A Practical Procedure for the Large-Scale Preparation of Methyl (2*R*,3*S*)-3-(4-Methoxyphenyl)glycidate, a Key Intermediate for Diltiazem

Toshiyuki Furutani, Ritsuo Imashiro, Masanori Hatsuda, and Masahiko Seki*

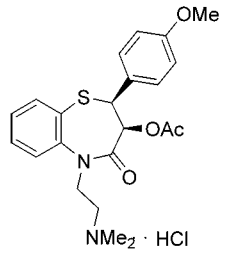
Product & Technology Development Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan

m-seki@tanabe.co.jp

Received February 24, 2002

Abstract: A practical synthesis of methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2**, a key intermediate for diltiazem (**1**), was developed. Treatment of methyl (*E*)-4-methoxycinnamate **3** with chiral dioxirane, generated from chiral ketone **4**, provided (−)-**2** in 77% ee and 89% yield. The crude mixture of (−)-**2** and **4** was efficiently separated by the use of novel and simple equipment performing a lipase-catalyzed transesterification and a continuous dissolution and crystallization to furnish the optically pure (−)-**2** and recovery of **4** in 74% and 91% yield, respectively.

Catalytic asymmetric synthesis has recently been recognized as one of the most expedient approaches to enantiomerically pure chiral compounds, and considerable efforts have been devoted to enhance the enantioselectivity as well as the catalytic activity.[1] Quite few examples[2] are, however, found in technology that have been applied to a practical large-scale preparation. Serious drawbacks of the method lie in the fact that they largely need an expensive chiral catalyst, a quite low temperature, or a costly workup to separate the product and chiral catalyst. We have recently reported a synthesis of methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2**,[3] a key intermediate[4] for diltiazem (**1**),[5] by means of a catalytic asymmetric epoxidation of methyl (*E*)-4-methoxycinnamate **3**[6] with chiral binaphthyl ketone **4**[7,8] used as the catalyst and subsequent separation of (−)-**2** and **4** through continuous dissolution and crystallization.[9] The synthesis is efficient in terms of mild reaction conditions (5−27 °C) and high recovery of **4** (88%). However, the yield of optically pure (−)-**2** (64%) proved still unsatisfactory for a practical use. Herein we describe a highly optimized and practical procedure for the preparation of (−)-**2** using an improved workup and equipment that involves a lipase-catalyzed transesterification of the unwanted enantiomer (+)-**2** [(2*S*,3*R*) enantiomer].



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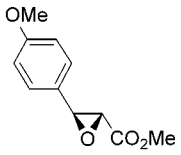
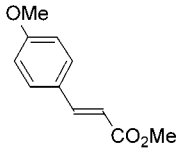


(-)-**2**



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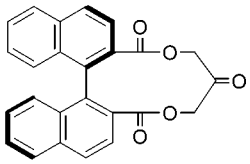

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The preparation of (−)-**2** from **3** was conducted as described in Scheme 1. Treatment of **3** with 5 mol % of **4** in the presence of Oxone (1 equiv) and $NaHCO_3$ (3.1 equiv) in aqueous 1,4-dioxane at 5 °C for 24 h and at 27 °C for 2 h provided (−)-**2** in 77% ee and 89% yield. There are two significant improvements over the previously reported procedure.[9] The first modification is the workup prior to the separation of (−)-**2** and **4**. We have previously extracted the products by adding $CHCl_3$ to the reaction mixture. However, choice of a halogenated solvent such as $CHCl_3$ is not environmentally benign and makes it difficult to recover 1,4-dioxane. Direct distillation of the reaction mixture and extraction of the products with toluene were thus performed. However, considerable ring opening of (−)-**2** to the corresponding diol was observed in the workup whose scale was larger than 0.1 mol. To avoid the decomposition of (−)-**2**, crystallization of (−)-**2** and **4** by adding water to the reaction mixture was attempted (Scheme 2). Addition of water (20 mL/g of initially added **3**) to the reaction mixture was found to directly crystallize (−)-**2** and **4**. Although the resulting solids contained an acceptable amount of (−)-**2** (85% ee,

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(2) For example, see: (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, 2599. (c) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Moyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208. (d) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (e) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

