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Improved Synthesis Process of Ambrisentan and Darusentan

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2-hydroxy-3-phenoxy-3, 3-diphenylpropinate (5) was prepared from benzophenone via Darzens, methanolysis and hydrolysis reaction. The compound (5) was salified with (S)-dehydroabietylamine (7) and diasterotropic resolution was carried out to provide the key intermediate (S)-2-hydroxy-3-methoxy-3, 3-diphenylpropionic acid (6). Compound (6) was condensed with 2-methylsulfonyl-4, 6-dimethylpyrimidine and 2-methoxysulfonyl-4, 6-dimethylpyrimidine to afford ambrisentan (1) and darusentan (7), respectively. Two products were with excellent charity and chemical purity. The total yield of the synthesis was 30.1% and 29.6%, respectively.

1. Introduction

Pulmonary arterial hypertension (PAH) is a unique and progressively debilitating disease which is characterized by elevated pulmonary arterial pressure secondary to vasoconstriction, hypertrophy, and remodeling of the pulmonary vasculature. PAH is associated with severe functional impairment and a poor prognosis, with a median survival of 2.8 years in untreated patients. The cause of death in the majority of patients is either right-sided heart failure (47%) or sudden cardiac death (26%) (D'Alonzo et al, 1991).
PAH is classified by the World Health Organization (WHO) according to etiology. WHO group 1 PAH is the most prevalent, and includes PAH associated with idiopathic etiology, genetic predisposition, congenital heart abnormali-ties, connective tissue disorder, portal hypertension, use of anorexigen, and human immunodeficiency virus. WHO groups 2-5 refer to PAH associated with left heart disease, lung disease, chronic thromboembolic disease, and miscel -laneous causes, respectively (Simonneau et al, 2004).
Progression and prognosis of PAH is nonlinear. Clinical status and severity are classified by the WHO functional classification scale. Functional classification I represents patients with the least restrictive symptoms (asymptomatic) on ordinary activities of daily living, while functional classification IV describes the most functionally impaired patients, in whom symptoms occur at rest. Functional classifications II and III refer to patients with slight limitations on activities of daily living and those with marked limitations on activities of daily living, respectively. WHO functional classification I and II are associated with the best prognosis, and have a median predicted survival of 58 months; class III has a less favorable prognosis of 36 months; and class IV is associated with the worst prognosis, having a median survival of 6 months (Galie et al, 2009; D'Alonzo et al, 1991).
The pathogenesis of PAH is the result of an imbalance between key mediators in the pulmonary circulation. This imbalance leads to increased thrombosis, vasoconstriction, and proliferation of smooth muscle and endothelial cells within the pulmonary vasculature. Among these mediators is endothelin-1, a potent vasoconstrictor that also stimulates the proliferation of smooth muscle cells. Levels of endothelin-1 have been established to be elevated in patients with PAH and contribute to progression of the disease. This observed increase in endothelin-1 levels is correlated with a proportional decrease in pulmonary blood flow and cardiac output. As a result, therapies that block the detrimental effects of endothelin-1 have been recently developed (Farber et al, 2004; Giaid et al, 1993).
Endothelin (ET) was isolated from the culture medium porcine vascular endothelin cells several decades ago, and later was found to be a highly potent vasoconstrictive peptide. ET systems, including ET-1, ETA and ETB receptors, were closely related with pathogenesis of (PAH). ET recepetor (ETR) antagonists constitute an important class of anti-PAH agents, among which the so-called "-sentan" class of drugs, such as ambrisentan,

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bosentan and darusentan have long been used for the treatment of PAH (figure 1) (Hrometz et al, 2008; Oudiz et al, 2009).

