.[21] This reaction separated the enantiomers from each



(2)

other, but did not separate the enantiomers from the meso isomer. Separation of enantiomers is a sequential kinetic resolution where the two acylation steps reinforce each other and increase the overall enantioselectivity.[21,22] Separation of the meso isomer relies on a single step and is therefore less selective.

A simple solution to this meso problem is to remove the meso isomer before resolution. For example, we resolved the pure racemate of **1** (available from Aldrich Chemical Co.) using a PCL-catalyzed acetylation yielding both enantiomers in ≥96% ee. Unfortunately, pure racemates of **2** and **3** are not commercially available. Guo *et al.* isolated the racemate of **2** by crystallization from ether and resolved it with lipase from *Pseudomonas* sp. (Amano lipase AK) yielding the diester of (R,R)-**2** in >98% ee.[22-24] In our hands, however, (±)-**2** did not crystallize from commercial mixtures of **2**.

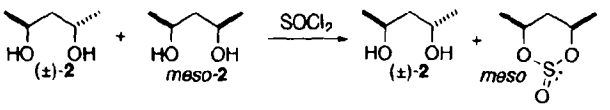
In this paper we report a simple isolation of (±)-**2** and (±)-**3** from commercial mixtures of the meso and racemic isomers by reaction with $SOCl_2$ to form cyclic sulfites. For **2**, the cyclic sulfite derived from the meso isomer formed more rapidly leaving unreacted (±)-**2** which was separated by a short silica gel column: 92% de, 55% of theory. For **3**, both isomers formed a cyclic sulfite, but the cyclic sulfite derived from the meso isomer decomposed more rapidly. The remaining sulfite was recovered and hydrolyzed yielding (±)-**3**, 84% de, 37% of theory. To resolve (±)-**2** and (±)-**3**, we used a PCL-catalyzed acetylation, but this reaction was not as enantioselective as the previously reported resolutions with CAL or lipase AK.

RESULTS

Isolation of (±)-2,4-pentanediol, (±)-2, from a commercial mixture of meso and racemic isomers

Although *meso*-**2** and (±)-**2** separated on TLC (silica gel, R_f 0.38, meso; 0.24, (±), ethyl ether), this separation was not satisfactory on a preparative scale. Only the fast-moving *meso*-**2** was isolated in pure form, because of tailing the racemic isomer was contaminated with meso.

More useful on a preparative scale was a selective reaction of *meso*-**2** with thionyl chloride. In the absence of base or catalyst, *meso*-**2** reacted with thionyl chloride faster than (±)-**2**, eq 3. The absence of base was important. In pyridine-dioxane we found that both diastereomers reacted at the same rate in agreement with a previous report.[25] We used this reaction to separate 5 g of a commercial mixture of meso and racemic isomers. To recover the diol, the reaction mixture was filtered through silica gel eluting the cyclic sulfite with hexane-ether 1:1, followed by ethyl acetate to elute (±)-**2**: 1.4 g, 27.5% yield; 55% of theory; 92% de by GC. As expected, the isolated

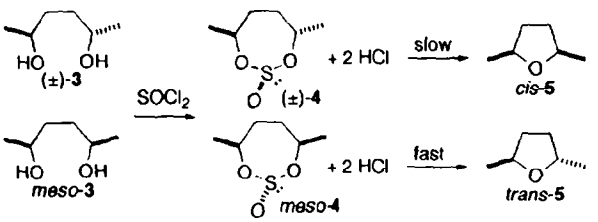


(3)

sulfite was enriched in sulfite derived from *meso*-**2**, 38% de.

Isolation of (±)-2,4-hexanediol, (±)-3, from a commercial mixture of meso and racemic isomers

Meso- and (±)-**3** have not been separated previously.[26] We first tried to separate the diastereomers by the same selective reaction with thionyl chloride that was successful for **2**. However, both diastereomers of **3** reacted rapidly to give cyclic sulfites, eq 4. Three sulfite stereoisomers were expected (racemic and two meso isomers),



(4)

but the TLC showed only two spots (R_f = 0.21, R_f = 0.12, toluene). We identified the slow-moving sulfite as the racemic isomer and the fast moving sulfite as one of the meso isomers. The slow-moving sulfite showed separate resonance for the methine protons (5.14, 4.32 ppm), consistent with the nonequivalent methine protons in (±)-**4**. Other cyclic sulfites also show large differences in chemical shifts for the axial and equatorial methine protons.[27] To confirm this assignment, this sulfite was hydrolyzed (1 N NaOH, 90°C, 5 min), a reaction known to proceed with retention of configuration at carbon,[28] to give (±)-**3**, >97% by GC. The fast moving sulfite showed a single resonance for the methine protons, consistent with a plane of symmetry in this compound. Based on the position of this resonance (4.99 ppm), we tentatively assigned the orientation of the methyl and oxygen as anti.[29]

