Dynamic Kinetic Resolution of Secondary Diols via Coupled Ruthenium and Enzyme Catalysis

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Enzymatic acylation of secondary symmetrical diols (as *meso*/*dl* mixtures) in combination with ruthenium-catalyzed isomerization of the diol led to efficient dynamic kinetic resolution. In this way, a *meso*/*dl* mixture of the diol was transformed to enantiomerically pure (*R*,*R*)-diacetate, making efficient use of all the diol material. For some of the flexible substrates, substantial amounts of *meso*-diacetates were formed as side products. The results indicate that the major part of the *meso* product is formed via an intramolecular acyl-transfer pathway.

Introduction

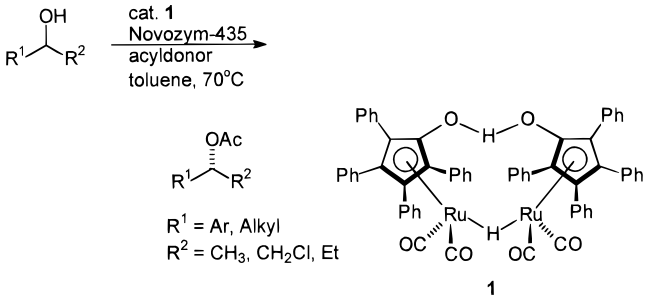
We recently reported on an efficient dynamic kinetic resolution of secondary alcohols employing an enzyme-catalyzed acylation in combination with a ruthenium-catalyzed racemization of the substrates (Scheme 1).[1] The reaction gave enantiomerically pure acetates in good yields with a variety of substrates.

During this work, we found in preliminary experiments that 2,5-hexanediol (**2**), as a 1:1 mixture of *meso* and *dl*, also underwent a dynamic kinetic resolution to give mainly one enantiomer. We have now studied this reaction in more detail and report on the transformation of *meso*/*dl* mixtures of symmetric diols to the C_2-symmetric *R*,*R* product. This new procedure gives access to synthetically important C_2-symmetric diols in high optical purity. These diols are a source of chiral auxiliaries and ligands[2] and have been used in the preparation of enantiomerically pure trans-2,5-disubstituted pyrrolidines,[3] phospholanes,[4] and thiolanes.[5]

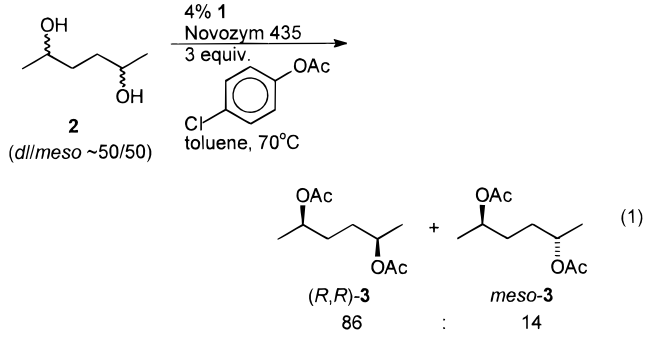
Results and Discussion

Treatment of 2,5-hexanediol (**2**), with 4 mol % of ruthenium catalyst **1**,[6] Novozym 435 (*Candida antarctica* lipase B), and 3 equiv of the acyl donor, 4-chlorophenyl acetate, in toluene at 70 °C gave diacetate **3** in 63% yield

Scheme 1



as a 86:14 mixture of (*R*,*R*)-**3** (>99% ee) and *meso*-**3** (eq 1, entry 1, Table 1). It should be kept in mind that the



theoretical maximum yield in enzymatic kinetic resolution of these diols is ca. 25%, because of the *meso* and *dl* forms normally being present in approximately equal amounts in the starting material.[7,8]

To avoid the undesired formation of *meso*-**3** in our system, the effects of altering parameters such as solvent, concentration, acyl donor, and stoichiometry of the

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(1) (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J. E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211. (b) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.

(2) For the importance of C_2-symmetric auxiliaries and ligands in asymmetric synthesis, see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(3) (a) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755. (b) Zwaagstra, M. E.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1993**, *4*, 2163. (c) Kim, M.-J.; Lee, I. S. *Synlett* **1993**, 767.

(4) (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(5) (a) Julienne, K.; Metzner, P.; Henryon, V.; Greiner, A. *J. Org. Chem.* **1998**, *63*, 4532. (b) Otten, S.; Fröhlich, R.; Haufe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 189.

