Efficient Synthesis of Antihyperglycemic (S)-α-Aryloxy-β-phenylpropionic Acid Using a Bifunctional Asymmetric Catalyst

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Antihyperglycemic (S)-α-aryloxy-β-phenylpropionic acid was prepared using catalytic asymmetric cyanosilylation as a key reaction to construct α-oxycarboxylic acid moiety.

Key words asymmetric catalysis; antihyperglycemic agent; PP AR; bifunctional catalyst

Antihyperglycemic thiazolidine-2,4-diones, such as troglitazone,11 rosiglitazone2 and pioglitazone,3 are believed to be ligands for peroxisome proliferator-activated receptor γ (PPARγ) and improve insulin resistance in insulin target organs.4,5 Recently some research groups revealed that α-oxo-β-phenylpropionic acids, as well as 5-benzylthiazolidine-2,4-diones, possess potent PPARγ agonistic activity and glucose lowering activity.6,7 According to this knowledge we synthesized novel oxime derivatives having α-oxo-β-phenylpropionic acid moiety, which indicates strong antihyperglycemic activity.8 In this series, compound 1 (Chart 1) shows potent antihyperglycemic activity compared to rosiglitazone.9 It is known that enantiomers of α-oxo-β-phenylpropionic acids show different antihyperglycemic activities,10 however, we are not aware of any practical methods for preparing optically active α-oxo-β-phenylpropionic acids.11–12 Meanwhile, some of the authors have developed a highly enantioselective cyanosilylation of aldehydes with broad substrate generality, using a Lewis acid–Lewis base bifunctional catalyst 4 (Chart 2).13,14 We now describe a practical route to 1 using catalytic asymmetric cyanosilylation as a key step.

Results and Discussion

Although excellent results were obtained from a wide range of aldehydes by the catalytic enantioselective cyanosilylation using 4, there have been no precedents of using an easily enolizable and unstable aryl acetaldehyde such as 313 as a substrate. Therefore, we were pleased when we found that application of the representative procedure (9 mol% of catalyst 4, 36 mol% of Bu3P(O), 1.8 eq of TMSCN [slow addition for 10 h], CH2Cl2 solvent at –40 °C for 60 h) gave the product cyanohydrin 2 in 89% yield with 97% ee on a 0.25 mmol scale of 3 (ca. 50 mg). However, on a 0.5 mmol scale, the reaction became slow and the ee of the product was decreased to 74% (80% yield for 60 h). A similar problem in scale-up of this reaction was also reported in ref. 14 and which was solved by adding MeOH as an additive. Thus, we tried the cyanosilylation using TMSCN pre-mixed with 10 mol% of MeOH.10 Then, the reaction rate and the enantioselectivity became satisfactory, and product 2 was obtained in 85% yield with 96% ee on a 0.5 mmol scale of the substrate. Therefore, the addition of proton source is essential for the present reaction (Chart 2).

Based on the previous mechanistic studies, a proposed catalytic cycle and possible role of the proton source are depicted in Chart 3. After the intramolecular transfer of the cyanide through dual activation of the aldehyde and TMSCN by the Lewis acid and the Lewis base (12), catalytically inactive species 13 should be generated. If the proton source is not present, the transfer of the silyl cation to the oxide of the product cyanohydrin might be slow. So, before the silyl cation is trapped by the oxide, it could promote a racemic reaction, thus decreasing the ee of the product.17 On the other hand, if the proton source (HCN) is present, the oxide should be immediately trapped by the proton and the silyl cation should be converted to TMSCN, thus regenerating the active catalyst 10. The resulting free cyanohydrin was proved to be silylated by TMSCN under the reaction conditions, thus the proton source should be regenerated. Therefore, the proton source should catalytically facilitate the regeneration of the active enantioselective catalyst.18,19

