Pergamon

Tetrahedron Letters 42 (2001) 8201–8205

TETRAHEDRON LETTERS

A novel synthesis of a key intermediate for diltiazem

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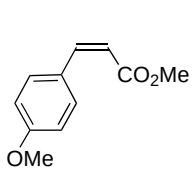
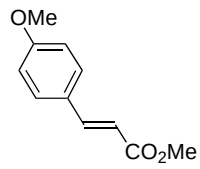
Received 6 August 2001; revised 13 September 2001; accepted 14 September 2001

Abstract—A practical synthesis of methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2a**, a key intermediate for diltiazem (**3**), was described. Treatment of methyl (*E*)-4-methoxycinnamate (*E*)-**1a** with chiral dioxirane, generated in situ from a catalytic amount of an 11-membered C_2-symmetric binaphthyl ketone **7a**, provided (−)-**2a** in 78% ee and 89% yield. The crude mixture of (−)-**2a** and **7a** was efficiently separated by the use of novel equipment performing continuous dissolution and crystallization to furnish the optically pure (−)-**2a** (>99% ee) and recovery of **7a** in 64 and 88% yields, respectively.

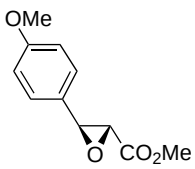
Diltiazem hydrochloride (**3**) is one of the most potent calcium antagonists and has been widely used in the world for over 20 years for the treatment of cardiovascular diseases.[1] Since methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2a** was recognized as a key intermediate for **3**,[2] extensive research has been directed toward an efficient synthetic method of (−)-**2a**. One of the most direct approaches to (−)-**2a** involves asymmetric epoxidation of methyl 4-methoxycinnamate **1**. Excellent enantioselectivity has been observed when a manganese–salen catalyst was employed as chiral catalyst.[3] However, it requires the poorly accessible methyl (*Z*)-4-methoxycinnamate (*Z*)-**1** as a starting material. Recent publications have shown that optically active glycidates can be obtained through asymmetric epoxidation of inexpensive (*E*)-cinnamates by chiral dioxiranes generated in situ from chiral ketones **4**,[4] **5**,[5] and **6**.[6] These dioxiranes are, however, not sufficiently effective toward the electron-poor olefins, and large amounts of **4**–**6** are necessary to obtain acceptable yields and enantioselectivities. To date, an industrial synthesis of (−)-**2a** has, therefore, been conducted by means of a poor-yielding (43% yield) kinetic resolution of racemic glycidate (±)-**2a** using a lipase-catalyzed enantioselective hydrolysis.[7]



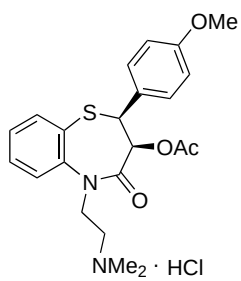
(*Z*)-**1a**



(*E*)-**1a**



(-)-**2a**



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Meanwhile, Yang et al. have developed the 11-membered C_2-symmetric biaryl ketones **7a**–**d** that catalyze epoxidation of various (*E*)-di- and tri-substituted olefins to provide epoxides with high stereoselectivities and in high yields.[8] We envisioned a possible use of the biaryl ketones **7a**–**d** as catalysts for the asymmetric epoxidation of methyl (*E*)-4-methoxycinnamate (*E*)-**1a** to obtain (−)-**2a**. The ketone catalysts **7a**–**d**, in contrast to **4**–**6**, might induce high reactivity as well as high

Keywords: asymmetric synthesis; epoxidation; epoxides; catalysts; crystallization.