(6) This catalyst is readily prepared from $Ru_3(CO)_{12}$ and tetraphenyl cyclopentadienone: Shvo, Y.; Menashe, N. *Organometallics* **1991**, *10*, 3885. For a modified procedure, see ref 1b.

(7) For studies on enzymatic kinetic resolutions of diols, see: (a) Mattson, A.; Öhrner, N.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1993**, *4*, 925. (b) Kim, M.-J.; Lee, I. S. *J. Org. Chem.* **1993**, *58*, 6483. (c) Nagai, H.; Moromoto, T.; Achiwa, K. *Synlett* **1994**, 289. (d) Caron, G.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1994**, *5*, 657. (e) Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231.

(8) Removal of the meso isomer before enzymatic resolution, which increases the theoretical yield to 50%, has been reported; see ref 7d.

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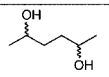
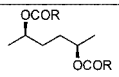
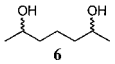
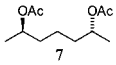
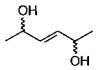
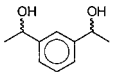
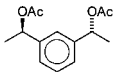
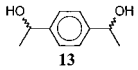
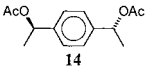
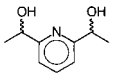
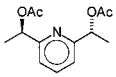
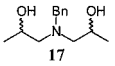
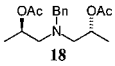
Table 1. Enzymatic Acylation of Secondary Diols Coupled with Ruthenium-Catalyzed Isomerization Employing Catalyst 1[a]

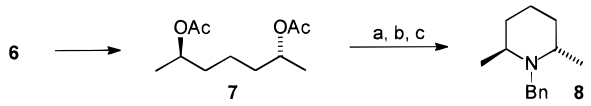
Entry	Substrate	Product	Time/h	%Yield[b]	%ee (*R,R/meso*)
1[h]	 **2**	 **3** (R = Me)	48	63	>99[c] (86/14)
2[i]	**2**	**3** (R = Et)	1	47	>99[c] (96/4)
3[i]	**2**	**3** (R = ^{i}Pr)	2	61	>99[c] (86/14)
4	 **4**	 **5**	24	90	>99[c] (38/62)
5	 **6**	 **7**	24	63	>97[d] (90/10)
6	 **9**	 **10**	24	43	>99[e] (74/26)
7	 **11**	 **12**	24	76	>99[f] (98/2)
8	 **13**	 **14**	24	77	>99[f] (98/2)
9	 **15**	 **16**	24	78	>99[f] (100/0)
10	 **17**	 **18**	24	64	>96[g] (89/11)

[a] The reactions were carried out on a 0.5 mmol scale using 4 mol % of catalyst **1**, 3 equiv of 4-chlorophenyl acetate (except in entries 2 and 3, see text), and 30 mg of enzyme in 1.0 mL of toluene under argon atmosphere. [b] Isolated yield. [c] The diastereomeric ratio and ee were determined on the diacetate by using chiral GC on a JW Cyclodex B column. [d] Enantiomeric excess determined by ^{1}H NMR (acetone-d_6) on the diastereomeric salt with (*R*)-MTPA after derivatization to **8** (see text). [e] The diastereomeric ratio and ee were determined on the bis-2-chlorobenzoic acid ester of the diol corresponding to the diacetate formed by using chiral HPLC on a Chirasil OD-H column. [f] The diasteromeric ratio and ee were determined on the diol corresponding to the diacetate formed, by using chiral HPLC on a Chirasil OD-H column. [g] Enantiomeric excess determined by ^{1}H NMR (acetone-d_6) on the diastereomeric salt with (*R*)-MTPA. [h] The reaction was carried out at a lower concentration (0.33 M). [i] The reaction was carried out with 160 mg enzyme/mmol substrate.

reagents were investigated. It was found that by increasing the amount of enzyme the reaction time could be shortened considerably (entries 2 and 3, Table 1). An improvement of the diastereoselectivity was made using 4-chlorophenyl propionate as the acyl donor, giving the (*R,R*)- and *meso*-diacetate in a 96/4 ratio, although in a lower yield (entry 2, Table 1).[9] Running the reaction with an even larger acyl donor, the 2-methylpropionate ester, gave a mixture of (*R,R*)-**3** and *meso*-**3** in an 86/14 ratio in 61% yield (entry 3, Table 1). Thus, a yield and selectivity comparable with the initial experiment (entry 1, Table 1) were obtained in only 2 h. Further increasing the size of the acyl group to the 2,2-dimethylpropionate gave no reaction, probably because of steric interactions in the active site of the enzyme. Carrying out the reactions at higher concentration (>0.5 M on substrate)

(9) Using 4-chlorophenyl acetate as acyl donor under these conditions (160 mg enzyme/mmol substrate) gave (*R,R*)-**3**/*meso*-**3** (80/20) in 55% yield after 1.5 h.

