Preparative Bioorganic Chemistry; 8.[1] Efficient Enzymatic Preparation of (1*R*,4*S*)-(+)-4-Hydroxy-2-cyclopentenyl Acetate

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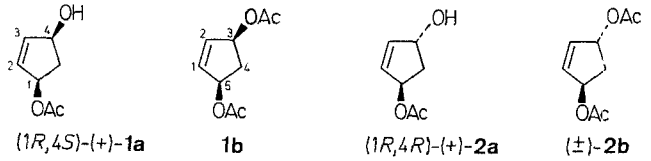
An efficient method for the preparation of (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate, a useful chiral starting material for the synthesis of prostaglandins, is described. A mixture of *cis*- and *trans*-3,5-diacetoxycyclopentene, readily obtainable on a preparative laboratory scale, was used as the substrate for the hydrolysis with commercially available pig pancreatic lipase (PPL). PPL hydrolyzed the substrate enantioselectively and substrate-selectively, yielding mainly the (+)-*cis*-monoacetate and *trans*-diacetate (Method A). The former was recrystallized to give the diastereomerically and optically pure (+)-*cis*-monoacetate. Ester exchange of *cis*/*trans* mixture of the diacetate in an organic solvent using enzymes as batch or flow system was also investigated (Method B). Method A was applicable to 0.25 mol of substrate, and yielded 0.127 mol (18 g, 51%) of optically pure (+)-monoacetate with recycling recovered materials.

Prostaglandins show various bioregulating activities including antihypertensive activity and smooth-muscle contracting effects. Because of these and other interesting properties, efficient and economical syntheses of prostaglandins in optically active form have been investigated.[2-4]

(1*R*,4*S*)-(+)-4-Hydroxy-2-cyclopentenyl acetate [(+)-**1a**] is a useful chiral starting material, which can be converted to intermediates for the synthesis of optically active prostaglandins.[4-6] Several groups have reported the enzymatic preparation of compound (+)-**1a** or its enantiomer[7-11] from *cis*-3,5-diacetoxycyclopentene (**1b**). As a result of work on prostaglandin syntheses in our laboratory,[1] we describe here an efficient preparation of (+)-**1a**.



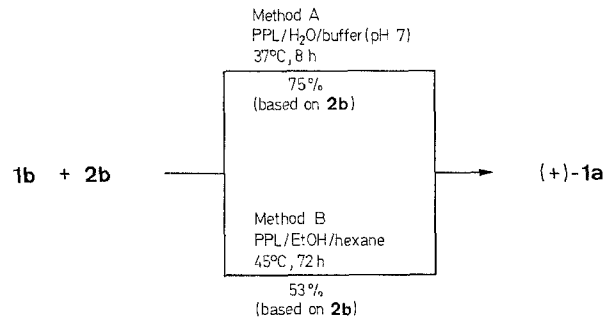
(1*R*,4*S*)-(+)-**1a** **1b** (1*R*,4*R*)-(+)-**2a** (±)-**2b**

The most regio- and stereoselective preparation of the *cis*-diacetate **1b** is the addition of singlet oxygen to cyclopentadiene as reported in the literature.[12] followed by acetylation. This method requires photochemical apparatus and a large amount of solvent (1800 mL of methanol for 6.4 g of cyclopentadiene); this has led to difficulties in the large-scale preparation of *cis*-**1b** in our laboratory. On the other hand, preparation of **1b** from cyclopentadiene via corresponding *cis*-dibromide has been reported.[13] This method requires a smaller amount of solvent, and it was therefore chosen for the preparation of **1b**. This route has been claimed[13] to be the stereoselective way to *cis*-diacetate **1b**. However, the product was found to be a 60:40–55:45 mixture of *cis*-**1b** and *trans*-**2b** by GLC and 100 MHz ^{1}H-NMR analyses. Instead of the originally reported trioctylisopropylammonium chloride, commercially available trioctylmethylammonium chloride was used as the phase-transfer catalyst in our conversion of the dibromide to the diacetate, and this is the only difference. The reaction temperature and other conditions were same as in the original report. The product was shown reproducibly to be a stereoisomeric mixture, perhaps owing to epimerization at the stage of dibromide. We therefore decided to utilize this mixture (*cis*:*trans* = 57.5:42.5) as the substrate for enzymatic hydrolysis.