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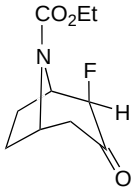
PII: S0040-4039(01)01762-2



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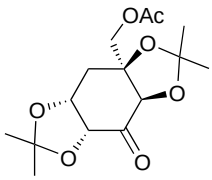

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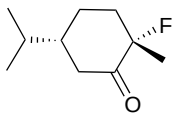

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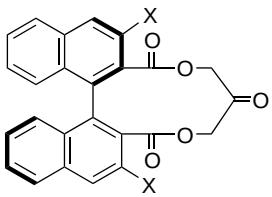
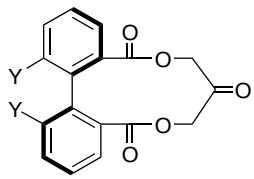


7a: X = H
7b: X = Cl



7c: Y = Cl
7d: Y = NO_2

enantioselectivity toward (*E*)-**1a** due to the electron-withdrawing lactone moieties and/or the π–π interaction between the aromatic groups in **7a**–**d** and (*E*)-**1a**. Stereocontrol using **7a**–**d** must come from ring opening of the intermediate dioxirane through *homotopic* cleavage, whereas, those derived from **4**–**6** must involve *heterotopic* cleavage. This can also be a contributing factor to the origin of good stereocontrol within **7a**–**d**. The ketones **7a**–**d** have the additional advantage of ease of preparation using our reported procedures.[9] Since a chromatographic purification of the product (−)-**2a** and the catalysts **7a**–**d** cannot be applied on a large-scale preparation, an alternative separating method is highly desirable. We describe herein a novel and practical synthesis of (−)-**2a** through the chiral dioxirane-mediated catalytic asymmetric epoxidation of (*E*)-**1a** using chiral binaphthyl ketone **7a** and subsequent efficient separation of the product (−)-**2a** and the catalyst **7a** based on the continuous dissolution and crystallization.

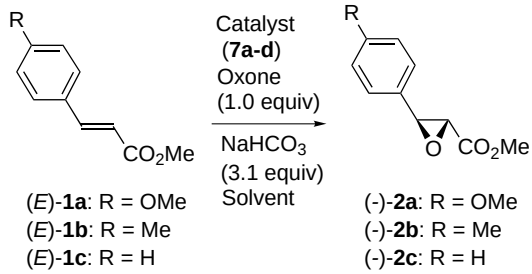
The biaryl ketones **7a**–**d** involving 1,1′-binaphthyl and 1,1′-biphenyl derivatives were screened for the epoxidation of (*E*)-**1a**. As depicted in Table 1, treatment of (*E*)-**1a** with Oxone (1.0 equiv.) and $NaHCO_3$ (3.1 equiv.) in the presence of **7a**–**d** (5 mol%) in DME–H_2O at 5–27°C for 27 h provided the desired epoxide (−)-**2a** in good enantioselectivities and yields (67–85% ee, 52–87% yield, Table 1, entries 1–4). The binaphthyl ketones **7a**,**b** proved to be more effective than biphenyl counterparts **7c**,**d** (Table 1, entries 1, 2 versus 3, 4). 3,3′-Dichloro-1,1′-binaphthyl ketone **7b** provided (−)-**2a** in 85% ee and 74% yield, and, in consistency with the reported epoxidation of (*E*)-4,4′-di-*tert*-butylstilbene,[8] the corresponding unsubstituted derivative **7a** gave a comparable result (76% ee, 87% yield) (Table 1, entries 1 and 2). Considering its ease of preparation, the chiral ketone **7a** was chosen as the catalyst for further optimization.

The role of a reaction solvent is of significance in terms of enantioselectivity and yield. While an aqueous solvent, DME–H_2O or CH_3CN–H_2O, has been frequently used for the dioxirane-mediated asymmetric epoxidation,[8] an inexpensive 1,4-dioxane–H_2O system is preferred in the present reaction to afford (−)-**2a** in 78% ee and 89% yield (Table 1, entry 6 versus entries 1 and 5). Use of a protic polar solvent such as CH_3OH as the co-solvent resulted in a poor yield (19%) albeit with a good enantioselectivity (72% ee) (Table 1, entry 7). In CH_3OH–H_2O, a considerable ring-opening of (−)-**2a** might lead to the poor yield. It is worth noticing that the reaction rate was remarkably high in acetone–H_2O to provide (−)-**2a** in excellent yield (93%) (Table 1, entry 8). Even though competing epoxidation with achiral dioxirane generated from acetone and/or direct epoxidation with Oxone should take place in the reaction, the moderate ee (49%) obtained in the acetone–H_2O system should reflect the easier formation of the dioxirane from **7a** than from acetone and/or the higher reactivity of the dioxirane derived from **7a** than the achiral oxidants. The biphasic solvent system (toluene–H_2O) did not produce (−)-**2a** at all (Table 1, entry 9).