Scheme 2[a]



[a]Key: (A) K_2CO_3, MeOH−H_2O, rt, 16 h, 82%; (B) MsCl, NEt_3, CH_2Cl_2, −15 °C, 1 h; (C) $BnNH_2$, rt, 96 h, 53% (two steps).

resulted in problems with solubility of the diol, and changing to more polar solvents led to no improvements. For all other substrates the reaction was carried out under the same conditions as the initial experiment although at a slightly higher concentration (0.5 M, entries 4−10, Table 1).

Thus, treatment of 2,4-pentanediol (**4**) under these reaction conditions afforded diacetate **5** in 90% yield. In this case, the *meso* form was the major isomer, giving the desired (*R,R*)-**5** in a total yield of 34% (entry 4, Table 1), i.e., not much better than a traditional kinetic resolution would accomplish.[10] However, a poor diastereoselectivity for this substrate has previously been reported in enzymatic kinetic resolution using *C. antarctica* lipase.[7a]

Reaction of 2,6-heptanediol (**6**), prepared by $NaBH_4$ reduction of the corresponding diketone,[11] under the same reaction conditions as above gave the diacetate **7** in 63% yield (entry 5, Table 1). Neither the enantiomeric excess nor the *R,R*/*meso* ratio could be determined directly on **7**,[12] and therefore, **7** was transformed to the known 2,6-dimethylpiperidine **8**.[13] NMR analysis of **8**, as its chiral salt with (*R*)-MTPA (PhC(OMe)(CF_3)COOH), showed that the enantiomeric excess was >97% and the ratio (*S,S*)-*trans*-**8**/*cis*-**8** was 90:10 (Scheme 2). It is not clear at present whether the small amount of *meso* compound is formed in the resolution process or in the transformation to **8**. Cyclization of a 2,5-dimesylate to the corresponding pyrrolidine has been reported to be stereospecific and to proceed with complete inversion,[3a] but in one case a lower degree of stereospecificity was observed.[3b,14] Separation of *cis*- and *trans*-piperidine **8** by chromatographic methods gave a pure sample of (*S,S*)-*trans*-**8**, of which the optical rotation was measured; $[\alpha]^{25}_D$ +77.0°, $c = 0.64$ in $CHCl_3$ (lit.[12] −72.2°, $c = 3.18$ in $CHCl_3$, temperature not specified).

When the allylic diol **9** was subjected to the same reaction conditions, a competing reaction deteriorated the yield of the diacetate (entry 6, Table 1). A considerable amount (ca. 40% isolated) of the γ-keto acetate was formed as a result of ruthenium-catalyzed isomerization of the double bond.[15]

The aromatic diols **11**[7e] and **13**[7e] (entries 7 and 8, Table 1) afforded enantiomerically pure diesters **12** and **14** in

(10) It was possible to separate the two diastereomers, (*R,R*)-**5** and *meso*-**5**, by flash chromatography.

(11) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675

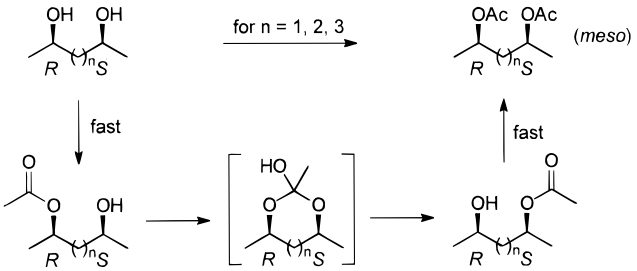
(12) It was not possible to separate the enantiomers of diacetate **7** or diol **6** by HPLC or GC using the chiral columns specified in the general Experimental Section. Derivatization to the bis-2-chlorobenzoic acid ester or mono- or bis-benzyl ether prior to chromatographic analysis did not improve the separation.

(13) (a) Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279. (b) Boga, C.; Manescalchi, F.; Savoia, D. *Tetrahedron* **1994**, *50*, 4709.

(14) In this case, the cyclization was carried out at a higher temperature (65 °C); see ref 3b.

