Organic Process Research & Development **2002**, *6*, 471–476

Hetero Diels–Alder-Biocatalysis Approach for the Synthesis of (*S*)-3-[2-{(Methylsulfonyl) oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol Methanesulfonate, a Key Intermediate for the Synthesis of the PKC Inhibitor LY333531[1]

Jean-Claude Caille*

PPG-SIPSY, Z. I. La Croix Cadeau B. P. 79, 49242, Avrille Cedex, France

C. K. Govindan* and Heiko Junga

PPG Industries Inc, 440 College Park Dr., Monroeville, Pennsylvania 15146, U.S.A.

Jim Lalonde and Yiming Yao

Altus Biologics Inc., 625 Putnam Avenue, Cambridge, Massachusetts 02139, U.S.A.

Abstract:

A cost-effective and easily scaled-up process has been developed for the synthesis of (*S*)-3-[2-{(methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate, a key intermediate used in the synthesis of a protein kinase C inhibitor drug through a combination of hetero Diels–Alder and biocatalytic reactions. The Diels–Alder reaction between ethyl glyoxylate and butadiene was used to make racemic 2-ethoxycarbonyl-3,6-dihydro-2H-pyran. Treatment of the racemic ester with *Bacillus lentus* protease resulted in the selective hydrolysis of the *R*-enantiomer and yielded *S*-2-ethoxycarbonyl-3,6-dihydro-2H-pyran in excellent optical purity, which was reduced to *S*-3,6-dihdro-2H-pyran-2-yl methanol. Tritylation of this alcohol, followed by reductive ozonolysis and mesylation afforded the product in 10–15% overall yield and with >99% ee and chemical purity. Details of the process development work done on each step are given.

Introduction

The title compound **1** (Scheme 1) is one of the two key intermediates used by Eli Lilly and Co in the synthesis of **2**, a protein kinase C inhibitor. Compound **2**, a staurosporine analogue is in clinical trials for the treatment of retinopathy and nephropathy in patients with diabetes mellitus. A recent paper from Lilly describes[2] the development of a process to make **1** and **2** in multikilogram quantities. In this process, an acyclic bis-indolylmaleimide is reacted with **1**, and the product obtained is converted to **2** in several steps as shown in Scheme 1.

The method chosen by Eli Lilly and Co to prepare **1** in large quantities is shown in Scheme 2. The synthesis is amenable to scale-up since yields in individual steps are high and key intermediates are solids that can be easily purified by crystallization. However, the method uses expensive starting materials and reagents such as (*R*)-chloro-2,3-propanediol or *R*-glycidol, vinylmagnesium bromide and potassium *tert*-butoxide.

Two moles of ozone are required to cleave the double bonds in the diallyl intermediate **3**. Overall yield of **1** obtained by this method was 45–52%. An evaluation of the Lilly method indicated to us that a lower-cost synthesis of **1** could be developed by the use alternate raw materials.

The Hetero Diels–Alder Strategy. A retro-synthetic analysis of **1** as shown in Scheme 3 indicates that 3,6-dihydro-2H-pyran derivatives could serve as key intermediates in the synthesis of **1** and that hetero Diels–Alder reactions could be used to make these 3,6-dihydropyran intermediates.

Hetero Diels–Alder reactions have been successfully employed to prepare complex, highly functionalized molecules, including natural products.[3] More recently, asymmetric versions of this powerful reaction have been developed either by incorporating chiral auxiliaries in the dienophile or by the use of asymmetric catalysis.[4] Incorporation of the glyoxyloyl group into an optically active molecule like (2*R*)-bornane-10,2-sultam followed by reaction with 1-methoxy-1,3-butadiene in the presence of europium catalysts has been reported to produce diastereoisomerically pure 3,6-dihydropyran derivatives.[5] However, the reaction of this sultam with butadiene did not occur readily and required pressures of up to 10 kbar.[6] Therefore, this reaction cannot be readily

* Corresponding authors.

(1) Part of this work has been described before. Caille, J.-C. U.S. Patent 6,300,106 B1, 2001.