Hydrolysis of **1b** + **2b** with the culture broth of bakers' yeast has been reported[14] to rapidly afford the corresponding *cis*-diol. However, this could not be used because of its high solubility in water; therefore the remaining optically active *trans*-mono- and diacetates were used as the starting material for the preparation of optically active prostaglandins.

In our preparation, crude commercial pig pancreatic lipase (PPL) was chosen as the hydrolyzing enzyme because of its modest price (6.5 U.S. dollars for 100 g from Sigma Co.)[10] as compared with other enzymes such as pig liver esterase[8,9] and acetylcholine esterase from electric eel.[11] Hydrolysis of **1b** + **2b** (10 g) with PPL (5 g) at 37°C and pH 7 for 8 h followed by extraction gave the crude mixture consisting of *trans*-diacetate **2b** (46.2%), *cis*-monoacetate **1a** (47.3%), and *trans*-monoacetate **2a** (6.5%) according to GLC analysis. Using PPL, hydrolysis of the *cis*-diacetate **1b** was also faster than that of the *trans*-diacetate **2b**. A monoacetate fraction was obtained by column chromatography of the crude product on silica gel. Although the *cis*- and *trans*-monoacetates **1a** + **2a** could not be

separated by this chromatography, recrystallization of this fraction[8] from pentane/ether gave crystalline (+)-**1a** in 75% yield from **1b** present in the substrate. Hydrolysis in water was shown to be a convenient method for the preparation of (+)-**1a** (Method A).



From an experimental viewpoint, this method has several drawbacks. During extractive work-up, the mixture became an intense emulsion caused by emulsifying impurities present in commercial crude PPL. In addition, a certain amount of *cis*-monoacetate may be hydrolyzed to the diol, whose extraction from water was difficult, lowering the yield of (+)-**1a**. Therefore we attempted ester exchange in an organic solvent[15] to avoid extraction from an aqueous phase.

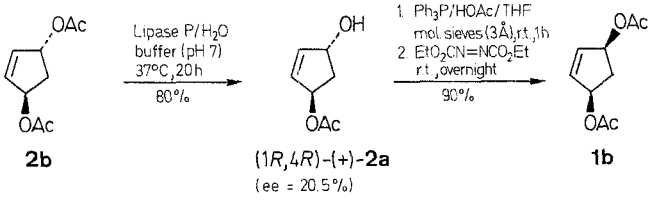
Preliminary experiments were performed with five different enzymes: PPL, lipase P (from *Pseudomonas*), A (*Aspergillus*), F-AP (*Rhizopus*), and M (*Mucor*). The substrate (500 mg, 2.7 mmol), 1-pentanol (960 mg, 10.9 mmol), enzyme (1 g), and heptane (10 mL) were vigorously shaken in a closed 20 mL-glass ampoule at 45 °C for 5 days. The alcoholytic ability of the five enzymes was compared by monitoring the reaction by TLC. The order of alcoholytic ability was found to be: lipase P > PPL > > lipase A, lipase F-AP, lipase M. Lipase P alcoholyzed almost all of the starting material to diols. The use of PPL gave the monoester most selectively as compared with the other enzymes. Therefore PPL was chosen as the alcoholytic enzyme, in organic solvents. Using PPL in this system, methanol, ethanol, and 2-propanol were compared with regard to ester exchange; hexane, toluene, and methanol were compared as solvents. The best result was obtained using ethanol and hexane.

Ester exchange of **1b** + **2b** (20 g) was carried out with PPL (40 g) at 45 °C for 72 h. The crude mixture obtained on filtration and concentration consisted of **2b** (45.8%), **1b** (15.9%), **1a** (31.6%), and **2a** (6.7%) according to GLC analysis. Diol **1c** (13%) was isolated after chromatographic purification. Chromatographic purification followed by recrystallization of the monoacetate fraction gave crystalline (+)-**1a** in 53% yield; formed from **1b** present in the substrate.

In spite of the smaller amount of nucleophilic reagent in used ester exchange in organic solvent as compared with hydrolysis in water, the yield of (+)-**1a** decreased but recovery of *cis*-diacetate and diol was observed, contrary to our expectation of the increase of monoacetate. This was assumed to be caused by both decrease of the rate of conversion of *cis*-diacetate to *cis*-monoacetate, and the difficulty to "wash-out"[16] *cis*-monoacetate from enzyme by non-polar solvents, resulting in further ester exchange to diol. In conclusion, hydrolysis was superior to the ester exchange with regard to the efficiency of the reaction.