(15) Bäckvall, J. E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459. See also: Trost, B. M.; Kulawiec, R. J. *Tetrahedron Lett.* **1991**, *32*, 3039.

Scheme 3. Formation of *Meso* Compound by Intramolecular Acyl Transfer



76 and 77% yield, respectively, and, importantly, with high diastereoselectivities (<2% *meso*). The pyridine derivative **15**[7e] behaved similarly, and diacetate **16** was isolated in 78% yield as a single enantiomer with no detectable amount of the *meso* isomer (entry 9, Table 1). The corresponding diol is a useful precursor for enantiomerically pure tridentate diphosphine ligands.[16] Aminodiol **17**[17] gave a result comparable to that of heptanediol **6** in terms of both yield and diastereoselectivity, producing diacetate **18** in 64% yield with an *R*,*R*/*meso* ratio of 89:11 (entry 10, Table 1). We were not able to separate these diastereomers, but an estimate of the enantiomeric excess was obtained by ^{1}H NMR analysis of the diastereomeric salt formed upon addition of (*R*)-MTPA.

In a previous report on the enzymatic resolution of diols using *C. antarctica* lipase, it was shown that considerable amounts of the *meso*-diacetate were formed when diol **4** was employed as the substrate.[7a] The authors proposed two possible reasons for its formation: (i) an intramolecular acyl transfer from the (*R*)-acetate to the (*S*)-alcohol in the monoacylated (*R*,*S*)-diol with subsequent enzyme-catalyzed acylation of the (*R*)-alcohol function released would give the *meso*-diacetate (Scheme 3);[18] (ii) the selectivity of the enzyme may differ for the diol and the monoacetylated product. Thus, if the acylation of the (*S*)-alcohol group in the (*R*)-acetoxy monoacetate of the (*R*,*S*)-diol is comparable in rate to the acylation of the (*R*,*R*)-diol, this would lead to formation of the *meso* compound.[19,20]

Our results support the first explanation since a clear trend in diastereoselectivity can be seen on going from pentanediol **2** to heptanediol **6**. A highly favored six-membered transition state for the pentanediol leads to a large amount of *meso* compound, which decreases with increased chain length. Further evidence in favor of the intramolecular acyl-transfer mechanism is given by the nonflexible aromatic substrates **11**, **13**, and **15**, which all give significantly lower amounts of the corresponding *meso*-diacetates.

Conclusion

We have demonstrated that an in situ isomerization of a substrate diol, as a mixture of *dl*/*meso*, by a ruthenium catalyst in combination with enzymatic acylation resulted in full transformation of the diol to enantiomerically pure diacetate. The yields and selectivities were consistently high, and in most cases ee's were >99%.

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Solvents for extraction and chromatography were technical grade and distilled. Column chromatography was performed with Merck 60 silica gel. Analytical high-pressure liquid chromatography (HPLC) was performed employing a Daicel, Chiralcel OD-H column. Solvents for HPLC use were spectrometricgrade. Flow parameters were isocratic at the stated conditions: method (hexane/^{i}PrOH, 0.5 mL/min). GLC analyses were performed with the following columns: Rescom SE54 and JW Cyclodex B.

All reactions were carried out under dry argon atmosphere in oven-dried (140 °C) glassware except for those reactions utilizing water as a solvent, which were run in air. Novozym 435 (*C. antarctica* lipase B; 8200 U/g) was a generous gift from Novo Nordisk A/S, Denmark. Substrate **4** was commercially available and used without further purification. 2,5-Hexanediol **2** and 2,6-heptanediol **6** were prepared by $NaBH_4$ reduction of commercially available 2,5-hexanedione and 2,6-heptanedione[11] using standard techniques. Compounds **1**,[6] **9**,[21] **11**,[7e] **13**,[7e] **15**,[7e] and **17**[17a] were prepared following literature procedures.