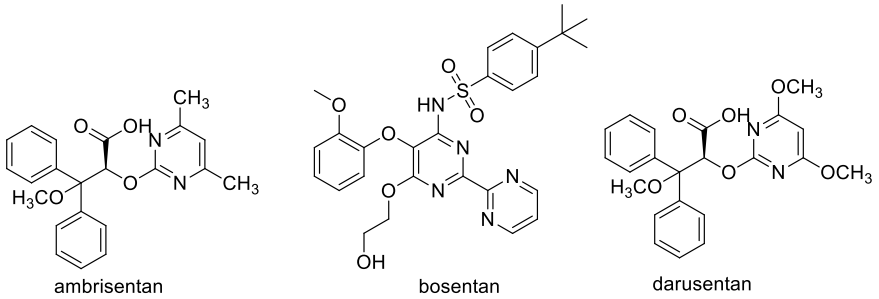

Figure 1: Structures of some selected ETR antagonists

The reported synthesis of ambrisentan and darusentan usually involve 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. The synthesis of optically pure ambrisentan mainly relied on resolution with expensive chiral amines, such as (S)-1-(4-chlorophenyl)ethylamine, (S)-1-(4-nitrophenyl) ethylamine and methyl L-prolinate (figure 2)] (Reichers et al, 1996; Amberg et al,1999; Satyanaryana et al, 2010; Gidwani et al, 2010; Zhou et al, 2010; Liu et al, 2011;). Dehydroabietylamine, which has three-ring phenanthrene skeleton in molecule, is one of important modified products of rosin, and it is also main components of disproportionate rosin amine, while chiral dehydroabietylamine was always applied in chiral resolution (Bolchi et al, 2007; Guo et al, 2007; Ballester et al, 1955; Gottstein et al, 1969; Lee et al, 1952; Bellucci et al, 1969).

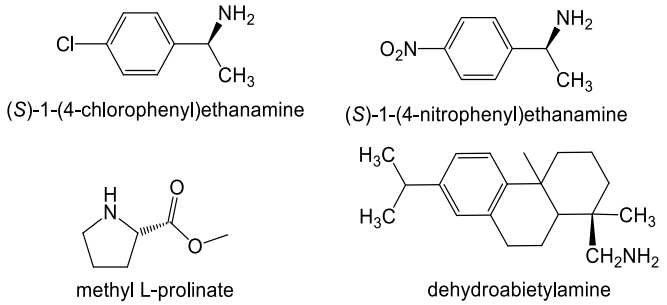

Figure 2: Chiral chemical for resolution of compound (5)

Thus, a new synthesis method was described in the paper (figure 3). First, compound (2) was reacted with methyl chloroacetate through Darzens reaction to afford compound (3), which was alcoholysis in CH_3OH in the presence of p-toluene sulfonic acid, then it was hydrolysis to afford the racemic compound (5). (S)-dehydroabietylamine, a cheap chiral amine, was selected as resolution chemical and (S)-methyl 2-hydroxy-3-methoxy-3, 3-diphenylpropanoate (6) was obtained through chiral resolution (Amberg et al,1999; Bolchi et al, 2007; Guo et al, 2007). The compound (6) was directly reacted with 4, 6-dimethyl-2-(methylsulfonyl) pyrimidine (5) and $NaNH_2$ in DMF to give (+)-ambrisentan. The compound (6) was directly reacted with 4, 6-dimethyl-2-(methoxysulfonyl) pyrimidine (5) and K_2CO_3 in DMF to give (+)-darusentan (figure 4) (Reichers et al, 1996; Guo et al, 2005).