The merit of the reaction in organic solvent was the insolubility of the enzyme and the ease of product isolation. We also tried a flow system producing (+)-**1a**. PPL powder (40 g) was filled in a column (2 cm × 20 cm) for flash chromatography without special immobilization, and this column was kept at 45 °C. A solution of the diacetate (20 g) in ethanol (32 mL)/hexane (400 mL) was passed repeatedly through this column at a flow rate of 10–12 mL/min. After 72 h, the mixture was found to consist of **2b** (49.5%), **1b** (18.8%), **1a** (26.5%), and **2a** (5.2%) by GLC analysis. This was almost the same result as that obtained from the batch system described above. After 72 h, when the substrate solution was replaced by a new batch, the activity of the column decreased to 1/2 of that of the initial packing. Stabilization of the enzyme is a further problem, which we are presently trying to solve.

The next task was the utilization of the *trans*-isomer present in the substrate. Acetylation of the *trans*-monoacetate with inversion of stereochemistry was supposed to regenerate the *cis*-diacetate.



Preparation of the *trans*-monoacetate from the *trans*-diacetate using methanol and butylamine (75% yield) has been reported.[14] The same conversion using a facile enzymatic procedure was attempted. Lipase P was shown to possess strong activity by the results of preliminary experiments on ester-exchange; this enzyme was therefore applied to the hydrolysis of the *trans*-diacetate.

The desired *trans*-monoacetate was obtained in 80% yield. Comparison of its optical rotation, $[\alpha]_D^{26}$ + 52.2° (MeOH), with the reported[14] value for an optical purity of 90%, $[\alpha]_D^{20}$ + 229° (MeOH), revealed 20.5% e.e. for our product. After hydrolysis with lipase P, no starting material was observed by TLC and GLC analyses. Therefore, almost no stereoselectivity was observed in the reaction *trans*-diacetate → *trans*-monoacetate. The optical rotation of the product was either due to partial removal of one enantiomer during hydrolysis with PPL, or one enantiomer of the *trans*-monoacetate was selectively hydrolyzed to the diol. Because of the rather low optical purity of the *trans*-monoacetate, this could not be directly used as a chiral starting material. According to our initial plan, *trans*-monoacetate **2a** was subjected to the conditions of the Mitsunobu esterification[17] (involving inversion) using acetic acid (1.1 equiv) to give *cis*-diacetate **1b** in 90% yield. GLC analysis proved the purity of **1b** thus obtained to be > 99%. In this way, the preparative cycle of the *trans*-isomer **2b** was established.

The whole preparative procedure was carried out with 0.25 mol of substrate **1b** + **2b**. Combination of the crystalline monoacetate **1a** obtained in the individual operation of the procedure, followed by further recrystallization gave 18.10 g (0.127 mol, 51%) of (+)-**1a**: mp 47.5–48 °C; $[\alpha]_D^{22}$ + 75.0° (c = 1.16, $CHCl_3$) [Lit.[9] mp 49–50 °C; $[\alpha]_D^{20}$ − 66° (c = 0.63, $CHCl_3$) for (−)-**1a**; Lit.[10] $[\alpha]_D^{20}$ + 65.6° (c = 2.3, $CHCl_3$) for (+)-**1a**; Lit.[11] mp 46–48.5 °C; $[\alpha]_D^{23}$ + 66.3° (c = 1.53, $CHCl_3$) for (+)-**1a**].

The optical rotation of (+)-**1a** was slightly higher than those reported previously; the optical purity of our product was confirmed to be almost 100% e.e. by 500 MHz ^{1}H-NMR analysis of the α-methoxy-α-trifluoromethylphenylacetate[18] (MTPA ester, **1d**).

In conclusion, a laboratory-scale method (~ 20 g) for the preparation of (+)-**1a** with the advantage of using a readily available substrate and an inexpensive commercial enzyme, including the involving a preparative reaction cycle of *trans*-isomer, was established. Utilization of this method and application of (+)-**1a** to the synthesis of prostaglandin-related natural products are now under way.

All boiling points and melting points are uncorrected. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. IR spectra were measured as films for oils on a Jasco IRA-102 spectrometer. ^{1}H-NMR spectra were recorded at 100 MHz on a JEOL JNM FX-100 spectrometer unless otherwise stated. Merck Kieselgel 60 (particle size 0.063–0.200 mm) were used for SiO_2 column chromatography. GLC analyses were performed with 5% PEG 20M (2 m, 90 °C + 2 °C/min) as a column and N_2 (1.0 kg/cm^2) as an eluent.