Although the ee value of the product (−)-**2a** increased from 78 to 80% ee when the reaction was conducted at lower temperature (5°C), a considerably longer reaction period (48 h) was required to complete the reaction (Table 1, entry 10 versus 6). Elevating the reaction temperature from 5–27 to 40°C accelerated the reaction, but the higher temperature gave poorer ee and yield (70% ee, 66% yield, Table 1, entry 11). Use of smaller amounts of **7a** resulted in the decrease of both yield and enantioselectivity, possibly due to the direct epoxidation with Oxone (Table 1, entry 12 versus 6). The reaction temperature and the amount of **7a** were thus optimized to 5–27°C and 5 mol%, respectively. In order to demonstrate the efficacy of the epoxidation, the protocol was applied to the epoxidation of 4-methyl- and unsubstituted cinnamates **1b** and **1c**. Although more oxidant and base [Oxone (2 equiv.), $NaHCO_3$ (6.1 equiv.)], as well as longer reaction periods (42–53 h) were needed to achieve the satisfactory conversion, corresponding optically active glycidates (−)-**2b** and (−)-**2c** were obtained in both good yields and enantioselectivities (Table 1, entries 13 and 14). These epoxides are a key intermediate for a platelet aggregation inhibitor[10] and a Taxol side chain,[11] respectively.

To evaluate a separating of (−)-**2a** and **7a** by crystallization, the solubility of (−)-**2a** and **7a** in isopropyl ether was first measured at various temperatures (Fig. 1). The solubility of **7a** was quite low and was almost unaffected by lowering the temperature, while (−)-**2a** was considerably less soluble at lower temperature. A mixture of (−)-**2a** and **7a** was partially dissolved in isopropyl ether and was subjected to filtration. On cooling the filtrate, (−)-**2a** should crystallize preferentially.

Table 1. Catalytic asymmetric epoxidation of methyl (*E*)-cinnamate derivatives (*E*)-**1a**–**c** with chiral dioxirane generated in situ from chiral ketones **7a**–**d** under various conditions[a]



(*E*)-**1a**: R = OMe
(*E*)-**1b**: R = Me
(*E*)-**1c**: R = H

(-)-**2a**: R = OMe
(-)-**2b**: R = Me
(-)-**2c**: R = H

Entry	Catalyst (mol%)	Substrate	Solvent[b]	*T* (°C)	*t* (h)	Yield[c] (%)	ee[c] (%)
1	**7a** (5)	(*E*)-**1a**	A	5–27	27	87	76
2	**7b** (5)	(*E*)-**1a**	A	5–27	27	74	85
3	**7c** (5)	(*E*)-**1a**	A	5–27	27	52	67
4	**7d** (5)	(*E*)-**1a**	A	5–27	27	86	68
5	**7a** (5)	(*E*)-**1a**	B	27	24	33	72
6[d]	**7a** (5)	(*E*)-**1a**	C	5–27	27	89	78
7	**7a** (5)	(*E*)-**1a**	D	25	4.5	19	72
8	**7a** (5)	(*E*)-**1a**	E	25	3.5	93	49
9	**7a** (5)	(*E*)-**1a**	F	25	24	0	–
10	**7a** (5)	(*E*)-**1a**	C	5	48	92	80
11	**7a** (5)	(*E*)-**1a**	C	40	1.5	66	70
12	**7a** (2)	(*E*)-**1a**	C	5–27	26	84	76
13[e]	**7a** (5)	(*E*)-**1b**	C	10–27	42	95	72
14[e]	**7a** (5)	(*E*)-**1c**	C	10–27	53	75	74