Over a period of days, the meso sulfite, *meso*-**4**, rearranged to *trans*-(±)-2,5-dimethyltetrahydrofuran (methine H: 4.13 ppm; 47% yield), *trans*-**5**, while the racemic sulfite, (±)-**4**, rearranged more slowly to *cis*-2,5-dimethyltetrahydrofuran (methine H: 3.93 ppm; 7.3% yield), *cis*-**5**. Monitoring these resonances relative to an internal standard showed that the *meso*-**4** did not epimerize to (±)-**4**. The tetrahydrofurans were distilled from the reaction mixture and their structures were confirmed by comparison of the ^{1}H- and ^{13}C-NMR spectra and GC/MS data with an authentic sample of **5** containing both isomers. Further, gas chromatography using a chiral stationary phase (Chiraldex G-TA) separated (±)-**5** into its two enantiomers, while *meso*-**5** eluted as a single peak.

This selective rearrangement of the sulfites was used to isolate (±)-**3** from a commercial mixture of (±)-**3** and *meso*-**3**. The commercial mixture (5.9 g) was reacted with thionyl chloride to prepare the sulfites and allowed to stir for 4 d at room temperature to allow *meso*-**4** to decompose. This mixture was treated with aqueous base to hydrolyze the remaining sulfite and (±)-**3** was isolated by column chromatography: 1.1 g, 84% de, 19% yield, 37% of theory.

Sequential Kinetic Resolution of (±)-2 and (±)-3

We screened three lipases as catalysts for the enantioselective acetylation of (±)-**2** and (±)-**3** with vinyl acetate: lipase from *Pseudomonas cepacia* (PCL), porcine pancreatic lipase (PPL), and lipase from *Candida rugosa* (CRL), eq 2 above, Table I. For each reaction, the relative yields and the enantiomeric purities of the diol, monoacetate and diacetate were monitored simultaneously by gas chromatography using a chiral stationary phase (Chiraldex G-TA).

To compare single step kinetic resolutions, researchers compare the enantioselectivities of the reactions as

Table I. Sequential Kinetic Resolution of (±)-**2** and (±)-**3** by Lipase-Catalyzed Acetylation with Vinyl Acetate.[a]

				remaining diol		monoacetate		diacetate	
substrate	lipase[b]	conv[c] (%)	time (d)	yield (%)	ee[d] (%)	yield (%)	ee[d] (%)	yield (%)	ee[d] (%)
(±)-**2**	PCL	60.0	10	0	nd[e]	79.9	14.4 S	20.1	78.2 R
(±)-**2**	PPL	36.2	15	33.3	62.5 S	61.0	52.9 R	5.7	78.5 R
(±)-**2**	CRL	33.8	15	33.9	37.5 R	64.6	61.0 S	1.5	0
(±)-**3**	PCL	51.5	9	20.6	72.5 S	55 8	1.3 S	23.6	93.9 R
(±)-**3**	PPL	36.7	8	36.6	27.3 S	53.4	0	10.0	92.8 R
(±)-**3**	CRL	20.6	8	60.1	49.1 R	38.6	80.0 S	1.3	47.4 S

[a]Lipase (30 - 50 mg) was suspended in a solution of diol (26 - 100 mg) in vinyl acetate (1 mL) and stirred at room temperature. Amounts and enantiomeric purities were measured by gas chromatography. Absolute configurations were determined by comparison of optical rotations with literature values, see Experimental Section. [b]PCL = lipase from *Pseudomonas cepacia* (Amano lipase PS), CRL = lipase from *Candida rugosa* (Sigma, previous name was *C. cylindracea*); PPL = porcine pancreatic lipase (Sigma). [c]Overall percent conversion = percent yield of monoacetate/2 + percent yield of diacetate. [d]ee = enantiomeric excess. [e]nd = not determined.