(2) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A.; Sullivan, K. A.; Gillig, J. R.; Neel, D. A.; Rito, C. J.; Jirousek, M. R. *J. Org. Chem.* **1998**, *63*, 1961–1973.

(3) For a review on hetero Diels–Alder reactions see: Bednarski. M. D.; J. P. Lissikatos. J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K.; 1991; Vol.2, p 661.

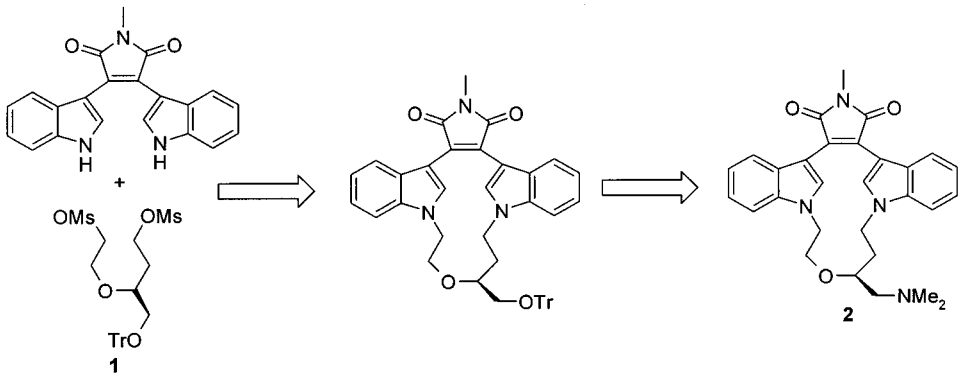
(4) (a) For a review on asymmetric hetero Diels–Alder reactions see: Waldman, H. *Synthesis* **1994**, 535–551. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc*. **1994**, *116*, 2812 and references therein.

(5) (a) Bauer, T.; Chapuis, C.; Kozak, J.; Jurczak, *J. Helv. Chim. Acta* **1989**, *72*, 482. (b) Bauer, T.; Chapuis, C.; Kozak, J.; Jurczak, *J. J. Chem. Soc., Chem. Commun*. **1990**, 1178.

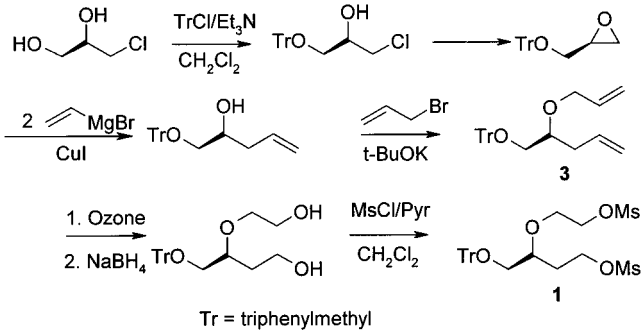
(6) Jurczak, J. Private communication.

10.1021/op020202a CCC: $22.00
Published on Web 03/16/2002

Scheme 1



Scheme 2



scaled up. Jorgensen and Johannsen[7] have reported that butadiene reacts slowly with isopropyl glyoxylate in the presence of 2,2′-isopropylidene-bis[(4*S*)-4-tertbutyl-2-oxazoline] and copper triflate to produce *S*-2-isopropyloxycarbonyl-3,6-dihdro-2H-pyran in 55% yield and 87% ee. This reaction is not considered to be of commercial importance since the catalyst is very expensive and used in relatively large quantities, the reaction is very slow, and the ee of the product is not high enough to obtain an optically pure product.