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(8) For a practical synthesis of **4**, see: (a) Seki, M.; Furutani, T.; Hatsuda, M.; Imashiro, R. *Tetrahedron Lett.* **2000**, *41*, 2149. (b) Furutani, T.; Hatsuda, M.; Imashiro, R.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4763. (c) Kuroda, T.; Imashiro, R.; Seki, M. *J. Org. Chem.* **2000**, *65*, 4213. (d) Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677. (e) Furutani, T.; Hatsuda, M.; Shimizu, T.; Seki, M. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 180. (f) Hatsuda, M.; Hiramatsu, H.; Yamada, S.; Shimizu, T.; Seki, M. *J. Org. Chem.* **2001**, *66*, 4437.

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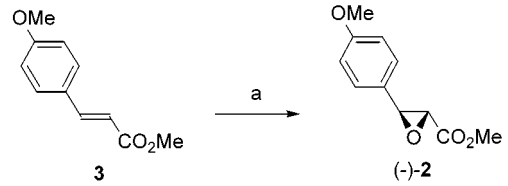
10.1021/jo025647b CCC: $22.00
Published on Web 05/21/2002

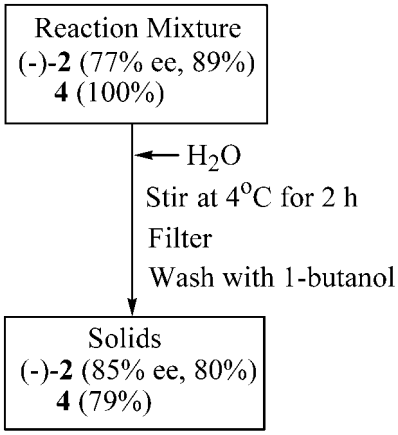
Scheme 1[a]



3 (-)-**2**

[a] Reagents and yields: (a) (i) **4** (5 mol %), Oxone (1 equiv), $NaHCO_3$ (3.1 equiv), 1,4-dioxane/H_2O, 5 °C, 24 h, 27 °C, 2 h, (ii) NaCl, extraction with 1,4-dioxane, (iii) evaporation, (iv) separation using equipment shown in Figure 1, 74% yield (>99% ee) with 91% recovery of **4**.

Scheme 2[a]

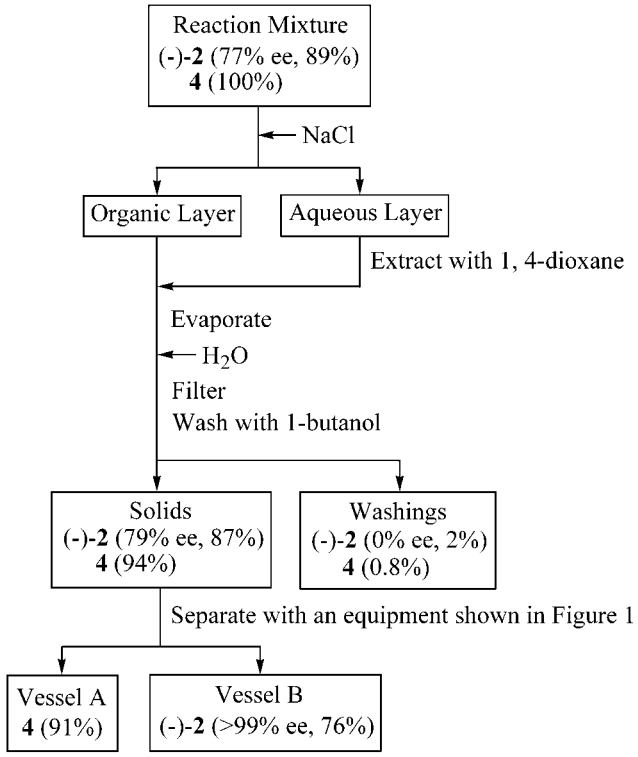


[a] The yields of (−)-**2** and **4** shown in the scheme are based on **3** and **4** that were initially added for the asymmetric epoxidation.