PPL was purchased from Sigma Co. Lipases P, A, F-AP and M were the gift from Amano Pharmaceutical Co. (Nagoya, Japan). Solvents and alcohols for enzymatic ester exchange were dried with molecular sieves 3A before use.

3,5-Diacetoxycyclopentene (1b + 2b):

According to the reported procedure,[19] 3,5-dibromocyclopentene is prepared from cyclopentadiene (33 g) as a crude solution in $CHCl_3$, and converted into a mixture of **1b** and **2b** almost according to the reported procedure[2] using trioctylmethylammonium chloride (Capriquat); yield: 48 g (52% from cyclopentadiene); bp 74–75 °C/0.5 Torr (Lit.[12] bp 69–70 °C/0.07 Torr); n_D^{23} 1.4521.

GLC: Retention time 15.4 min (**2b**, 42.5%); 16.1 min (**1b**, 57.5%).

MS: m/z = 124 (M^+ – AcOH, 23.1%).

IR (film): ν = 1740 (C=O); 1235, 1030 cm^{-1} (C–O).

^{1}H-NMR ($CDCl_3$): δ of **1b** = 1.73 [dt, 0.58 H, J = 15.0, 4.0 Hz, CH(OCOCH$_3$)CH$_2$CH(OCOCH$_3$)]; 2.09 (s, 3.48 H, OCOCH$_3$); 2.89 [dt, 0.58 H, J = 15.0, 7.5 Hz, CH(OCOCH$_3$)CH$_2$CH(OCOCH$_3$)]; 5.55 (ddd, 1.16 H, J = 1.0, 4.0, 7.5 Hz, CHOCOCH$_3$); 6.13 (d, 1.16 H, J = 1.0 Hz, CH=CH); δ of **2b** = 1.29 [br s, 0.42 H, CH(OCOCH$_3$)CH$_2$CH(OCOCH$_3$)]; 2.06 (s, 2.52 H, OCOCH$_3$); 2.25 [dd, 0.42 H, J = 5.4, 5.4 Hz, CH(OCOCH$_3$)CH$_2$CH(OCOCH$_3$)]; 5.81 (ddd, 0.84 H, J = 0.8, 5.4, 5.4 Hz, CHOCOCH$_3$); 6.00 (d, 0.84 H, J = 0.8 Hz, CH=CH).

(1*R*,4*S*)-4-Hydroxy-2-cyclopentenyl Acetate (1a):

Method A, Hydrolysis of **1b** + **2b** using PPL: Enzyme PPL (5 g) and **1b** + **2b** (10 g, 54.3 mmol) are added to 0.1 M phosphate buffer solution (pH 7, 50 mL) and the mixture is vigorously stirred at 37 °C while pH 7 is maintained by continuous addition of 1 M KOH solution using a pH controller. After 8 h, the mixture is saturated with NaCl and extracted with EtOAc (5 × 50 mL). The organic solution is washed with brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give an oil; yield: 8.1 g.

GLC: Retention time 15.4 min (**2b**, 46.2%); 20.1 min (**1a**, 47.3%); 22.3 min (**2a**, 6.5%).

The product mixture is separated by silica-gel column chromatography (40 g); yields: **2b**, 3.6 g (36%); **1a** + **2a**, 4.0 g (52%). The latter mixture is recrystallized from pentane/Et_2O (1:1, 20 mL) to give crystalline **1a**; yield: 3.2 g (75% from **1b** present in the starting material).

Method B, Ester Exchange of **1b** + **2b** using PPL (Batch System): Enzyme PPL (40 g) and **1b** + **2b** (20 g, 0.186 mol) are added to a solution of EtOH (32 mL) in hexane (400 mL) and the mixture is vigorously stirred at 45 °C. After 72 h, the mixture is filtered and the filtrate is concentrated *in vacuo* to give an oil; yield: 18.2 g.

GLC: Retention time 15.4 min (**2b**, 45.8%); 16.1 min (**1b**, 15.9%); 20.1 min (**1a**, 31.6%); 22.3 min (**2a**, 6.7%).

This product mixture is separated by silica-gel column chromatography (90 g); yields: **1b** + **2b**, 9.7 g (48.5%); **1a** + **2a**, 5.3 g (34%). The latter mixture is recrystallized from pentane/Et_2O (1:1, 25 mL) to give crystalline **1a**; yield: 4.5 g (53% from **1b** present in the starting material).