Of the two potential Diels−Alder reactions shown in Scheme 3, the reaction between trityloxyacetaldehyde and butadiene looks very attractive. This reaction would be highly atom economic and if it can be done with a chiral catalyst, would lead directly to 2-*S*-trityloxymethyl-3,6-dihydro-2H-pyran **6** (Scheme 4) that could be used in place of **3**. There is precedent in the literature for such a hetero Diels−Alder reaction. Ghosh and co-workers[8] have reported that benzyloxyacetaldehyde reacts with Danishefsky's diene in the presence of Cu(II)-bis(oxazoline) complexes to yield the corresponding dihydropyranone in 75% yield and 85% ee. A complex mixture was obtained as the product when butadiene was allowed to react with trityloxyacetaldehyde in the presence of metal complexes.[6] Therefore, we concentrated our efforts on developing a process based on the reaction of butadiene with a glyoxylic acid ester. We expected that it would be possible to resolve 2-carboalkoxy-3,6-dihydropyrans through selective enzymatic hydrolysis of one of the enantiomers. Our proposed synthesis of **1** using a hetero Diels−Alder-biocatalysis approach is shown in Scheme 4. In this study, we report the details of the development of a commercial process to make **1** based on this synthetic scheme.

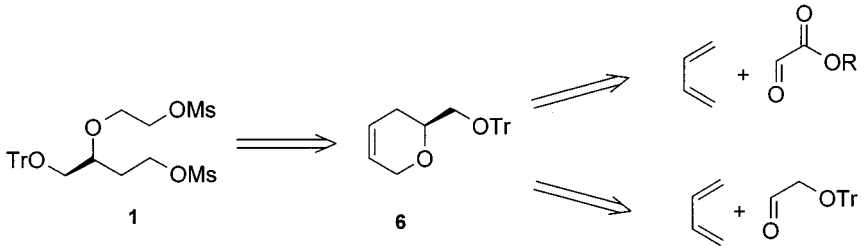
Results and Discussion

Synthesis of 2-Carboethoxy-3,6-dihydro-2H-pyran, *R*,*S*-4. We chose to develop the reaction between butadiene and ethyl glyoxylate because these two raw materials are commercially available and relatively inexpensive. It has been reported that the reaction between butadiene and ethyl glyoxylate ethyl hemiacetal affords 2-carboethoxy-3,6-dihydro-2H-pyran in 46% yield.[9] The reaction between butyl glyoxylate and butadiene has been reported to give 41% yield of the corresponding 3,6-dihydropyran ester.[9]

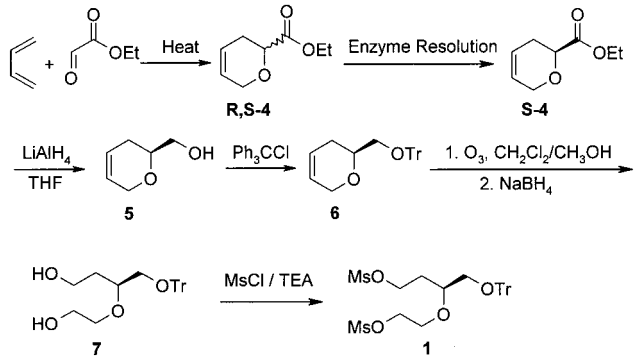
Ethyl glyoxylate is commercially available as a 50% solution in toluene, and all our experiments were carried out with this solution. The presence of a solvent during the reaction is beneficial since it helps solubilize the oligomers and polymers formed during the reaction and makes the reaction mixture less viscous and easily stirred. To carry out the Diels−Alder reaction, ethyl glyoxylate solution and hydroquinone were charged to an autoclave and heated to 150−170 °C. An excess of butadiene was then pumped into the reaction mixture over 1−2 h. The vapor pressure of butadiene at 160 °C is ∼40 bar. Due to the presence of solvents, the maximum pressure observed during the reaction was of the order of 15−16 bar. A pressure drop was observed as butadiene was consumed and the pressure stabilized at 10−11 bar. Temperature was a critical factor in obtaining good conversions. Below 155 °C, conversion of ethyl glyoxylate to the product was lower, and up to 20% of ethyl glyoxylate was recovered even when an excess of butadiene was used. Under similar conditions <5% of ethyl glyoxylate remained unreacted at 160−170 °C. The reaction was not carried out at higher temperatures, since DSC data indicated that ethyl glyoxylate is not very stable above 220 °C. Ethyl glyoxylate that remains unreacted can be recovered and recycled if desired. The reaction has also been carried out by charging all the reactants together at the beginning, but this procedure offered no improvement in yield or purity. The addition of butadiene gradually to the reaction mixture

(7) Johanson M.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 573.
(8) Gosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427−2430.
(9) Abuzov, A. Y.; Klimov, E. M.; Klimova, E. I. *Dokl. Akad. Nauk SSSR* **1962**, *142*, 341−343.