[a] The reactions were conducted on a 10 mmol scale with 2 or 5 mol% of catalyst **7a**–**d**, except entry 6.
[b] A: DME–H_2O; B: CH_3CN–H_2O; C: 1,4-dioxane–H_2O; D: CH_3OH–H_2O; E: acetone–H_2O; F: toluene–H_2O.
[c] Determined by HPLC analysis of the crude mixture after aqueous work-up.
[d] The reaction was conducted on a 0.5 mol scale.
[e] The reactions were conducted by employing 2.0 equiv. of Oxone and 6.2 equiv. of $NaHCO_3$.

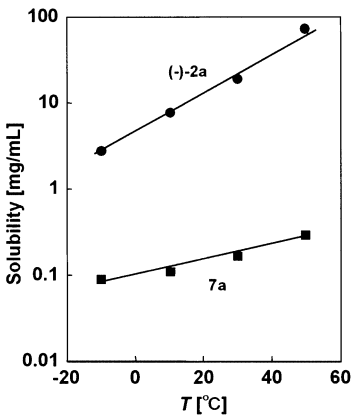


Figure 1. Solubility of (–)-**2a** (●) and **7a** (■) in isopropyl ether.

Thus, we devised a simple and efficient equipment for effecting the clear separation of (–)-**2a** and **7a** by *continuously performing the dissolution and crystallization* (Fig. 2). The equipment has two vessels (A and B) kept at 30 and 20°C, respectively, and fitted with a glass filter. The solvent (isopropyl ether) was circulated between the two vessels by means of a lab pump. To test the efficiency of the equipment, a model study was undertaken using a mixture of (–)-**2a** (5 g) and **7a** (500 mg). The mixture was loaded in vessel A with isopropyl ether (60 mL) and, after circulating isopropyl ether for 8 h, the solids formed in each vessel were filtered. Complete separation of (–)-**2a** and **7a** was accomplished to obtain analytically pure (–)-**2a** (4.53 g, 91%) and **7a** (454 mg, 91%) from vessels B and A, respectively.

Changes in the concentration of (–)-**2a** and **7a** during the separation in each vessel are shown in Fig. 3. The concentration of (–)-**2a** in vessel A was initially higher than that in vessel B and, in ca. 6 h, they reached the same point before decreasing simultaneously. In contrast, the concentration of **7a** in the circulating solvent (isopropyl ether) was low and was largely unchanged in both vessels. These observations demonstrate that the epoxide (–)-**2a** preferentially crystallized out in vessel B, while the catalyst **7a** was left undissolved in vessel A to result in the efficient separation of (–)-**2a** and **7a**.

The procedure was then applied to the isolation of (–)-**2a** and **7a** from the reaction mixture obtained by the asymmetric epoxidation of (*E*)-**1a**. The crude mixture of (–)-**2a** (78% ee, 89% yield, Table 1, entry 6) and **7a** was loaded on vessel A with isopropyl ether and was allowed to undergo the separation described above. Through this treatment, the ketone catalyst **7a** and virtually optically pure (–)-**2a** (>99% ee) were obtained from vessel A and B in 88 and 64% yields (based on (*E*)-**1a**), respectively.[12]

