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First way of enantioselective synthesis of moxifloxacin intermediate

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A new method of enantioselective synthesis of (*S*,*S*)-2,8-diazobicyclo [4.3.0] nonane was found by using (*R*)-2-amino-2-phenyl-ethanol as chiral induction reagent. The entire synthetic process included 8 steps which were easy to operate with high yield. The purification method was only simple recrystallization or even used directly in the next step without further purification. The total yield was 29%.

enantioselective synthesis, moxifloxacin intermediate, (*S*, *S*)-2, 8-diazobicyclo [4.3.0] nonane

1 Introduction

Moxifloxacin is a fourth-generation synthetic fluoroquinolone antibacterial agent developed by Bayer AG. It is marketed worldwide (as the hydrochloride) under the brand names Avelox, Avalox, and Avelon for oral treatment. Since its appearance in the market in September 1999, its sales increased rapidly year by year. In 2002, its sale was $ 333 million, which ranked as the world's top ten best-selling antibiotic drugs of that year. In the same year, it was listed in China and covered in the scope of the national medical insurance in 2004. Meanwhile, its sale increased dramatically and astonishingly. In 2007, the urban sample hospital purchase amounted to 216 million RMB, with an increase of 75.1% over the previous year. Due to the hot market of moxiflxacin, it is becoming more and more important for developing new efficient synthetic method in order to decrease the production cost.

(*S*,*S*)-2,8-diazobicyclo [4.3.0] nonane (**14**) is a crucial intermediate of moxifloxacin, which was also used for constructing quinolone and naphtyridine derivatives having antibacterial effectiveness [1]. So far, many synthetic methods have been reported (Scheme 1). Most of these synthetic routes start from the relatively cheap material pyridine-2,3-dicarboxylic acid (**1**) which could be transformed into the piperidine ring of the target molecule through high pressure hydrogenation. The pyrrolidine ring could be constructed through imide formation with benzyl amine, reduction with LAH, and debenzylation with Pd/C [2–6], or could be formed with 2, 3-bis(chloromethyl)pyridine (4) and $TsNH_2$ [4]. An alternative protocol using 2-allylidene-1,1-dimethylhydrazine (**8**) and 1-benzyl-1*H*-pyrrole-2,5-dione (**7**) as raw materials could construct 6-benzyl-5*H*-pyrrolo[3,4-b]pyridine-5,7 (6*H*)-dione (**10**) in two steps [7−10]. However, all those methods couldn't avoid the resolution method which obtain the chiral product by using different kinds of chiral sources, such as tartaric acid and mandelic acid, (*S*)-α-phenylethylamine, or even enzymatic resolution [11]. As we known, only up to 50% of a desired enantiomer could be obtained through chiral resolution step, which means relative low yield and great waste by using those synthetic methods. Herein, we report the first enantioselective way of synthesis (*S*,*S*)-2,8-diazobicyclo [4.3.0] nonane (**14**) by using the cheap (*R*)-2-amino-2-phenylethal as chiral source.

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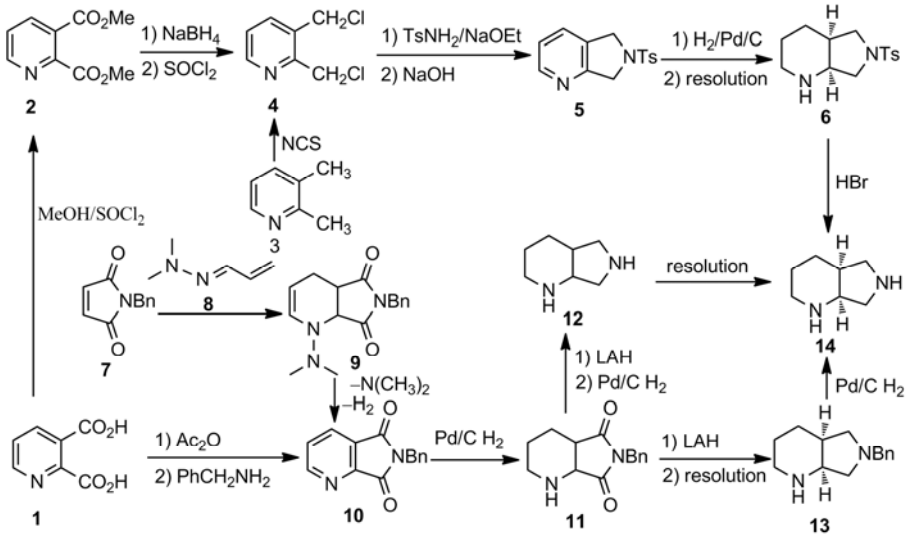


Scheme 1 Synthetic routes in references.

2 Experimental

2.1 Reagents and instruments

All reactions that required anhydrous conditions were carried by standard procedures under nitrogen atmosphere. Commercially available reagents from Alfa Aesar and Aldrich were used as received. The solvents were dried by distillation over the appropriate drying reagents. ^{1}H NMR spectra were recorded on commercial instruments (600 MHz or 300 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were collected on commercial instruments (151 MHz or 75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0).

