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# Synthesis of (+)-Ambrisentan via Chiral Ketone-Catalyzed Asymmetric Epoxidation

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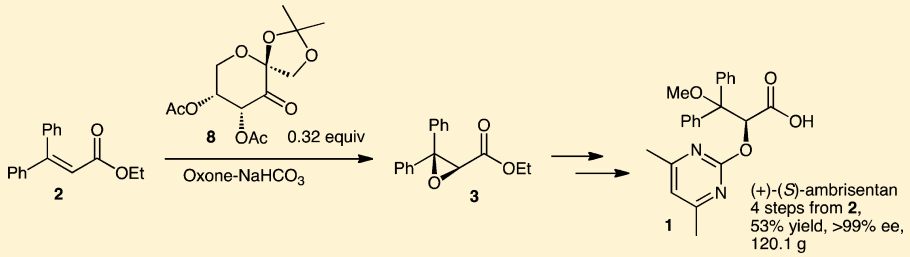
Supporting Information




**ABSTRACT:** The synthesis of optically pure (+)-ambrisentan has been achieved from 3,3-diphenylacrylate in four steps with 53% overall yield and >99% ee at the >100 g scale without column purification. The chiral epoxide intermediate was prepared via asymmetric epoxidation with a fructose-derived diacetate ketone as catalyst.

(+)-Ambrisentan (**1**), under the brand names *Letairis* in the United States and *Volibris* in Europe, is an endothelin-1 (ET-1) receptor antagonist and clinically used for the treatment of pulmonary arterial hypertension.[1,2] The reported synthesis of ambrisentan usually involves the epoxide formation via Darzens reaction with benzophenone and methyl chloroacetate, acid-catalyzed epoxide ring-opening with MeOH, nucleophilic substitution with 4,6-dimethyl-2-(methylsulfonyl)pyrimidine (**5**), and hydrolysis of ambrisentan methyl ester (**6b**) (Scheme 1).[1−3] The synthesis of optically pure ambrisentan mainly relied on resolution with various chiral amines.[1b,2,3] During our studies on chiral ketone-catalyzed asymmetric epoxidation,[4] we found that diacetate ketone **8** prepared in one pot from readily available ketone **7** can also epoxidize electron-deficient olefins such as $\alpha,\beta$-unsaturated esters (Figure 1).[5−7] Herein, we wish to report the application of this epoxidation to the synthesis of enantiomerically enriched (+)-ambrisentan.

Asymmetric epoxidation of ethyl 3,3-diphenylacrylate (**2**)[8] was carried out at the 0.6 mol scale with 0.32 equiv of diacetate ketone **8** under the standard epoxidation conditions.[6b] The corresponding epoxide (**3**) was obtained with 90% conversion and 85% ee (Scheme 1). The crude epoxide was treated with $BF_3{\cdot}Et_2O$ (1.3 mol %) in MeOH to give alcohol **4** (84% ee), which was directly reacted with 4,6-dimethyl-2-(methylsulfonyl)pyrimidine (**5**) and $K_2CO_3$ in DMF to give ester **6a** in 83% ee. The crude ester was hydrolyzed with 3.8 N aqueous NaOH solution to give ambrisentan Na salt. The aqueous solution was washed with ether to remove any organic impurities[9] and then acidified to pH ≈ 1 with concentrated HCl to precipitate ambrisentan. To our delight, it was found that (±)-ambrisentan is much less soluble than (+)-ambrisentan in ethyl acetate and water and was separated from (+)-ambrisentan by simple filtration. (+)-Ambrisentan (**1**) (120.1 g) was obtained in 53% total yield and >99% ee in four steps from ethyl 3,3-diphenylacrylate (**2**) (Scheme 1).

In summary, optically pure (+)-ambrisentan was synthesized at the 120 g scale (53% overall yield, >99% ee) in four steps from ethyl 3,3-diphenylacrylate (**2**). The chiral epoxide intermediate was prepared via asymmetric epoxidation with a fructose-derived diacetate ketone as catalyst. No column purification was required for the entire process. The optical purity of (+)-ambrisentan was readily enhanced by taking advantage of the poor solubility of the racemic form. All these features make the current process practical for the large-scale preparation of (+)-ambrisentan.

## EXPERIMENTAL SECTION

**General Methods.** All commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200−300 mesh). $^1$H NMR spectra were recorded on a 400 MHz NMR spectrometer and $^{13}$C NMR spectra were recorded on a 100 MHz NMR spectrometer. IR spectra were recorded on a FT-IR spectrometer. Melting points were uncorrected. Ethyl 3,3-diphenylacrylate was prepared according to the reported procedure.[8]

**(*S*)-3,3-Diphenyloxirane-2-carboxylic Acid Ethyl Ester (3).** To a vigorously stirred solution of ethyl 3,3-diphenylacrylate (**2**) (151.4 g, 0.60 mol) in $CH_3CN$ (3.0 L) and aqueous $Na_2(EDTA)$ ($1 \times 10^{-4}$ M) (3.0 L) at 0 °C was added $(n\text{-Bu})_4NHSO_4$ (12.2 g, 0.036 mol). A mixture of Oxone (1.85 kg, 3.0 mol) and $NaHCO_3$ (0.78 kg, 9.3 mol) was pulverized, and a small portion of this mixture was added