General Procedure for the Ruthenium- and Enzyme-Coupled Resolution of Secondary Diols. Catalyst [$Ru_2(CO)_4(\mu$-H)($C_4Ph_4COHOCC_4Ph_4$] (**1**) (22 mg, 0.02 mmol) and Novozym 435 (30 mg) were placed in a long Schlenk flask, and the atmosphere was changed to argon. Argon was bubbled through a solution of α,α′-dihydroxy-1,3-diethylbenzene (**11**) (83 mg, 0.5 mmol; *dl*/*meso* ∼50/50) and 4-chlorophenyl acetate (0.26 g, 1.5 mmol) in toluene (1.0 mL), followed by transfer to the ruthenium catalyst and enzyme. The reaction was stirred under argon for 24 h at 70 °C. The reaction mixture was filtered and separated on silica (pentane/Et_2O 9:1) to yield α,α′-diacetoxy-1,3-diethylbenzene (**12**) (95 mg, 76%). The NMR-spectra were in agreement with the data previously reported in the literature.[7e] Diacetate **12** (85 mg, 0.51 mmol) was hydrolyzed by treatment with K_2CO_3 (207 mg, 1.5 mmol) in methanol/water (4:1) for 16 h at room temperature. The methanol was evaporated, and the aqueous phase was extracted with Et_2O (4 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and reduced in vacuo. The residue was filtered through a short plug of Celite (Et_2O) to give diol **11** (56 mg, 99%).The ee and diastereomeric ratio were determined by chiral HPLC analysis (hexane/^{i}PrOH 9:1): ee >99%, *R*,*R*/*meso* 98/2, racemic/meso **11** was used as reference.

2,5-Diacetoxyhexane (3). Following the general procedure, but using 1.5 mL of toluene and running the reaction 48 h, diol **2** gave diacetate **3** in 63% yield. The ee and diastereomeric ratio were determined on **3** by chiral GC; ee >99%, *R*,*R*/*meso* 86/14. The NMR spectra were in agreement with the data previously reported in the literature.[1b]

2,4-Diacetoxypentane (5). Following the general procedure, diol **4** gave diacetate **5** in 90% yield. The ee and diastereomeric ratio were determined on **5** by chiral GC; ee >99%, *R*,*R*/*meso* 38/62. The NMR spectra were in agreement with the data previously reported in the literature.[22]

2,6-Diacetoxyheptane (7). Following the general procedure, diol **6** gave diacetate **7** in 63% yield. ^{1}H NMR, δ: 4.87 (m, 2H), 2.01 (s, 6H), 1.64−1.20 (m, 6H), 1.91 (d, J = 6.2 Hz,

(16) Sablong, R.; Newton, C.; Dierkes, P.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4933.

(17) (a) Dubois, L.; Fiaud, J.-C.; Kagan, H. B. *Tetrahedron* **1995**, *51*, 3803. (b) Zhang, H.-C.; Harris, B. D.; Costanzo, M. J.; Lawson, E. C.; Maryanoff, C. A.; Maryanoff, B. E. *J. Org. Chem.* **1998**, *63*, 7964.

(18) Liu, K. K.-C.; Nozaki, K.; Wong, C.-H. *Biocatalysis* **1990**, *3*, 169.

(19) An observation where the rate of the first acylation of the slow reacting *S*,*S* isomer of diol **4** is of the same magnitude as the second acylation of the fast reacting *R*,*R* isomer in a lipase catalyzed kinetic resolution has been reported: Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942.

(20) The (*S*,*S*)-**4** isomer has been shown to be almost totally unreactive toward acylation using lipase from *C. antarctica*; see ref 7a.

(21) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

(22) Itoh, O.; Ichikawa, Y.; Katano, H.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1353.

6H). ^{13}C NMR δ: 170.6, 70.7, 35.6, 21.32, 21.27, 19.9. The ee and diastereomeric ratio were determined after derivatization to the known piperidine **8**,[13] which was obtained as a 90:10 mixture of (*S*,*S*)-*trans*-**8** and *cis*-**8** with >97% ee of the *S*,*S* enantiomer (see below).

2,6-Dimethyl-*N*-benzylpiperidine (8). Diacetate **7** (268 mg, 1.24 mmol) was hydrolyzed by treatment with K_2CO_3 as described above for diacetate **12** to give 2,6-heptanediol **6** (134 mg, 82%). According to ref 3a, a solution of diol **6** (128 mg, 0.97 mmol) and NEt_3 (0.35 mL, 2.52 mmol) in CH_2Cl_2 (4 mL) was cooled to −15 °C. Methanesulfonyl chloride (0.18 mL, 2.32 mmol) was added dropwise while the temperature was maintained between −20 and −15 °C. After the addition was complete, the mixture was allowed to warm to 0 °C and then poured into cold 1 M HCl (10 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated Na_2CO_3(aq) (10 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the bis(methanesulfonate) as a colorless oil, which was used in the next step without further purification. The dimesylate was dissolved in benzylamine and stirred at ambient temperature for 96 h. The reaction mixture was poured into cold 2 M NaOH (20 mL) and extracted with pentane (3 × 20 mL). After drying over Na_2SO_4, filtration, and evaporation of the solvent, ^{1}H NMR analysis of the residue showed a 90:10 mixture of *trans*- and *cis*-**8**. The excess benzylamine was distilled off, and chromatography (pentane) of the residue afforded the title compound as a colorless oil as a 90:10 mixture of *trans*- and *cis*-**8** (104 mg, 53%). The first fraction contained pure *trans*-**8**: $[\alpha]^{25}_D$ +77° (*c* = 0.64, $CHCl_3$) (lit.[13] −72.2°, *c* = 3.18 in $CHCl_3$, temperature not specified). The NMR spectra were in agreement with the data previously reported in the literature.[13b] The ee was determined by ^{1}H NMR (acetone-d_6) on the benzylic protons after treatment with 1 equiv of (*R*)-MTPA (PhC(OMe)(CF_3)COOH); ee >97%.