80% based on **3**), recovery of **4** was unsatisfactory (79% based on initially added **4**). An alternative procedure was then undertaken which consisted of addition of NaCl to the reaction mixture to separate phases and extraction of the spent aqueous phase with another portion of 1,4-dioxane (Scheme 3). The combined organic phases were distilled to recover 1,4-dioxane in 83% yield. Then, to the residue was added water to form a precipitate, which upon filtration and subsequent washing with 1-butanol afforded colorless water-free solids (water <1 wt %) containing an acceptable amount of (−)-**2** (79% ee, 87%) and **4** (94%).

The second significant improvement was made on the separation of (−)-**2** and **4**. We have previously developed an efficient separating system based on continuous dissolution and crystallization of the crude product.[9] If the unwanted enantiomer (+)-**2** may selectively be converted to an oily *n*-butyl ester concomitantly during the separation, the yield of (−)-**2** should be improved. Thus, we designed a system that includes a lipase column for the transesterification[10] of unwanted (+)-**2** (Figure 1). The system has two vessels (A and B) initially kept at 25 and 18 °C, respectively, and fitted with a glass filter. A column containing Celite-immobilized lipase SM (*Serratia marcescens*)[11] was placed above the inlet of vessel A. The crude mixture of (−)-**2** and **4** was loaded into vessel A with isopropyl ether containing 3.8 wt % of 1-butanol. The solvent was then circulated between the

Scheme 3



two vessels using a lab pump. After 23 h, 80% of the unwanted enantiomer (+)-**2** was selectively converted to an oily *n*-butyl ester, and the circulation was further continued for 2 h at lower temperature (10 °C for vessel A and 5 °C for vessel B). Through these treatments were obtained optically pure (−)-**2** (74% based on **3**) and **4**[12] (91% based on initially added **4**) both in excellent yields from vessel B and A, respectively. It is worth noticing that the equipment needs only a very small amount of lipase SM (absorbed on Celite, 1.2 g for 1 mol scale separation) since the amount of the substrate i.e. (+)-**2** is vastly little (ca. 10% of the total amount of **2**) and the selectivity of the transesterification is unprecedentedly high (*E*-value = >100).[13]

In conclusion, a practical synthetic method of a key intermediate (−)-**2** for diltiazem was accomplished. The present methodology, involving the dioxirane-mediated asymmetric epoxidation of methyl (*E*)-4-methoxycinnamate **3** and subsequent efficient separation of the product (−)-**2** and chiral catalyst **4**, represents one of the best approaches to (−)-**2**. Although it may have some limitations on the generality of the substrates other than **3**, the strategy used in this study would be of help for the industrial chemists to apply the modern catalytic asymmetric synthesis to their large-scale preparation of chiral compounds.

Experimental Section

General Method. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane used as an internal standard. Optical rotations were measured at the indicated temperature with a sodium lamp (D line, 589 nm). All solvents and reagents were used as received.

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(12) The recovered catalyst **4** could be used again for the asymmetric epoxidation without any decrease in the chemical and optical yields.

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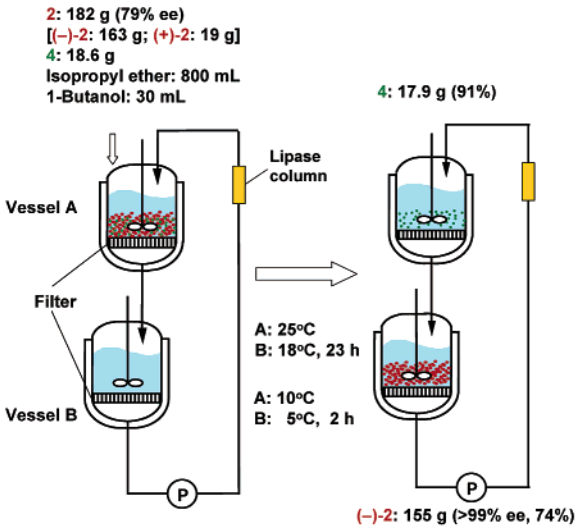

Figure 1. Separation of (−)-**2** and **4**.