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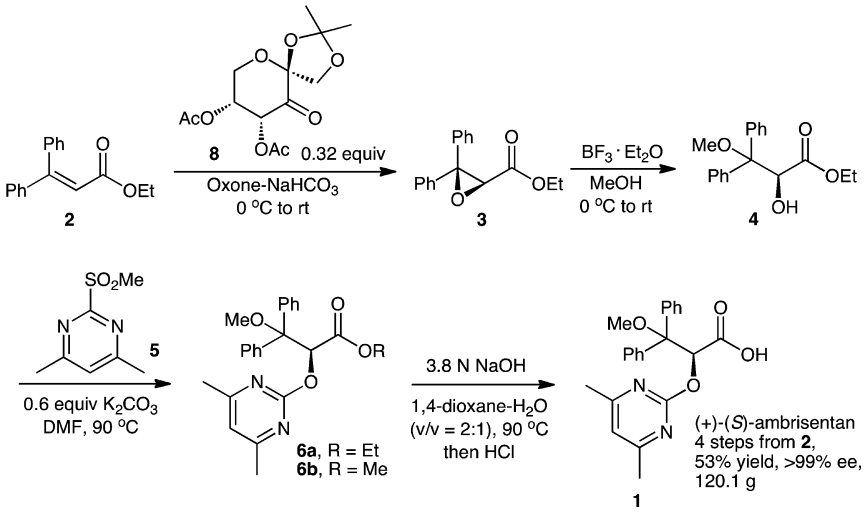
**Scheme 1**



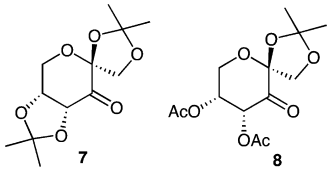




**Figure 1.** Chiral ketone catalysts.

to the reaction mixture to bring the pH to >7.0. Then, a solution of ketone **8** (57.8 g, 0.19 mol) in $CH_3CN$ (1.5 L) was added. The remainder of the Oxone and $NaHCO_3$ was added to the reaction mixture portionwise over a period of 4.5 h. Upon stirring at 0 °C for additional 20 h, the reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to give crude epoxide **3** as orange oil (~190.0 g, 90% conversion by $^1$H NMR, crude yield >99%), which was directly used for the next step. For the analysis, small amounts of the epoxide were purified by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate = 1:0 to 20:1). Colorless oil: $[\alpha]_D^{20}$ = +27.4 (*c* 1.0, $CHCl_3$) (85% ee); IR (film) 1757, 1726 cm$^{-1}$;[10] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48−7.43 (m, 2H), 7.39−7.29 (m, 8H), 4.07−3.94 (m, 2H), 3.98 (s, 1H), 0.97 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.0, 139.0, 135.6, 128.7, 128.5, 128.3, 128.1, 127.0, 66.6, 62.1, 61.4, 14.0; HRMS Calcd for $C_{17}H_{16}O_3$ ($M^+$) 268.1099; found 268.1104.

**(*S*)-2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid Ethyl Ester (4).** To a stirred solution of the above epoxide (**3**) (~0.6 mol) in MeOH (120 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (1.0 mL, 8.0 mmol). Upon stirring at 0 °C overnight (the epoxide was consumed as judged by TLC), the reaction mixture was quenched with water (5.0 mL) and concentrated. The resulting yellow oil was dissolved in ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude alcohol **4** as yellow oil (~190.0 g, crude yield >99%), which was directly used for the next step. For the analysis, small amounts of the alcohol were purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 20:1). Colorless oil: $[\alpha]_D^{20}$ = +3.3 (*c* 1.0, $CHCl_3$) (84% ee); IR (film) 3496, 1729 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.27 (m, 10H), 5.15 (d, *J* = 8.8 Hz, 1H), 4.14−4.04 (m, 2H), 3.18 (s, 3H), 2.94 (d, *J* = 8.8 Hz, 1H), 1.15 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.5, 141.1, 140.3, 129.0, 128.7, 128.0, 127.81, 127.76, 127.6, 85.0, 73.9, 61.8, 52.6, 14.1. Anal. Calcd For $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.96; H, 6.72.