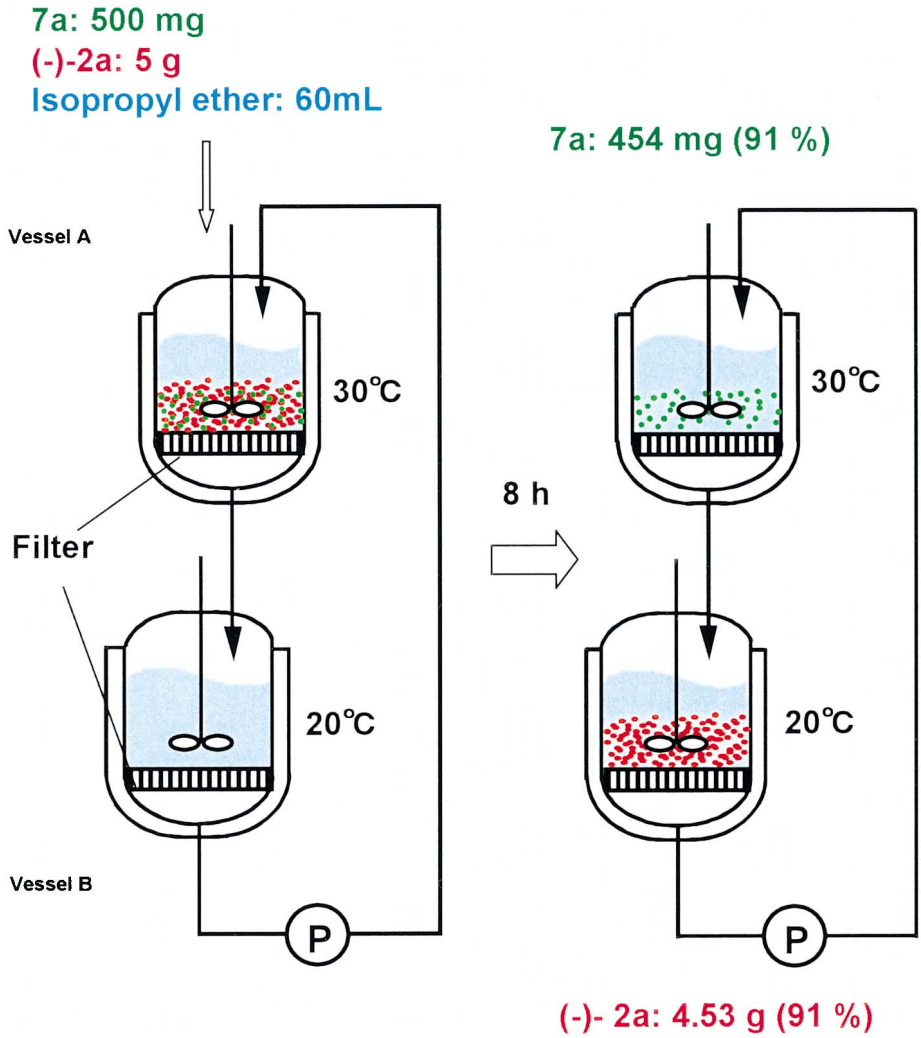


Figure 2. Separation of (–)-**2a** and **7a** by continuous dissolution and crystallization.

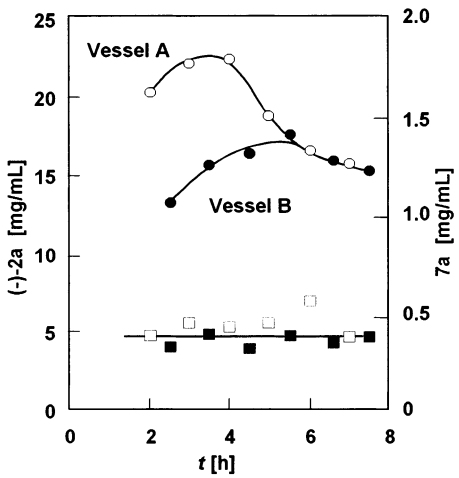


Figure 3. Changes in the concentration of (–)-**2a** (○: vessel A; ●: vessel B) and **7a** (□: vessel A; ■: vessel B) during the continuous dissolution and crystallization.