Scheme 3



Scheme 4



is a safer process, since it minimizes the potential for the exothermic polymerization of butadiene at higher temperatures.

The crude product obtained in the Diels−Alder reaction contained several impurities including unreacted ethyl glyoxylate, toluene, ethyl glyoxylate diethyl acetal, and butadiene oligomers and polymers. Most of these impurities were separated from the product by fractional distillation. However, complete removal of ethyl glyoxylate diethyl acetal by distillation was difficult without significant yield loss since its boiling point was close to that of the product. Product after distillation was 90−95% pure and it was used without further purification in the next step. The isolated yield of **4** based on the amount of ethyl glyoxylate consumed ranged from 50 to 60%.

Enzymatic Resolution of *R,S*-4. The resolution of racemic esters by selective enzymatic hydrolysis of one of the isomers is a well-known process. Many types of hydrolases work in this application.[10] To be economical, the enzyme should be inexpensive, commercially available, and highly active. It is also preferable to find an enzyme to selectively hydrolyze ***R*-4** to the acid, which can then be removed easily by base extraction. ***S*-4** can then be easily recovered from the reaction mixture in high optical purity even if the enzyme is only moderately selective.

Twenty-eight commercially available hydrolases (Chiroscreen EH, Altus Biologics) were screened to identify an enzyme that has the above characteristics. Initial screenings were performed on small scale in a phosphate buffer (1 mL) at pH 7 using 20 μL of ester and 100 mg of the enzyme. Aliquots of the ester were analyzed by GC to determine the extent of hydrolysis and selectivity. To determine the enantioselectivity factor E,[11] the optical purity of the hydrolyzed acid was also determined after conversion of the acid to its methyl ester. Several commercial formulations of *B. lentus* protease and ChiroCLEC-BL (cross-linked enzyme crystals from Altus Biologics) exhibited E-values > 50. Aqueous formulations of *B. lentus* protease were selected for further studies because of their lower cost. The low cost of the enzyme also eliminated the need for its recovery and reuse.

Reaction conditions for the resolution of **4** were optimized using a ~5% solution of *B. lentus* protease. Optimization studies were performed using 0.3 mL of protease formulation, 1 g of **4**, and 1 mL of 0.3 M phosphate buffer. Results of our optimization studies can be summarized as follows: (1) raising the temperature of the reaction from 25 to 45 °C increased the activity of the enzyme (conversions of 42.5 and 52%, respectively, in 1 h) but reduced the selectivity slightly (from an E value of 36.7 to 31.4). (2) The presence of cosolvents such as toluene or acetonitrile reduced the activity of the enzyme. (3) At higher substrate concentration, relatively higher enzyme levels were required to get the same rate conversion. (4) The pH of the reaction mixture was an important factor in obtaining good selectivity and conversion. At pH 7, selectivity was high (E = 36.6), but conversion was lower (39.3%) after 16 min. At pH 8, higher conversion was obtained (50.5%) over the same period at the expense of selectivity (E = 31.5). At higher pH (>9), nonselective base-catalyzed hydrolysis of the ester was observed. (5) The rate of the reaction was slower when buffer concentration was high. Thus, the conversion obtained in 1 M phosphate buffer was only about 25% of that obtained in 0.1 and 0.3 M phosphate buffers under similar conditions (7 vs 27%).

Even on large scale, the resolution of **4** was carried out easily by stirring the ester, buffer, and enzyme together at 20−30 °C. The pH during the reaction was maintained at 7−8 by the addition of sodium hydroxide. The reaction was followed by chiral GC for the ee of ***S*-4** in the organic phase and was stopped when the desired ee was achieved. It was possible to obtain 35−40% recovery of ***S*-4** with ee ≥99.5%. After the reaction, a solvent was added, and ***S*-4** was extracted out and recovered. As can be seen from the Experimental Section, unlike that in many other enzyme-catalyzed processes, the throughput in our process is high, and work-up of the product is simple. As has been mentioned before, the low cost of the enzyme also eliminated the need for its recovery and reuse, thus making this resolution an easy process to scale up.