2,5-Diacetoxy-3-hexene (10). Following the general procedure, diol **9** gave diacetate **10** in 43% yield. The NMR spectra were in agreement with the data previously reported in the literature.[21] The diacetate was hydrolyzed and derivatized with 2-chlorobenzoic acid before determination of ee and de. Diacetate **10** (62 mg, 0.31 mmol) was hydrolyzed as described above for diacetate **12** to give 2,5-hexenediol (**9**) (30 mg, 83%), which was used without further purification in the next step. To a magnetically stirred solution of diol **9** (30 mg, 0.26 mmol), DCC (128 mg, 0.62 mmol), and DMAP (1.6 mg, 0.013 mmol) in CH_2Cl_2 (3 mL) was added 2-chlorobenzoic acid (97 mg, 0.62 mmol), and the reaction was stirred at room temperature until judged complete by TLC. The mixture was filtered through a short plug of Celite (Et_2O), and the organic phase was washed with 1.2 M HCl and 2 M NaOH and subsequently dried over Na_2SO_4. After evaporation of the solvents, the residue was chromatographed (pentane/Et_2O 9:1) to give **2,5-bis(2-chlorobenzoyloxy)-3-hexene** in quantitative yield. ^{1}H NMR (mixture *R*,*R*/*meso*), δ: 7.80 (m, 2H), 7.46−7.37 (m, 4H), 7.31 (m, 2H), 5.94 (m, 2H), 5.65 (m, 2H), 1.47 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (mixture *R*,*R*/*meso*), δ: 164.9, 133.5, 132.3, 131.5, 131.3, 131.2, 131.0, 130.6, 126.5, 71.5, 71.4, 20.19, 20.16. The ee and diastereomeric ratio were determined by HPLC analysis (hexane/^{i}PrOH 96:4); *R*,*R*/*meso* 74:26; ee >99%.

α,α′-Diacetoxy-1,4-diethylbenzene (14). Following the general procedure, diol **13** gave diacetate **14** in 77% yield. The NMR spectra were in agreement with the data previously reported in the literature.[7e] The ee and diastereomeric ratio were determined by HPLC analysis after hydrolysis of the diacetate as described above for diacetate **12** (hexane/^{i}PrOH 9:1); *R*,*R*/*meso* 98:2; ee >99%.

α,α′-Diacetoxy-1,3-diethylpyridine (16). Following the general procedure, diol **15** gave diacetate **16** in 78% yield. The NMR spectra were in agreement with the data previously reported in the literature.[7e] The ee and diastereomeric ratio were determined by HPLC analysis after hydrolysis of the diacetate as described above for diacetate **12** (hexane/^{i}PrOH 9:1); *R*,*R*/*meso* 100:0; ee >99%.

***N*,*N*-Bis-(2-acetoxypropyl)benzylamine (18).** Following the general procedure, diol **17** gave diacetate **18** in 64% yield as a 89:11 mixture of *R*,*R*/*meso*. ^{1}H NMR, δ: 7.32−7.20 (m, 5H), 5.03 (m, 2H), 3.66 (s, 2H), 2.65 (dd, *J* = 13.4, 6.8 Hz, 2H), 2.50 (dd, *J* = 13.4, 5.6 Hz, 2H), 2.01 (2, 6H), 1.17 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR δ: 170.5, 139.1, 128.8, 128.1, 127.0, 69.0, 59.8, 59.3, 21.3, 18.2. The ee was determined by ^{1}H NMR (acetone-d_6) on the benzylic protons after treatment with 1 equiv of (*R*)-MTPA (PhC(OMe)(CF_3)COOH); ee >97%.

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