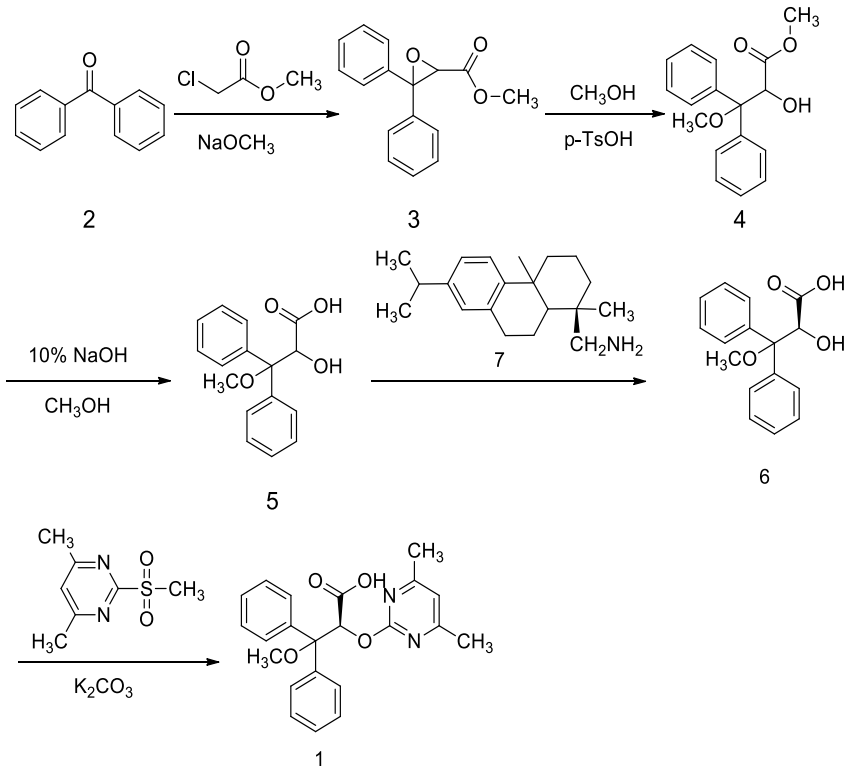

Figure 3: Synthesis route of ambrisentan

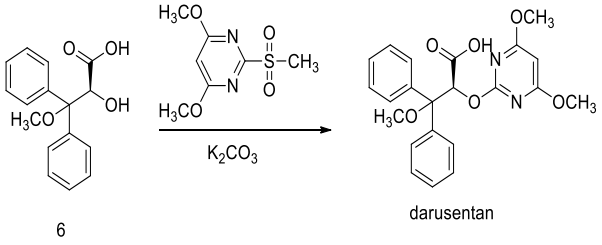

Figure 4: Synthesis route of darusentan

2. Experimental

All reagents were obtained from Sigma-Aldrich and CDN Isotope. Analytic TLC was performed on silica gel plates (Merck silica gel 60 F_{254}). Mass spectra were recorded using a Quattro micro API mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument (Bruker Corporation, Germany). All values are reported as chemical shifts in δ units (ppm) relative to tetramethylsilane as internal standard. HPLC analyses were performed using a Merck Lichrosorpher RP Select-B 5μm column. The following abbreviations are used in the experimental section: DMF, dimethylformamide; NaOMe, sodium methoxide; THF, tetrahydrofuran.

Synthesis of methyl 3, 3-diphenyloxirane-2-carboxylate (3)
To a solution of sodium methanolate (4.3 g, 79.6 mmol) in dry THF (25 mL) was added the solution of benzophenone (7.2 g, 39.5 mmol) and methyl chloroacetate (6.6 g, 60.8 mmol) in dry THF (15 mL) and stirred at -10 °C for 2 h. The mixture was quenched with water (50 mL). The solution was extracted with diethyl ether (80 mL×3). The organic phases were combined and washed with saturated NaCl. The solution was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford a light yellow oil. The residue (3) can apply in next step without further purification (8.24 g, 82.1%).
^{1}H-NMR ($CDCl_3$): δ 3.52 (s, 3H), 3.99 (s, 1H), 7.32-7.45 (m, 10H).

Synthesis of 2-hydroxy-3-methoxy-3, 3-diphenylpropanoic acid (5)

To a solution of compound (3) (8.2 g, 31.6 mmol) in methanol (40 mL) was added p-toluene sulfonic acid (0.5 g) and stirred at for 0.5 h to afford the solution containing compound (4). Aqueous solution of NaOH (10% wt.) (60 mL) was added to the solution of compound (4) and the mixture was stirred at refluxed for 1h (ester disappeared by TLC). The solution was evaporated in order to remove a lot of methanol. The residue was acidified to pH 2 by conc. HCl. The solution was stirred for overnight and white solid stayed at the aqueous layer. The precipitate was filtered and deeply dried under vacuum to afford (5). (7.34 g, 85.3%).
^{1}H-NMR ($CDCl_3$): δ 3.22 (s, 3H), 5.14 (br, 1H), 5.20 (d, 1H), 7.18-7.37 (m, 10H), 12.30 (1H, br).