We have demonstrated that *R*-3,6-dihydro-2H-pyran-2-carboxylic acid can be recovered from the aqueous phase

(10) Bornscheuer, U. T.; Kazlaauskas R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999.
(11) Chen, C. S.; Sih, C. J.; Girdukas, G. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

by acidification and extraction. In principle, the acid can be converted to an ester, reequilibrated to a racemic mixture, and recycled through the process although the economic viability of this approach has not been determined.

Reduction of *S*-4. The reduction of ***S*-4** to (*S*)-3,6-dihydro-2H-pyran-2-yl methanol **5** was carried out easily by adding the ester slowly to solutions of lithium aluminum hydride (LAH) in THF or adding LAH solution to the ester. The reaction was done at 0−10 °C to reduce racemization. The ee of the alcohol **5** obtained was generally close to that of the starting ester. Purification of **5** can be carried out by vacuum distillation, but we have demonstrated that the crude product can be used as such in the next step. The yield of the product in this step was 85−90%.

We have also demonstrated that this reduction can be done using sodium borohyride (SBH) and methanol. However, the reaction is difficult to control since SBH does not react without methanol. The reaction between methanol and SBH can become uncontrollable on large scale. Our previous experience with similar reductions is that temperature control is difficult in such reactions and racemization can occur at higher temperatures. Therefore, LAH was chosen for scale-up.

Tritylation of 5. Tritylation of *R*-glycidol was done in dichloromethane by the Lilly group. Due to waste disposal issues associated with this solvent, we chose to do the tritylation of **5** in pyridine.[12] Reaction mixtures were worked up by water quench followed by filtration and recrystallization of the crude product. Recrystallization of the crude product was done from 2-propanol containing small amounts of triethylamine. The addition of triethylamine was necessary to avoid the formation of trityl isopropyl ether by solvolysis of the product when heated in 2-propanol. The yield of the product in this step was 75−80%. Impurities such as ethyl glyoxylate diethyl acetal carried over from previous steps were removed during the isolation of **6**. Crystallization of **6** may also offer an opportunity for enantiomeric enrichment if it is required.

Reductive Ozonolysis of (*S*)-2-Trityloxymethyl-3,6-dihydro-2H-pyran, 6. Ozone is one of the best reagents that can be used to cleave a C═C bond.[13] The reaction of ozone with olefins is extremely fast. However, in absence of a reactive solvent, ozonides and peroxides that are often very unstable are produced as major products. These products decompose on warming to give complex mixtures. The mechanism of ozonolysis of olefins has been studied extensively, and the Criegee mechanism is well accepted.

Ozonolysis of an olefin in the presence of methanol produces a methoxy hydroperoxide and a carbonyl compound as products. It is well known that these intermediates can be reduced with sodium borohydride to produce alcohols. Although **6** could give intermediates different from **3** during ozonolysis, we anticipated that the intermediates formed from **6** would be reduced by sodium borohydride to yield **7**.

Ozonolysis of **6** was studied at temperatures ranging from −78 to −0 °C in mixtures of dichloromethane and methanol. To determine the stability of the intermediates formed, carbon and proton NMR spectra of the reaction mixtures were recorded at low temperatures in CD_2Cl_2/CD_3OD mixtures. The intermediates formed were found to be stable below −30 °C. Diol **7** was obtained in high yields when the reaction mixture was quenched with aqueous sodium borohydride. If the reaction mixture was warmed to room temperature before the quench, a complex mixture of products formed as indicated by NMR spectrum. Similarly, only polymeric products were formed when the ozonolysis was carried out without methanol even at −78 °C. When ozonolysis was done at −5 to 0 °C in the presence of methanol, formation of trityl methyl ether was noticed, a result similar to which has been observed before.[2] Diol **7** was obtained in near quantitative crude yield when ozonolysis was done below −30 °C, followed by the addition of the reaction mixture to cold, aqueous sodium borohydride solution. The product was used without further purification in the next step.