In conclusion, a practical synthetic method of the key intermediate (–)-**2a** for diltiazem (**3**) was accomplished through an asymmetric epoxidation of methyl (*E*)-4-methoxycinnamate (*E*)-**1a** using the chiral ketone **7a** and subsequent efficient separation of (–)-**2a** and **7a**. Although the enantioselectivity of the reaction is not perfect, the chemical yield is high and the crude product is purified using a continuous dissolution and crystallization to provide enantiomerically pure (–)-**2a**, while at the same time recovering **7a** both in excellent yields. The present method is advantageous in terms of ease of operation, ready accessibility of the reagents and mild reaction conditions that permit the practical large-scale preparation. The novel and simple separating equipment should find wide application for obtaining not only the optically pure glycidic acid derivatives but also other valuable chiral compounds that have hitherto been difficult to apply for a large-scale preparation due to lack of effective technology for separating the product and chiral catalyst.

Acknowledgements

The authors gratefully thank Drs. Kimiaki Hayashi and Ken-ichi Nunami, Tanabe Seiyaku Co., Ltd, for giving them an opportunity to publish this work.

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12. **A typical procedure for the catalytic asymmetric epoxidation of (*E*)-1a** (Table 1, entry 6): To a solution of methyl (*E*)-4-methoxycinnamate (*E*)-**1a** (96.1 g, 0.5 mol) and ketone catalyst **7a** (9.9 g, 25 mmol) in a mixed solvent of 1,4-dioxane (1.3 L) and H_2O (0.65 L) were successively added Oxone (307.4 g, 0.5 mol) and $NaHCO_3$ (130.2 g, 1.55 mol) at 5°C. The suspension was mechanically stirred at 5°C for 1 h and at 10°C for 23 h. The mixture was then warmed up to 27°C and stirring was continued for 3 h. The resulting suspension was treated with H_2O (2.5 L) and the mixture was extracted three times with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent provided the crude mixture of (−)-**2a** (93 g, 89% yield, 78% ee) and **7a** (9.9 g). The yield and the ee value of (−)-**2a** and **7a** were determined by HPLC (Chiralcel OD, hexane/*i*-PrOH = 10:1, 220 nm, 40°C).

Isolation of the product (−)-2a and chiral catalyst 7a through continuous dissolution and crystallization: The equipment for separating (−)-**2a** and **7a** used in this study has two vessels (vessel A and B) and a circulating pump (FMI Lab Pump Model RP-SY, Fluid Metering, Inc.), as shown in Fig. 2. 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 temperature of vessel A and B was initially kept at 25 and 18°C, respectively. The crude mixture of (−)-**2a** (93 g, 78% ee) and **7a** (9.9 g) obtained by the asymmetric epoxidation (see above) was loaded on vessel A with isopropyl ether (400 mL), and stirred. When the inner temperature of vessel A reached 25°C, the suspension was filtrated through the glass filter to vessel B, and another portion of isopropyl ether (400 mL) was loaded on vessel A. When the inner temperature of vessel B reached at 18°C, a few crystals of (−)-**2a** were added to vessel B with stirring. Then, the filtrate was circulated with the lab pump (30 mL/min) in a closed system for 10 h at these temperatures and at more reduced temperatures [10°C (vessel A) and 5°C (vessel B)] for 2 h. The crystals left on vessel A were collected to recover **7a** (8.7 g, 88% yield based on the initially added **7a**). After removing **7a** from vessel A, the temperature of isopropyl ether was elevated to 20°C to furnish, by filtration, (−)-**2a** (>99% ee, 66.6 g, 64% yield based on (*E*)-**1a**) from vessel B. (−)-**2a**: mp 88°C. $[\alpha]_D^{24}$ −205 ($c = 1.00$ in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS) 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, $CDCl_3$, 25°C, TMS) $\delta = 168.7$, 160.2, 127.1, 126.9, 126.6, 114.3, 114.0, 57.8, 56.4, 55.2, 52.4. IR (KBr) $\nu = 1748$, 1613 cm^{-1}. MS (70 eV): 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.