Hydrolysis of 2b Using Lipase P:

Lipase P (0.2 g) and **2b** (1.0 g, 5.43 mmol) are added to 0.1 M phosphate buffer solution (pH 7, 50 mL) and the mixture is vigorously shaken at 37 °C. After 20 h, the mixture is saturated with NaCl and extracted with EtOAc (5 × 10 mL). The organic extract is washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give an oil (0.9 g) which is purified by silica-gel column chromatography (10 g) to give (1*R*,4*R*)-(+)-**2a**; yield: 620 mg (80%); n_D^{24} 1.4638; $[\alpha]_D^{26}$ + 52.2° (c = 1.49, MeOH) [Lit.[14] $[\alpha]_D^{20}$ + 229° (c = 0.04, MeOH].

GLC: Retention time 22.3 min (98.5%).

MS: m/z = 124 (M^+ – H_2O, 5.0%).

IR (film): ν = 3420 (O–H); 1735 (C=O); 1240, 1050, 1020 cm^{-1} (C–O).

^{1}H-NMR ($CDCl_3$): δ = 1.70 [br s, 1 H, CH(OCOCH$_3$)CH$_2$CH-(OH)]; 2.07 (s, 3 H, OCOCH$_3$); 2.17 [ddd, 1 H, J = 3.5, 3.5, 7.5 Hz, CH(OCOCH$_3$)CH$_2$CH(OH)]; 5.07 (br m, 1 H, CHOH); 5.81 (br m, 1 H, CHOCOCH$_3$); 6.03 (d, 1 H, J = 7.5 Hz, CH=CH); 6.14 (d, 1 H, J = 7.5 Hz, CH=CH); an OH signal is not observed due to broadening.

***cis*-3,5-Diacetoxycyclopentene (1b):**

Monoacetate (1*R*,4*R*)-(+)-**2a** (430 mg, 2.4 mmol), triphenylphosphine (942 mg), and AcOH (0.2 mL) are dissolved in dry THF (4.5 mL), molecular sieves 3A (1 g) are added, and the mixture is stirred for 1 h at room temperature. Then, diethyl azodicarboxylate (630 mg) is added dropwise at room temperature and stirring is continued at room temperature overnight. The mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is dissolved in benzene (5 mL) and purified by silica-gel column chromatography (20 g) to give pure **1b**; yield: 500 mg (90%); n_D^{23} 1.4523.

GLC: Retention time 16.1 min (97.7%).

MS: m/z = 124 (M^+ – AcOH, 51.8%).

IR (film): ν = 1740 (C=O); 1235, 1020 cm^{-1} (C–O).

^{1}H-NMR ($CDCl_3$): δ = 1.73 [dt, 1 H, J = 15.0, 4.0 Hz, CH(OCOCH$_3$)CH$_2$CH(OCOCH$_3$)]; 2.09 (s, 6 H, OCOCH$_3$); 2.89 [dt, 1 H, J = 15.0, 7.5 Hz, CH(OCOCH$_3$)CH$_2$CH(OCOCH$_3$)]; 5.55 (ddd, 2 H, J = 1.0, 4.0, 7.5 Hz, CHOCOCH$_3$); 6.13 (d, 2 H, J = 1.0 Hz, CH=CH). This ^{1}H-NMR spectrum is identical with that reported previously.[12]

Preparative-Scale Production of (+)-1a:

Step 1, first hydrolysis of **1b** + **2b** as in Method A above: The mixture **1b** + **2b** (57.5:42.5, 46 g, 0.25 mol) is hydrolyzed with PPL (23 g) for 8 h to give the crude product mixture (45 g).

GLC: Retention time 15.4 min (**2b**, 43.9%); 16.1 min (**1b**, 4.3%); 20.1 min (**1a**, 45.8%); 22.3 min (**2a**, 6.0%).

This mixture is separated by silica-gel column chromatography (250 g); yield: 17.4 g (**1b** + **2b**); 17.4 g (**1a** + **2a**). The latter mixture is recrystallized from pentane/Et_2O (1:1, 90 mL) to give crystalline **1a**; yield: 13.05 g.

Step 2, second hydrolysis of **1b** + **2b**: The mother liquor of the recrystallization described above is acetylated to give the diacetates. These are combined with the diacetates obtained in the first hydrolysis to give the second substrate (**1b**:**2b** = 15:85, 23 g, 0.125 mol). In the same manner as above, this mixture is hydrolyzed with PPL (11 g) for 20 h to give a crude product.