Preparation of 1. The conversion of **7** to **1** in high yields has been described by the Lilly group. The reaction of the diol with methane sulfonyl chloride was carried out in dichloromethane in the presence of triethylamine. The crude product was then recrystallized from a mixture of ethyl acetate and heptane. The reaction can also be done in ethyl acetate, eliminating the use of dichloromethane. Care should be exercised to remove all traces of acid from **1** since the trityl group can cleave in the presence of acids, causing the decomposition of product. The yield of the product in this step was 85−90%. The chemical purity was >99% and ee was >99.5%.

Summary

We have developed a commercial process for the synthesis of **1** through a combination of chemical and biocatalytic reactions. Our overall yields are lower than that reported in the previous synthesis.[2] However, cost estimates indicate that our process is very cost-competitive since we have been able to eliminate the use of several expensive reagents and simplify the overall process. The first four steps of the process have been successfully scaled up to make several hundred kilograms of **6**, closely matching laboratory yields, purity, and ee. Further efforts to reduce the cost of manufacturing **1** will be concentrated on the recovery and recycle of *R*-3,6-dihydro-2H-pyran2-carboxylic acid. Chiral hetero Diels−Alder reactions have found applications in the synthesis of other pharmaceutical intermediates such as compactin and mevinolin.[4,5] The strategy described in this work should be applicable to these and similar compounds.

Experimental Section

Raw Materials. All raw materials used in this study were purchased from commercial sources and used without further purification.

Analytical. HPLC analyses were performed on Varian 9000 series or HP1100 series instruments using reverse-phase mode. A Zorbax Rx or XDB C8 column was used for the

(12) Green T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: 1999, p 102−104.
(13) For a review see: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978.

analyses of **1**, **7**, and **8**. Detection wavelength was 210 nm. Gradient elution of solvents from 60% water (modified with 0.02% phosphoric acid) and 40% acetonitrile to 40% water over 20 min, followed by holding for 20 min gave satisfactory separations of most components. Solvent flow rate was 1.5 mL min^{-1}. GC analyses were performed on a HP-6890 gas chromatograph with FID detector. A DB-1 column from J&W Scientific was used for analyses of reaction mixtures and products in the first three steps. GC conditions: 80 °C−3min−10 °C/min−250 °C−10min, He flow at 1 mL/min. A β-Dex column from Supelco or Cyclodex-B column from J&W Scientific was used for the chiral purity analysis of **5**. GC conditions: 100 °C−10min−1 °C/min−115 °C−5 min. NMR spectra were recorded on a Bruker EM-500 spectrometer in $CDCl_3$ unless otherwise noted.

Preparation of 2-carboethoxy 3,6-Dihydro-2H-pyran 4: General Procedure. A high-pressure autoclave was charged with a 50% solution of ethyl glyoxylate in toluene and BHT (1 wt % based on the weight of ethyl glyoxylate solution). The mixture was heated to 150−170 °C and butadiene (1.2−1.4 mol/mol of ethyl glyoxylate) was added over a period of 1−1.5 h. After the addition, the mixture was stirred at the same temperature until a GC analysis of the reaction mixture showed no further decrease in the level ethyl glyoxylate (8−10 h). Excess butadiene was then purged out with nitrogen. The solvent was removed in vacuo on a rotary evaporator, and the residue was distilled fractionally under vacuum. The fraction distilling at 85−95 °C and 10−20 millibar was collected. The yield of **4** after accounting for recovered ethyl glyoxylate varied from 50 to 60%, depending on reaction conditions. The product thus obtained was 90−95% pure on the basis of area % GC analysis. In some experiments, volatile products were first separated from the oligomers and polymers by flash vacuum distillation, and the distillate obtained was subjected to fractional distillation. The purity of the product obtained in this case was ∼97%. The structure of the product was confirmed by GC−MS analysis and NMR spectra. ^{1}H NMR (500 MHz) δ 1.32 (t, 3H), 2.38 (m, 2H), 4.22 (m, 1H), 4.26 (q, 3H), 4.3 (dd, 2H), 5.74 (m, 1H), 5.84 (m, 1H). ^{13}C NMR (500 MHz) δ 14.08, 27.61, 60.95, 65.41, 71.99, 122.81, 125.96, 171.27.