Catalytic Asymmetric Epoxidation of 3. To a solution of methyl (*E*)-4-methoxycinnamate **3** (192 g, 1 mol) and the catalyst **4** (19.8 g, 50 mmol) in a mixed solvent of 1,4-dioxane (2.4 L) and H_2O (1.44 L) were successively added Oxone (614.8 g, 1 mol) and $NaHCO_3$ (260.4 g, 3.1 mol) at 5 °C. The suspension was mechanically stirred at 5 °C for 24 h. The mixture was then warmed to 27 °C, and stirring was continued for 2 h. Into the mixture was added NaCl (280 g), and the mixture was stirred for 5 min. The organic phase was separated, and the aqueous phase was extracted twice with 1,4-dioxane (2 × 500 mL). The combined extracts containing (−)-**2** (186 g, 89% yield, 77% ee) and **4** (19.8 g, 100%) were distilled at 27 °C for 4 h under reduced pressure (18 mmHg) to recover 1,4-dioxane [3.12 L (water content 10%), recovery 83%]. Into the residue was added water (1.5 L), and the mixture was stirred at 5 °C for 30 min. The crystals formed were collected and washed with water (600 mL) and *n*-BuOH (200 mL) to provide the crude mixture (water content <1 wt. %) of (−)-**2** (182 g, 87% yield, 79% ee) and **4** (18.6 g, 94%). The yield and the ee value of (−)-**2** and **4** were determined by HPLC (Chiralcel OD, hexane/*i*-PrOH = 10:1, 220 nm, 40 °C; (−)-**2**, 8.1 min; (+)-**2**, 9.8 min).

Separation of Product (−)-2 and Catalyst 4. The equipment for separating (−)-**2** and **4** used in this study has two vessels (vessel A and B), an immobilized lipase column, and a circulating pump as shown in Figure 1. The vessels (working volume 0.5 L) are made of glass and are equipped with a water jacket, a mechanical stirrer, and a glass filter (pore size 50 μm). The lipase column (working volume 0.01 L) is made of glass. The temperature of vessel A and B was initially kept at 25 and 18 °C, respectively. The crude mixture of (−)-**2** (182 g, 79% ee) and **4** (18.6 g) obtained by the asymmetric epoxidation (see above) was loaded on vessel A with isopropyl ether (400 mL) and 1-butanol (15 mL) and stirred. Celite-immobilized Lipase SM (1.2 g) was used in the lipase column. When the inner temperature of vessel A reached 25 °C, the suspension was filtered through the glass filter to vessel B, and another portion of isopropyl ether (400 mL) and 1-butanol (15 mL) was loaded into vessel A. When the inner temperature of vessel B reached 18 °C, seed crystals (ca. 100 mg) of (−)-**2** were added to vessel B with stirring. Then, the filtrate was circulated by the lab pump (30 mL/min) in a closed system for 23 h at these temperatures and at lower temperatures [10 °C (vessel A) and 5 °C (vessel B)] for 2 h. The crystals remaining in vessel A were collected and washed by isopropyl ether (50 mL) to recover **4** (17.9 g, 91% based on initially added **4**), and the crystals formed in vessel B were collected and washed with MeOH (50 mL) to give (−)-**2** (>99% ee, 155 g, 74% based on **3**). (−)-**2**: mp 88 °C; $[\alpha]^{24}_D$ −205 (*c*, 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.05 (d, J = 1.7 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.51 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.2, 127.1, 126.9, 126.6, 114.3, 114.0, 57.8, 56.4, 55.2, 52.4; IR (KBr) ν 1748, 1613 cm^{-1}; MS *m*/*z* 208 (M^+). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.14; H, 5.50. The circulating fluid obtained after the separation contained (−)-**2** (6.1 g, 2.9%), (+)-**2** (3.4 g, 1.6%), **4** (0.25 g, 1.3%), and (+)-*n*-butyl ester (15.6 g, 6.2%) transesterified from (+)-**2** (HPLC, Chiralcel OD, hexane/*i*-PrOH = 10:1, 220 nm, 40 °C; (−)-**2**, 8.1 min; (+)-**2**, 9.8 min, (−)-*n*-butyl ester, 6.0 min; (+)-*n*-butyl ester, 6.4 min).

Celite-Immobilized Lipase SM.[11] Aqueous Lipase SM solution (30 mL) was thoroughly mixed in a 500 mL flask with Celite (30 g), and the mixture was dried at 30 °C under reduced pressure to give 36.5 g of the Celite-immobilized Lipase SM having an activity of 8.2 U/mg (olive oil hydrolysis activity).

JO025647B