Our synthetic procedure is depicted in Chart 2. Refluxing 2 with 12 N HCl in degassed ethanol gave the α-hydroxyster 5 and undesired hydrolyzed and/or debenzylated compounds. To recover these compounds, esterification and benzylation were performed and 5 was obtained from 2 in a yield of 81% in all. The α-hydroxyster 5 was initially converted to the α-phenoxyester 6 under standard Mitsunobu reaction conditions, i.e. a solution of diethyl azodicarboxylate in toluene was added to the solution of 5 and 4-t-butylphenol in toluene for 5 min at 0 °C. The chemical yield was 50% and by-product 1920 was obtained in 20% yield. A plausible reaction mechanism for generating 19 is depicted in Chart 4. We supposed that α-keto acid 17 is generated to some extent by deprotonation of the intermediate 14 instead of phenol 16, then...
deprotonation of 17 at the β-position gives 18 which reacted with 14 to afford 19. To avoid the side reaction, we prolonged the addition time of diethyl azodicarboxylate to 10 h so that the yield of 6 was improved to 80% and by-product 19 could not be detected. Next we further optimized the reaction conditions to avoid chromatographic purification after the Mitsunobu reaction. We adopted the modified Mitsunobu reaction developed by Pelletier and Kincaid2 in which triphenylphosphine resin and di-tert-butyl azodicarboxylate (DBAD) are employed (a solution of DBAD in toluene was added for 10 h). After treatment of the reaction products with TFA in order to decompose excess DBAD and its hydrazine dicarboxylate, triphenylphosphine resin and its oxide were removed by filtration. Evaporation and aqueous work up gave crude 6. To avoid chromatographic purification, the obtained crude 6 was converted to easily crystallizable carboxylic acid 7 via deprotection of the benzyl group by hydrogenation and subsequent alkaline hydrolysis. After aqueous work up and crystallization, 7 was obtained in 70% yield (3 steps from 5). Esterification gave the phenol 8, which was subjected to the modified Mitsunobu reaction with the oximealcohol 9 as mentioned above and subsequent alkaline hydrolysis to afford the desired (S)-α-aryloxy-β-phenylpropionic acid 1 without purification by chromatographic technique in 70% yield (2 steps).

In summary, an efficient synthesis of non-thiazolidine-2,4-dione antihyperglycemic agent 1 has been achieved by the use of a bifunctional asymmetric catalyst. We also utilized Pelletier’s modified Mitsunobu reaction conditions in which triphenylphosphine resin and di-tert-butyl azodicarboxylate is
used for avoiding chromatographic purification. This report provides a synthetic method which could be applicable to antihyperglycemic agents having chiral α-oxy-β-phenylpropionic acid moiety. Further extension of this route to a large scale synthesis and evaluation of the pharmaceutical use of 1 is currently under investigation.

**Experimental**

Melting points (mp) were determined with a Yanaco melting point apparatus and are not corrected. Infrared (IR) spectra were measured with a Nicolet FTIR spectrophotometer. 1H- and 13C-NMR spectra were recorded on a Varian Mercury 400 or 500 spectrometer. Chemical shifts were expressed in δ ppm from the internal standard tetramethylsilane (TMS). MS or high-resolution mass spectra (HR-MS) were obtained on a JEOL JMS-D 300 mass spectrometer. Optical rotations ([α]D) were determined on a Jasco DIP-360 polarimeter. HPLC was performed on a Shimadzu HPLC system using a Shimadzu LC-10Advp pump, SPD-M10Avp detector, and a Chiralpak AD-RH (CH3CN/pH 2.2 buffer solution of phosphoric acid 0.2M) column detector, and a Jasco OD (2-propanol/hexane, 1/100) after conversion to the corresponding TBDMS ether. The absolute configuration of 2 was determined to be R by the comparison of the optical rotation with the reported value after the conversion to 3-(4-hydroxyphenyl)lactic acid. [α]D: +17.5° (c = 1.04, H2O) (lit. [α]D: +19.8° c = 1.45, H2O) for R enantiomer.

(R)-Ethyl-3-(4-benzyloxyphenyl)-2-hydroxypropionate (5) To a solution of ethyl (R)-3-(4-hydroxyphenyl)lactate (247 mg, 1.17 mmol) in degassed EtOH (30 ml) was added 25% Aq. H2SO4 (0.2 ml). The reaction mixture was stirred for 14 h at room temperature. The solvent was removed and the residue was extracted with EtOAc (30 ml×2). The combined organic layer was washed with water and brine, dried over Na2SO4, and concentrated. The residue was purified by chromatography on silica gel (CH2Cl2/EtOAc, 1/1) to give 5 (157 mg, 26%) as a colorless oil.