Resolution of 2-Carboethoxy-3,6-dihydropyran *R,S*-4. A 1-L reactor was charged with 360 mL of a pH 7 phosphate buffer (made by dissolving 39.2 g KH_2PO_4 and 10.37 g of NaH_2PO_4 in 1 L water) and 150 g of 2-carboethoxy-3,6-dihydropyran. The pH of the mixture was readjusted to 7.0 by the addition of 50% sodium hydroxide. A commercial formulation of *B. lentus* protease (90 mL, ∼5% solution of the enzyme) was then added, and the mixture was stirred at room temperature for 8 h. The pH of the reaction mixture was maintained between 7 and 8 by the addition of 50% sodium hydroxide solution with an automatic pH controller. Samples of the organic phase were analyzed periodically by GC to determine the extent of reaction. After 8 h, the ee of *S*-ester in organic phase was >99.5%. The pH of the mixture was adjusted to 8, and the mixture was extracted twice with 100 mL each of toluene. Organic phases were combined, washed with 100 mL of saturated sodium chloride, and filtered through Celite. Toluene was removed in vacuo to obtain 58.0 g of ***S*-4** as a yellow oil (38% recovery). Purity of the crude product was >97%, and ee was 99.5% as determined by GC.

Preparation of (*S*)-3,6-Dihydro-2H-pyran-2-yl methanol 5. A 1-L, four-neck round-bottom flask was equipped with a mechanical stirrer, thermometer, and 500-mL addition funnel.

The flask was purged with nitrogen and charged with 500 mL of 1 M lithium aluminum hydride solution in THF. The solution was cooled to 0−5 °C. A solution of 150 g of ***S*-4** in 140 mL of tetrahydrofuran was added at 0−8 °C over 80 min. After the addition, the reaction mixture was stirred at 6−12 °C for 2 h. The reaction mixture was quenched at 5−10 °C by careful addition of 19 mL of water. To the mixture was then added 19 g of 15% sodium hydroxide solution and 58 mL of water gradually. The reaction mixture was stirred at room temperature for 2 h. The precipitated aluminum hydroxide was removed by filtration. The precipitate was washed four times with 100 mL portions of warm THF. The filtrates were combined and THF was stripped in vacuo. To the residue was added 300 mL of toluene and the solvent was again removed in vacuo to obtain 103.2 g (94%) of yellow oil. Purity of the product was 97% as determined by GC analysis.

Preparation of (*S*)-2-Trityloxymethyl-3,6-dihydro-2H-pyran 6. A 3-L, four-neck round-bottom flask equipped with a mechanical stirrer, thermocouple, and 125-mL addition funnel was charged with 269 g of trityl chloride, 5.4 g of DMAP and 600 mL of pyridine. A clear, yellow solution resulted after 5 min of stirring. The temperature dropped from 23 to 14 °C. The mixture was heated to 20 °C over 15 min, and 100 g of **5** was added over 20 min. An exotherm from 20 to 30 °C was observed. The reaction mixture was heated to 50 °C over 20 min and stirred overnight. The reaction mixture (brown slurry) was cooled to 20 °C. Water (1 L) was added over 20 min. An exotherm from 20 to 26 °C was noted, and a fine solid separated out. The mixture was stirred at 5−10 °C for 1 h. The solids were collected by filtration and washed with 0.7 L water. The solids were washed on the filter with 0.5 L of heptane and sucked dry on the filter for 30 min. The crude product was recrystallized from 1.2 L of a mixture of 9:1 2-propanol and triethylamine. The crystals were filtered and washed with 200 mL of heptane and vacuum-dried. The yield of the product was 240.7 g (77.2%). Mp 120−123 °C. ^{1}H NMR δ 1.74 (m, 2H) 2.96 (br s 1H) 3.07 (br m 1H) 3.4−3.7 (m, 3H) 4.64−4.82 (m, 2H) 7.19 (m, 3H) 7.26 (m, 6H) 7.43 (m, 6H).