GLC: Retention time 15.4 min (**2b**, 77.9%); 20.1 min (**1a**, 11.5%); 22.3 min (**2a**, 10.6%).

This mixture is separated by silica-gel column chromatography (100 g); yields: **2b**, 14.7 g; **1a** + **2a**, 4.15 g. The latter mixture is recrystallized from pentane/Et_2O (1:1, 20 mL) to give crystalline **1a**; yield: 1.65 g.

Step 3, hydrolysis of **2b** using lipase P: Diester **2b** obtained in the second hydrolysis and the monoesters **1a** + **2a** obtained from the mother liquor of the above recrystallization are combined and used as the substrate (17.2 g, **2b**:**1a**:**2a** = 84.6:4.1:10.3). In the same manner as above, this mixture is hydrolyzed with lipase P (3.4 g) for 10 h. This time, the pH of the reaction mixture was maintained at 7 by the continuous addition of 1 M KOH solution. The crude extract is purified by distillation *in vacuo* to give **2a**; yield: 9.3 g (70% based on **2b** + **2a** present in the substrate); bp 83–85 °C/2 Torr.

GLC: Retention time 22.3 min (94.0%).

Step 4, Mitsunobu reaction of **2a**: Monoacetate **2a** (9.3 g, 70.4 mmol), triphenylphosphine (20.4 g, 77.9 mmol), and AcOH (4.3 mL) are dissolved in dry THF (100 mL), molecular sieves 3A (22 g) are added, and the mixture is stirred for 1 h at room temperature. Then, diethyl azodicarboxylate (13.6 g) is added dropwise at room temperature and stirring is continued overnight. The mixture is then filtered and the

filtrate is concentrated *in vacuo*. The residue is purified by distillation *in vacuo* to give **1b**; yield: 8.6 g (72%); bp 80–85°C/1 Torr.

GLC: Retention time 16.1 min (93.9%).

The product thus obtained was found to be contaminated with 3–5% of *trans*-diacetate **2b** by ^{1}H-NMR analysis.

Step 5, hydrolysis of regenerated **1b**: According to Method A, diacetate **1b** (8.6 g, 47 mmol) is hydrolyzed with PPL (4.3 g) for 6 h. Work-up as in Method A gives crystalline **1a**; yield: 5.13 g.

Step 6, further recrystallization of **1a**: All crystalline **1a** is combined (19.83 g) and recrystallized from pentane/Et_2O (1:1, 50 mL) to give (1*R*,4*S*)-(+)-**1a**; yield: 18.0 g (51% from original substrate); mp 47.5–48°C; $[\alpha]_D^{22}$ + 75.0° (*c* = 1.16, $CHCl_3$).

GLC: Retention time 20.1 min (single peak).

$C_7H_{10}O_3$	calc.	C 59.14	H 7.04
(124.2)	found	58.87	6.91

MS: *m/z* = 124 ($M^+ - H_2O$, 10.6%).

IR (film): *v* = 3450 (O–H); 1725 (C=O); 1240, 1090, 1060, 1025 cm^{-1} (C–O).

^{1}H-NMR ($CDCl_3$): δ = 1.66 [dt, 1H, *J* = 15.0, 4.0 Hz, CH(OCOCH$_3$)CHHCH(OH)]; 2.08 (s, 3H, OCOCH$_3$); 2.79 [dt, 1H, *J* = 15.0, 7.5 Hz, CH(OCOCH$_3$)CHHCH(OH)]; 4.71 (m, 1H, CHOH); 5.50 (m, 1H, CHOCOCH$_3$); 5.98 (d, 1H, *J* = 7.0 Hz, CH=CH); 6.12 (d, 1H, *J* = 7.0 Hz, CH=CH); OH signal not observed due to broadening. Except for the OH signal, the ^{1}H-NMR spectrum is identical with the reported[9] spectrum.

Determination of the Optical Purity of 1a:

The MTPA esters (*R*)- and (*S*)-**1d** are prepared from (+)-**1a** according to the reported procedure.[18]

^{1}H-NMR (Bruker AM-500, 500 MHz, $CDCl_3$): δ = 1.994 [s, 3H, (*S*)-**1d**, 100%]; 2.021 [s, 3H, (*R*)-**1d**, 100%].

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