Table 2. Calculated Enantioselectivities and Relative Rate Constants for the Two Steps in a Lipase-Catalyzed Acetylation of (±)-**2** and (±)-**3**.[a]

substrate	lipase	E_1	E_2	S	$E_{T(max)}$
(±)-**2**	PCL	1.7	8.0	6.9	7.3
(±)-**2**	PPL	5.1	2.0	11	5.6
(±)-**2**	CRL	3.9[b]	4.8	16	1.1
(±)-**3**	PCL	3.1	19	4.3	30
(±)-**3**	PPL	1.7	22	3.8	19
(±)-**3**	CRL	13.4[b]	3.7	5.9	2.3[b]

[a]E_1 = enantioselectivity for acetylation of diol, E_2 = enantioselectivity for acetylation of monoacetate, S measures the relative rate constants of the two steps. The first step is faster when S > 1. These values were calculated by fitting the data in Table I and other data at lower conversions to the equations for sequential kinetic resolutions in references 21 and 22. Unless otherwise noted the lipases favored the (R)-enantiomer. The maximum overall enantioselectivity, $E_{T(max)}$, occurs when S = 1, but significant reinforcement of the two steps occurs whenever 10 > S > 0.1. [b]Reaction favors the S enantiomer.

measured by the enantiomeric ratio, E.[30] To compare the overall enantioselectivity of sequential kinetic resolutions, researchers must calculate three quantities: E_1, E_2, and S. The variables E_1 and E_2 represent the enantioselectivities of the first and second steps, respectively, while S represents the specificity of the enzyme for the first and second substrate. S measures the relative rate constants of the two steps.[31] We calculated E_1, E_2, and S from the data in Table 1 by iteration using the equations of sequential resolutions,[21,22] Table 2.

The most enantioselective enzyme, PCL, showed only moderate enantioselectivity toward the (R,R)-enantiomers of **2** and **3**. The maximum overall enantioselectivity for the two steps was 7.3 for **2** and 30 for **3**, but the actual overall enantioselectivity is a little less than this maximum. The maximum reinforcement of the enantioselectivity of the two steps occurs when S = 1, but substantial reinforcement occurs whenever the rates are within a factor of ten (10 > S > 0.1). For the resolution of **2** and **3** with PCL, S was 6.9 and 4.3, respectively, so the two steps reinforce each other, but somewhat less than the maximum amount. Using PCL as the catalyst for resolution, we obtained (R,R)-**2**-diacetate in 78% ee, >97% de, and (R,R)-**3**-diacetate in 94% ee, >97% de. This

resolution also removed the small amount of meso isomer. Preliminary results suggest that the enantioselectivity is higher when vinyl butyrate is the acylating reagent.

While this work was in progress, Mattson *et al*[20] reported that lipase from *Candida antarctica* (CAL) is a highly enantioselective catalyst for the resolution of (±)-**2** and (±)-**3**. They reported isolated yields, rather than the actual composition of the reaction mixture, so we could not calculate the enantioselectivities and relative rate constants for the two steps from their data. Nevertheless, it is clear that CAL is much more enantioselective than PCL. Amano lipase AK also shows higher enantioselectivity toward (±)-2.[22,24]

Thus, the best route to enantiomerically and diastereomerically pure **2** is to remove the meso isomer by way of the sulfite ester and then to resolve the racemate with CAL or Amano lipase AK. Enantiomerically-pure and almost diastereomerically-pure **3** can be prepared by direct resolution of commercial samples of **3** with CAL. For higher diastereomeric purity, we suggest that before resolution the meso diastereomer be removed by the sulfite method described in this paper.

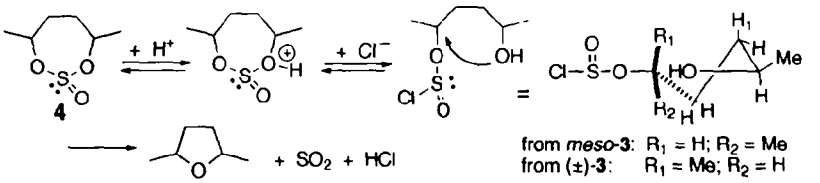
DISCUSSION

We described a way to enrich a mixture of *meso*- and (±)-**2** in the racemic diastereomer by selectively converting *meso*-**2** to its sulfite ester using thionyl chloride. We find this method simpler and faster than previously reported methods to separate the diastereomers, including crystallization at low temperature[22,32] and fractional distillation of the sulfite esters.[33]

The meso diastereomer of **2** reacts faster than (±)-**2** with thionyl chloride probably because the resulting sulfite is more stable. The cyclic sulfite of *meso*-**2** adopts a chair conformation with an axial SO group and equatorial methyl groups. On the other hand, the cyclic sulfite (±)-**2** adopts the less stable twist-chair conformations to avoid a 1,3 diaxial interaction between the methyl group and the exocyclic oxygen.[34] Consistent with this suggestion, molecular mechanics calculations (MM+) showed that the sulfite from *meso*-**2** is more stable by 2.2 kcal/mol.