Ozonolysis: Low-Temperature NMR Studies. (1) A solution of 0.2 g of **6** in 0.4 mL of CD_2Cl_2 was cooled in a dry ice−acetone bath, and ozonated air was bubbled through until the solution turned blue. The solution was then purged with nitrogen to remove excess ozone. Proton NMR spectrum of the solution was recorded at −40 °C and showed only very broad peaks, indicating the presence of polymeric products. A white precipitate formed when the solution was diluted with acetone. (2) A solution of 0.2 g of **6** was prepared in a mixture of 1.5 mL of CD_2Cl_2 and 1 mL of

CD_3OD.The solution was cooled in a dry ice−acetone bath. Ozonolysis was carried out as above, and the resulting solution was split into two portions. CMR and PMR spectra of first portion were recorded at −40 °C. The second portion was warmed to room temperature, and NMR spectra were recorded after 1.5 h. The spectra of the latter sample were very different from that of the former and showed the presence of a complex mixture.

Preparation of (*S*)-3-(2-Hydroxyethoxy)-4-(triphenylmethoxy)-1-butanol 7. A jacketed reactor equipped with a fritted gas inlet, thermocouple, and dry ice condenser were charged with 71.5 g (0.2 mol) of **6**, 350 mL of dichloromethane, and 250 mL of methanol. The clear, yellow solution was cooled to −40 °C, and ozonated air (generated by a PCI ozone generator) was bubbled through the solution at −40 to −25 °C until the solution turned light blue (∼85 min). Nitrogen was bubbled through the reaction mixture at −45 to −50 °C for 20 min until the blue color disappeared.

A 1-L flask was charged with 17.5 g of sodium borohydride and 500 mL of 0.02 N caustic and cooled to −5 °C with stirring. The cold reaction mixture obtained after ozonolysis was added to the sodium borohydride solution over 10 min. The mixture was then allowed to slowly warm to room temperature and stirred overnight. The phases were separated, and the aqueous phase was back-extracted with 50 mL of dichloromethane. The combined organic phases were evaporated to dryness on a rotary evaporator to obtain 81.9 g (100%) of viscous oil that was used in the following experiment.

Preparation of (*S*)-3-[2-{(Methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol Methanesulfonate 1. A 2-L reactor was charged with solution of 81.9 g (0.21 mol) of (*S*)-3-(2-hydroxyethoxy)-4-(triphenylmethoxy)-1-butanol obtained in the previous experiment and 700 mL of dichloromethane and 87 mL of triethylamine. The mixture was cooled to 0−5 °C, and a solution of 43.5 mL of methane sulfonyl chloride in 50 mL of dichloromethane was added at 0−5 °C over 80 min. The reaction mixture was the stirred for 1 h and then diluted with 500 mL of dichloromethane. It was then extracted twice with 315 mL of water and once with 315 mL of saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate and filtered. The solution was evaporated to dryness on rotary evaporator to obtain 111.1 g of crude product. The crude product was dissolved in 345 mL of ethyl acetate at 35−40 °C and filtered. The filtrate was charged to a 2-L reactor, and 690 mL of heptane was added dropwise over 3.5 h. The mixture was stirred for 90 min and then filtered in a pressure filter. The filter cake was reslurried in 300 mL of heptane and filtered, washing the crystals with additional heptane. The crystals were dried in vacuo to obtain 96.7 g (84.5%) of **1**. HPLC analyses indicated the product to have ee and chemical purity >99%.

Acknowledgment

We express our appreciation to PPG Industries Inc. for permission to publish this work. We acknowledge the help of Dr. Tim Flood in recording and interpreting NMR spectra and of Dr. Felicia Tang with HPLC analyses. We also thank Professor Janusz Jurczak (Polish Academy of Sciences, Warszawa, Poland) for preliminary work.

Note Added after ASAP: There were errors in the **Preparation of (*S*)-2-Trityloxymethyl-3,6-dihydro-2H-pyran 6** published in the version posted ASAP March 16, 2002. The corrected version was posted ASAP April 26, 2002.

Received for review January 2, 2002.

OP020202A