Synthesis of (S)-2-hydroxy-3-methoxy-3, 3-diphenylpropanoate (6)
The solution of compound (5) (14 g, 51.4 mmol) in methyltertiarybutylether (140 mL) was stirred and refluxed for 0.5 h. Dehydroabietylamine (7) (14.7 g, 51.4 mmol) in methyltertiarybutylether (50 mL) was added dropwise in 10 min. After addition, the reaction mixture was stirred for 1 h under reflux temperature. The reaction mixture was cooled to 0 °C and continued to stir for 2 h. The solid ((R, S)-diastereoisomers) was precipitated from the solution, filtered, washed with acetonitrile. The filtrate was diluted with water (100 mL) and acidified to pH 2 by conc. HCl. The aqueous solution was extracted with methylteriarybutylether (50 mL×4). The organic phases were combined and washed with water (80 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford white residue. The residue was recystallized from toluene to afford (6) as a white solid. (5.53 g, 39.5%).
^{1}H-NMR ($CDCl_3$): δ 3.22 (s, 3H), 5.14 (br, 1H), 5.20 (d, 1H), 7.18-7.37 (m, 10H), 12.30 (1H, br). $[\alpha]_D^{20}$ =12.3°(c=1.8% in ethanol).

Synthesis of (+)-ambrisentan (1)
To a solution of compound (6) (3.6 g, 13.1 mmol) and NaNH2 (1.0 g, 25.6 mmol) in DMF (20 mL) was added 4, 6-dimethyl-2-(methylsulfonyl) pyrimidine (3.63 g, 19.6 mmol) in DMF (10 mL) slowly. After addition, the reaction was stirred for 5 h at room temperature. The solution was quenched with water (20 mL) and acidified to pH 2 by 10% H_2SO_4 aqueous solution. The mixture was extracted with ethyl acetate (50 mL ×4). The combined organic layers were washed with water (30 mL) and saturated NaCl solution (30 mL). The organic layer was dried over Na2SO4, filtered and concentrated under reduced pressure. The resulting residue was recrystallized from iso-propyl alcohol (30 mL) and water (40 mL), and precipitate formed was filtered off. The cake was deeply dried under vacuum to afford (1) as a white solid. (4.27 g, 86.1%).
^{1}H-NMR ($CDCl_3$): δ 2.39 (s, 6H), 3.32 (s, 3H), 6.43 (s, 1H), 6.70 (s, 1H), 7.28-7.40 (m, 8H), 7.53-7.56 (d, 2H). MS-EI (m/z): 377(M-H). HPLC (XDB-C18, CH_3OH/10mmol/L NaH_2PO_4 + 0.1% H_3PO_4 = 70/30, 1.0 mL/min): t_R 5.2 min (>99.0%); ee= 99.0%.

Synthesis of (+)-darusentan (2)
To a suspension of compound (6) (10 g, 36.7 mmol) and K2CO3 (2.5 g, 18.4 mmol) in DMF (100 mL) was stirred for 0.5 h. 4, 6-dimethyl-2-(methylsulfonyl) pyrimidine (6.83 g, 36.7 mmol) in DMF (20 mL) was added slowly. After addition, the mixture was stirred at 90 °C for 3 h. The solution was quenched with water (20 mL) and acidified to pH 2 by 10% H_2SO_4 aqueous solution. The mixture was extracted with ethyl acetate (100 mL ×4). The combined organic layers were washed with water (30 mL) and saturated NaCl solution (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was recrystallized from diethyl ether (100 mL) and precipitate formed was filtered off. The cake was deeply dried under vacuum to afford (2) as a white solid. (13.1 g, 87.6%).
^{1}H-NMR ($CDCl_3$): 3.32 (s, 3H), 3.83 (s, 6H), 5.75 (s, 1H), 6.11 (s, 1H), δ 7.22-7.43 (m, 10H), δ 7.53-7.56 (d, 2H). MS-EI (m/z): 377(M-H). HPLC (XDB-C18, CH3CN/10mmol/L NaH_2PO_4 + 0.1% H_3PO_4 = 40/60, 0.8 mL/min): t_R 6.2 min (>99.0%); ee= 99.0%.