We also described a way to enrich a mixture of *meso*- and (±)-**3** in the racemic diastereomer. This enrichment is based on the more rapid decomposition of the cyclic sulfite derived from *meso*-**3** under acidic conditions.

To rationalize why the cyclic sulfite derived from (±)-**3** reacts more slowly, we considered the likely mechanism for the decomposition of the cyclic sulfites, Scheme 1. This proposed mechanism is similar to the



Scheme 1. Possible mechanism of decompostion of cyclic sulfites in acid. The cyclic sulfite derived from (±)-**3** reacts slower because it encounters a larger 1,3-diaxial interaction between R_1 and H_1.

mechanism of chloride-assisted hydrolysis of sulfite esters in acidic media.[35] Protonation at an alcohol oxygen, followed by displacement by chloride gives the acyclic chlorosulfite.[36] Recyclization by nucleophilic attack of the alcohol oxygen on carbon yields the tetrahydrofuran and releases SO_2 and HCl. A molecular model of this cyclization step shows that aligning the attacking hydroxyl group opposite to the leaving chlorosulfite group creates a 1,3-diaxial interaction between H_1 and R_1. In the sulfite derived from (±)-**3**, R_1 = Me, so the reaction is slower than in the sulfite derived from *meso*-**3**, where R_1 = H. Fronza *et al.* proposed a similar mechanism for the cyclization of 1,4-diols to tetrahydrofurans mediated by triphenylphosphine and *N*-bromosuccinimide.[37]

EXPERIMENTAL SECTION

General. All chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) unless otherwise noted. Silica gel supported on aluminum (Whatman Ltd, Maidstone, UK) was used for thin-layer chromatography, and silica gel (either TLC grade, BDH Chemicals or 70-230 mesh, Aldrich) was also used for column chromatography. A capillary column with a chiral stationary phase (Chiraldex G-TA, 0.25 mm x 30 m from Advanced Separation Technologies Inc., Whippany, NJ) was used for analyses by gas chromatography. Enzymes and enzyme assays have been described previously.[38] The PC Model software (version 88.0 from Serena Software, Bloomington, Indiana) was used for molecular mechanics calculations.

Isolation of (±)-2,4-pentanediol, (±)-2. Thionyl chloride (2.7 mL, 37 mmol) was added dropwise over 10 min to an open flask containing a 1:1 mixture of the meso and racemic stereoisomers of **2** (5.0 g, 48 mmol) dissolved in dichloromethane (120 mL) and cooled to 8°C. After addition was complete, the flask was closed with a moisture trap filled with calcium chloride and the solution was stirred for 30 min. No remaining *meso*-**2** could be detected by TLC at this time (R_f 0.38, ethyl ether). The solvent was evaporated under vacuum and the residue was chromatographed on silica gel (30 g). The sulfite eluted with ethyl ether/hexane (1:1, 250 mL); then the diol eluted with ethyl acetate (300 mL). The ethyl acetate fractions were evaporated yielding (±)-**2** as a colorless oil: 1.4 g, 55% of theory; 92% de by gas chromatography; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.12 (m, 2), 2.90 (s, 2), 1.57 (t, 2, ^3J = 6 Hz), 1.20 (d, 6, ^3J = 6 Hz). A sample of the sulfite (200 mg), hydrolyzed to the diol (reflux in 1 mL of 5 N NaOH for 10 min) and extracted into ethyl ether, contained mostly *meso*-**2** (38% de) according to gas chromatography.