**(*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid Ethyl Ester (6a).** To a stirred solution of the above ethyl ester (**4**) (~0.6 mol) in DMF (945 mL) was added $K_2CO_3$ (26.1 g, 0.19 mol). After the reaction mixture was stirred at rt for 30 min (the mixture became dark green), 4,6-dimethyl-2-(methylsulfonyl)pyrimidine (**5**) (154.7 g, 0.83 mol) was added in one portion at rt. Upon stirring at 90 °C for 15 h, the reaction mixture was cooled to rt and diluted with ethyl acetate (2.5 L) and water (1.0 L). The organic layer was washed by 2 N citric acid (0.5 L) and brine (1.0 L), dried over $MgSO_4$, filtered, and concentrated to give crude ester **6a** as red oil (284.0 g, crude yield >99%), which was directly used for the next step. For the analysis, small amounts of ester **6a** were purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1). Colorless oil: $[\alpha]_D^{20}$ = +82.9 (*c* 1.0, $CHCl_3$) (83% ee); IR (film) 1750, 1596 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.33−7.19 (m, 6H), 6.70 (s, 1H), 6.12 (s, 1H), 4.01−3.85 (m, 2H), 3.50 (s, 3H), 2.38 (s, 6H), 0.93 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.5, 168.7, 163.9, 142.5, 141.3, 128.5, 128.03, 127.97, 127.94, 127.5, 127.4, 115.0, 83.8, 79.2, 60.7, 53.9, 24.0, 13.9; Anal. Calcd For $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.72; H, 6.47; N, 6.83.

**(*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic Acid (Ambrisentan) (1).** To a stirred solution of the above ester (**6a**) (~0.6 mol) in 1,4-dioxane (1.4 L) was added an aqueous solution of NaOH (3.8 N) (110.0 g, 2.76 mol) in distilled water (0.72 L) at rt. Upon stirring at 90 °C overnight (ester **6a** disappeared by TLC), the reaction mixture was concentrated to remove the organic solvent and washed with ethyl ether (0.5 L × 2) to remove any organic impurities.[9] The aqueous layer was acidified with concentrated HCl to pH ≈ 1.0 (large amounts of white solid appeared) and extracted with ethyl acetate (2.0 L). At this point, some solid stayed at the interface of the organic and aqueous layer. The whole mixture was filtered by suction. The filter cake (24.9 g) was found to be ambrisentan in nearly racemic form (<10% ee). The layers of the filtrate were separated. The aqueous layer was extracted with ethyl acetate (1.0 L × 2). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The resulting residue was stirred with ethyl acetate (0.5 L) and filtered with suction to give (+)-ambrisentan as white solid (100.0 g, 99% ee) (the ee was determined after it was converted to the methyl ester with $TMSCHN_2$). The mother liquid was concentrated, stirred with ethyl acetate (0.1 L), and filtered to give another batch of white solid (20.1 g, 99% ee). A total 120.1 g of (+)-ambrisentan was obtained (53% combined yield in four steps from ethyl 3,3-diphenylacrylate): $[\alpha]_D^{20}$ = +170.0 (*c* 0.5, MeOH), lit.[2d] $[\alpha]_D^{20}$ = +183.37 (*c* 0.5, MeOH); IR (film) 3434, 1731, 1599 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (d, *J* = 8.0 Hz, 2H), 7.39−7.20 (m, 8H), 6.70 (s, 1H), 6.33 (s, 1H), 3.35 (s, 3H) 2.37 (s, 6H); $^1$H NMR (400 MHz, DMSO) $\delta$ 12.51 (s, 1H), 7.37−7.19 (m, 10H), 6.94 (s, 1H), 6.16 (s, 1H), 3.39 (s, 3H) 2.34 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6, 169.7, 163.6, 140.6, 139.6, 128.62, 128.56, 128.1, 128.04, 127.95, 127.87, 115.3, 84.4, 77.8,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53.5, 23.9; $^{13}$C NMR (100 MHz, DMSO) $\delta$ 169.0, 163.2, 142.6, 141.4, 127.8, 127.7, 127.6, 127.2, 127.0, 114.7, 83.1, 77.6, 53.0, 23.3.

**(*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid Methyl Ester (6b).**[2d] To a stirred solution of (+)-ambrisentan (0.19 g, 0.50 mmol) in THF/MeOH (2:1) (3.0 mL) was added $TMSCHN_2$ (2 M in hexane) (0.5 mL, 1.0 mmol) at rt. Upon stirring at rt for 30 min, the reaction mixture was concentrated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 20:1) to give ambrisentan methyl ester (**6b**) as white solid (0.16 g, 81%): $[\alpha]_D^{20}$ = +139.0 (*c* 0.5, MeOH) (99% ee), lit.[2d] $[\alpha]_D^{25}$ = +135.8 (*c* 0.5, MeOH); mp 132−135 °C; IR (film) 1754, 1596 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (d, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.34−7.20 (m, 6H), 6.70 (s, 1H), 6.15 (s, 1H), 3.45 (s, 3H), 3.42 (s, 3H), 2.38 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.6, 169.3, 163.8, 142.2, 141.1, 128.6, 128.2, 128.0, 127.9, 127.57, 127.55, 115.1, 83.9, 79.1, 53.7, 51.7, 24.0.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

NMR spectra, X-ray structure of (+)-ambrisentan (**1**), and HPLC data for the determination of ee values. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ ACKNOWLEDGMENTS

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