3. Result and discussion

3.1 Yield-influencing factors of compound (3)

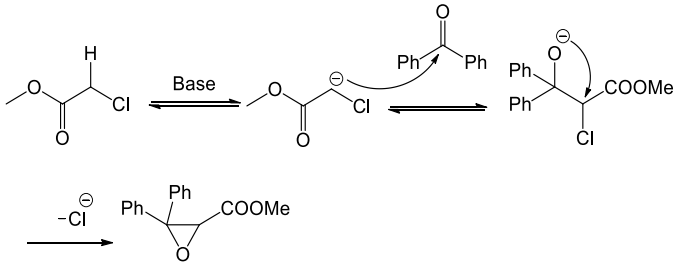

Figure 4: Reaction mechanism of Darzens rection

Benzophenone was reacted with methyl chloroacetate via Darzens, methanolysis and hydrolysisis reaction, and 2-hydroxy-3-phenoxy-3, 3-diphenylpropinate (5) was obtained (Figure 4). The process of Darzens reaction starts when sodium methanolate attacks the halogenated position at the ester to easily form a carbanion and the carbanion is aresonance-stabilized enolate because of the ester. This nucleophile attacks another carbonyl component to form a new carbon–carbon bond. The first two steps are same as a base-catalyzed aldol reaction. The oxygen anion in this aldol-like product then does an intramolecular S_N2 attack on the formerly-nucleophilic halide-bearing position, displacing the halide to form an epoxide. So the reaction sequence is a condensation reaction, since amount of HCl was formed when the two reactant molecules join. The reaction release heat rapid when methyl chloroacetate was added, while the reaction was beneficial to positive direction through reducing the reaction temperature, which decreased or avoided the hydrolysis of compound (3), so the reaction temperature is influenced the yield of compound (3) (Newman et al, 1951).

Table 1: Reaction temperature influence the yield of compound (3)

temperature/°C	20	10	0	-10
yield	63.1	74.9	82.1	83.2

We conducted the experiment process how reaction temperature influenced the yield of compound (3). The other reaction condition was fixed while the reaction temperature was changed, and the result was showed in table 1. We could draw a conclusion that the yield of compound (3) was increased when the reaction temperature was decreased. While the reaction temperature was decreased to 0 °C, the temperature was almost no effect to the yield, so the reaction temperature was selected as 0 °C.

3.2 The process of resolution compound (5) to compound (6)

In this paper, dehydroabietylamine, (S)-1-(4-chlorophenyl) ethylamine, (S)-1-(4-nitrophenyl) ethylamine and methyl L-prolinate were tested to solve the question of optical resolution. The best results were obtained using dehydroabietylamine (c.y. 39.5%, ee>99%(HPLC)), (S)-1-(4-nitrophenyl) ethylamine (c.y. 38%, ee>99% (HPLC)), methyl L-prolinate (c.y. 39.1%, ee>99%(HPLC)) and (S)-1-(4-chlorophenyl)ethylamine (c.y. 30%, ee>99% (HPLC)). The application of methyl L-prolinate should prepare an equimolar amount, while dehydroabietylamine and (S)-1-(4-nitrophenyl) ethylamine only half an equivalent was required. The disadvantage of methyl L-prolinate and (S)-1-(4-nitrophenyl) ethylamine is extremely expensive. According to Jansen (2001), methyl L-prolinate could not be completely recycled because free methyl L-prolinate tends to form diketopiperazines. Dehydroabietylamine is a more cheap, natural chiral resolution chemical than (S)-1-(4-chlorophenyl) ethylamine, (S)-1-(4-nitrophenyl) ethylamine and methyl L-prolinate. Optical resolution is to give (S, S)-hydroxy acid salt, which is isolated from the solution of MTBE (methyltertiarybutylether) with yield of about 70% respect to the racemate in both cases.

4. Conclusions

In summary, we have discussed that the resolving agent dehydroabietylamine is very efficient in separating the enatiomers of 2-hydroxy-3-methoxy-3, 3-diphenylpropanoate. This resolving agent is highly specific for the desired single isomer. Then two compounds were obtained through reaction of single isomer and pyrimidine.

Acknowledgements

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