1H-NMR (400 MHz, CDCl3) δ: 1.28 (3H, t, J = 7.0 Hz), 2.71 (1H, d, J = 6.0 Hz), 2.92 (1H, d, J = 6.5, 14.0 Hz), 3.07 (1H, dd, J = 4.5, 14.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 4.37—4.42 (1H, m), 5.04 (2H, s), 6.91 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 7.30—7.34 (5H, m). 13C-NMR (125 MHz, CDCl3) δ: 14.04, 39.51, 61.45, 69.80, 71.21, 114.59, 127.29, 127.74, 128.39, 128.55, 130.40, 136.93, 157.62, 174.15. IR (KBr) cm⁻¹: 3393, 2262, 1513, 1242, 1177, 1026. HR-MS: 339.1104 (Calcd for C18H20O4Na: 339.1103). The enantiomeric excess was determined by HPLC analysis using Chirapak OD (2-propanol/hexane, 1/100) after conversion to the corresponding TBDMS ether. The absolute configuration of 2 was determined to be R by the comparison of the optical rotation with the reported value after the conversion to 3-(4-hydroxyphenyl)lactic acid. [α]D: +17.5° (c = 1.04, H2O) (lit. [α]D: +19.8° c = 1.45, H2O) for R enantiomer.
A solution of 5 (896 mg, 2.90 mmol) in toluene (9.0 ml) was added 4-t-butylphenol (671 mg, 4.47 mmol) and triphenylphosphine-resin (3 mmol/g, 4.0 g, 12.0 mmol), and the mixture was stirred magnetically. To the stirred reaction mixture, a solution of DBAD (1.03 g, 4.47 mmol) in toluene (9.0 ml) was slowly added over 10 h at 0 °C, and the mixture was stirred for another 16 h at room temperature. After completion of the reaction, TFA (5 ml) was added. After 1 h, the reaction mixture was filtered (Celite®) and the residue was washed with EtOAc and H₂O. The combined filtrate was separated and the organic layer was washed with H₂O and brine, and dried over Na₂SO₄. The solvent was removed and the residue was collected by filtration using isopropyl ether to give the title compound 6 (6 ml) as colorless crystals. The title compound 6 was obtained as a colorless oil (2.05 g, quant.).

HR-MS: 323.2044 (Calcd for C₂₃H₂₃N₂O₂ 323.2043). 1H-NMR (400 MHz, CDCl₃) δ: 1.23 (3H, t, J = 7.0 Hz), 1.07 (4H, m), 3.14—3.17 (2H, m), 4.15—4.21 (2H, m), 4.68—4.71 (1H, m), 6.73—6.78 (4H, m), 7.16 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz). 13C-NMR (125 MHz, CDCl₃) δ: 14.11, 31.46, 34.09, 38.29, 61.30, 78.28, 114.80, 115.26, 126.29, 125.80, 130.68, 144.39, 154.57, 155.51, 171.59. (Liquid film) cm⁻¹: 3241, 2963, 1731, 1514, 1238, 1187. HR-MS: 323.1503 (Calcd for C₁₄H₁₀O₂ 323.1504). Anal. Calcld for C₁₄H₁₀O₂: C, 71.99; H, 7.04.

References and Notes
9) Unpublished data.
20) 1H-NMR (400 MHz, CDCl₃) δ: 1.00 (3H, t, J = 7.0 Hz), 1.32 (3H, t, J = 7.0 Hz), 3.21 (2H, d, J = 6.0 Hz), 3.97 (2H, dq, J = 2.5, 7.0 Hz), 4.25 (2H, dq, J = 1.5, 7.0 Hz), 5.03 (2H, s), 5.04 (1H, t, J = 6.0 Hz), 5.07 (2H, s), 6.86 (1H, s), 6.89 (2H, d, J = 8.5 Hz), 6.90 (2H, d, J = 8.5 Hz). 7.14 (2H, d, J = 8.5 Hz), 7.29—7.48 (10H, m), 7.70 (2H, d, J = 8.5 Hz). 13C-NMR (125 MHz, CDCl₃) δ: 13.86, 14.27, 31.20, 38.20, 60.90, 61.15, 69.89, 69.98, 79.88, 114.49, 114.66, 123.94, 126.33, 127.42, 127.47, 127.90, 128.02, 128.25, 128.54, 130.65, 132.46, 136.70, 137.05, 141.11, 157.73, 159.22, 164.15, 170.62. IR (liquid film) cm⁻¹: 3235, 2963, 1731, 1514, 1238, 1187. HR-MS: 323.1739 (Calcd for C₁₄H₁₀O₂Na 323.1738). Anal. Calcld for C₁₄H₁₀O₂Na: C, 71.99; H, 7.04.