Isolation of (±)-2,5-hexanediol, (±)-3. Thionyl chloride (3.7 mL, 51 mmol) was added dropwise over 10 min to an open flask containing a 1:1 mixture of the meso and racemic stereoisomers of **3** (5.9 g, 50 mmol) dissolved in chloroform (100 mL) at room temperature. After addition was complete, the flask was closed with a moisture trap filled with calcium chloride and the ratio of isomers was monitored by ^{1}H NMR (methine H; racemic sulfite: 5.14 and 4.32; meso sulfite: 4.99 ppm). After 4 d most of the meso sulfite has been converted to the tetrahydrofuran. The solvent was evaporated under vacuum and the residue was refluxed in aqueous NaOH (5 N, 25 mL, 125 mmol) for 1 h to hydrolyze the sulfites. The reaction mixture was evaporated to dryness and triturated with 3 x 50 mL of ethyl acetate. The ethyl acetate portions were combined, concentrated under vacuum and chromatographed on silica gel eluting with a gradient of ethyl acetate (50 to 100%) in hexane to give (±)-**3** as a colorless oil: 1.1 g, 37% of theory; 84% de by gas chromatography. The ^{1}H-NMR of the purified material was identical to the starting mixture.

Conversion of (±)- and meso-*4 to* cis *and* trans-*5.* Thionyl chloride (40 µL; 0.55 mmol) was added by syringe to a solution of diol **3** (1.0 mL, 0.5 M; 1:1 mixture of meso and racemic) and dioxane (26 mM) in $CDCl_3$. Before addition, a ^{1}H-NMR spectrum showed a 10:10:1 ratio of (±)-**3** to *meso*-**3** to dioxane. After 24 h at room temperature, the ^{1}H NMR spectrum showed a 6.9:3.1:1 ratio of (±)-**4** to meso-**4** to dioxane and a 0.7:4.7.1 *cis*-**5** to *trans*-**5** to dioxane. Thus, the formation of *trans*-**5** caused the decrease in *meso*-**4** and not the epimerization of *meso*-**4** to (±)-**4**.

Characterization of cis- *and* trans-*5.* Thionyl chloride was added to a 1:1 mixture of *meso*- and (±)-**3** in ethyl ether as above and stirred for 7 d at room temperature. The solvent was evaporated under reduced pressure and distilled at atmospheric pressure affording **5** as a colorless oil (yield). ^{1}H NMR ($CDCl_3$, 200 MHz) major: δ 3.97 (m, 2 H), 1.83 (m, 4 H), 1.28 (m, 4 H), 1.04 (m, 6 H); minor: δ 3.74 (m, 2 H), ^{13}C NMR ($CDCl_3$, 75.3 MHz) major: δ 75.0, 34.0, 32.8, 21.1; minor: δ 74.1; gas chromatography (30°C, Chiraldex G-TA) 3 peaks (6.35, 5.92, 5.10 min) in a 1.3 : 1.3 : 1 ratio corresponding to the two enantiomers of *trans*-**5** and *meso*-**5**. An authentic sample of 2,5-dimethyltetrahydrofuran showed identical ^{1}H-NMR, ^{13}C-NMR and GC, except the ratio of the two isomers was 1:1.

Enzymic Resolution of (±)-2,4-Pentanediol, (±)-2. The diol (±)-**2** (26 mg, 0.25 mmol, 92% de) was dissolved in vinyl acetate (1.0 mL) and the enzyme (PCL: 30 mg; PPL: 50 mg; or CRL: 30 mg) was added. The mixture was stirred at room temperature and the products were analyzed on the GC column at 102°C: **2**-diacetate, 6.87 (R), 7.31, **2**-monoacetate, 7.06, 7.75 (R); **2**, 7.53, 7.98 (R) min. The optical purities and relative yields of **2**, **2** monoacetate

and **2**-diacetate are reported in Table I. The absolute configuration of the preferred enantiomer was determined by comparison of the rotation of an isolated sample of **2** with the reported negative rotation for (R,R)-**2**.[39]

Enzymic Resolution of (±)-2,5-Hexanediol, (±)-3. The diol **3** (100 mg, 0.85 mmol, 84% de) was dissolved in vinyl acetate (10 mL) and the enzyme PCL (200 mg) was added. The mixture was stirred at room temperature and the products were analyzed on the GC column at 90°C: **3**-diacetate, 25.75 (R), 21.85; **3**-monoacetate, 22.7 (R), 20.20; **3**, 21.06 (R), 18.61 min. Acetylation of **2** (59 mg, 0.50 mmol) by PPL (100 mg) or CRL (100 mg) in vinyl acetate (4.0 mL) were carried out and analyzed in the same way. The optical purities and relative yields of **3**, **3**-monoacetate and **3**-diacetate are reported in Table I. The absolute configuration of the preferred enantiomer was established by comparison of the rotation of an isolated sample of **3** with the reported negative rotation for (R,R)-**3**.[18b]

Acknowledgments

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