2.2 Synthesis

*(R)-3-methoxycarbonylmethlene-5-phenyl-3,4,5,6-tetrahydro-2H-1,4-oxazin-2-one (**15**)*

A solution of (*R*)-2-amino-2-phenyl-ethanol (13.7 g, 100 mmol) in 100 mL methanol was added dropwise to a solution of dimethyl acetylenedicarboxylate (14.2 g, 100 mmol) in 150 mL of methanol with stirring for 1 h. After being stirred for additional 3 h, the mixture was evaporated in vacuo with temperature no more than 35 °C. Compound **15** was obtained as brown oil which after recrystallization from ether-petroleum ether gave colorless needles. Yield was 85%. Mp: 67–69 °C. $[\alpha]_D^{20}$: –258 (c = 0.6, $CHCl_3$) [12].

*(4S)-1, 6-dioxo-4-phenyl-1,3,4,6,7,8-hexahydropyrido-[2, 1-c] [1,4]oxazine-9-carboxylic acid methyl ester (**16**)*

Acryloyl chloride (7.5 g, 65 mmol) was added dropwise to a solution of compound **15** (16 g, 65 mmol) in 300 mL THF at room temperature. The reaction finished after refluxed for 3 h. Then the mixture was cooled to room temperature, poured into 150 mL of saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The resulting oil was recrystallization from ether-petroleum ether to give compound **16** as a white powder. Yield was 85%. Mp: 128 °C. $[\alpha]_D^{20}$: +102 (c = 1.1, $CHCl_3$) [13].

*[4S-4α,9α,9αα]-1, 6-dioxo-4-phenyloctahydropyrido [2, 1-c] [1, 4] oxazine-9-carboxylic acid methyl ester (**17**)*

A solution of lactam **16** (15 g, 50 mmol) and 5% Pd/C (5 g) in 150 mL of EtOH/EtOAc (10:1) was placed under hydrogen (1 atm) for 6 h. The catalyst was removed by filtration on celite. After concentrated in vacuo, compound **17** was isolated as a white solid (14.3 g, 95%). Mp: 108 °C. $[\alpha]_D^{20}$: +119 (c = 1.0, $CHCl_3$) [14].

*(2R,3S)-methyl-2-(benzylcarbamoyl)-1-((R)-2-hydroxy-1-phenylethyl)-6-oxopiperidine-3-carboxylate (**18**)*

To a solution of **17** (7.6 g, 25.2 mmol) in 100 mL toluene was added benzyl amine (2.7 g, 25.2 mmol) and triethylamine (7.65 g, 75.6 mmol) successively, the reaction was stirred at 85 °C over 6 h until the full transformation of the material. Then, the reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in 300 mL EtOAc and washed with water (100 × 3) and brine (100 × 2). The combined organic layers were dried (Na_2SO_4)

and concentrated in vacuo to give brown crystalline solid. The product was recrystallized from methanol to give colorless solid. Yield was 85%. ^{1}H NMR (600 MHz, DMSO) δ = 8.17 (s, 1H), 7.33 (dd, J =14.0, 6.5, 5H), 7.31–7.27 (m, 3H), 7.15–7.04 (m, 2H), 6.04 (dd, J = 11.7, 4.1, 1H), 4.51 (dd, J = 14.4, 6.0, 1H), 4.40 (dd, J = 14.4, 5.4, 1H), 4.26 (s, 1H), 4.03 (dd, J = 11.8, 4.1, 1H), 3.88 (t, J = 11.7, 1H), 3.41 (s, 1H), 3.20 (s, 4H), 2.75–2.57 (m, 1H), 2.47–2.29 (m, 1H), 2.04 (dd, J = 12.8, 7.0, 1H), 1.90 (dd, J = 14.4, 6.9, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.14, 171.95, 171.06, 137.90, 134.91, 128.91, 128.86, 128.76, 128.67, 127.98, 127.68, 61.60, 58.22, 58.16, 52.13, 44.17, 41.34, 29.46, 19.28. HRMS (ESI): calcd. for $C_{23}H_{27}N_2O_5$(M+H): 411.1914; found: 411.1914.

*(R)-2-((4aR,7aS)-6-benzyl-2,5,7-trioxooctahydro-1H-pyrrolo [3, 4-b]pyridin-1-yl)-2-phenylethyl acetate (**20**)*

To a solution of **18** (2.05 g, 5 mmol) in 20 mL methanol was added sodium hydroxide (300 mg, 7.5 mmol) dissolved in 2 mL water, the resulting mixture was stirred at room temperature over 5 h and then adjusted the solution pH to 2 with 3 mol L^{-1} HCl at 0 °C. Then the solution was concentrated in vacuo below 40 °C and the resulting residue was dissolved in 100 mL water and extracted with EtOAc (100 × 2). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a white foam product **19** which was used without further purification. HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_5$(M+H): 397.1758; found: 397.1767.

To the above dried product was added 30 mL acetic anhydride and excess lithium acetate, the mixture was stirred at 100 °C over 12 h and then cooled to room temperature. After filtration, the solution was evaporated in vacuo. After usual workup, the product was purified by recrystallization with methanol/ethyl ether. The combination of the two step yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 (m, 10H), 6.10 (t, J = 6.9, 1H), 4.90 (dd, J = 11.5, 6.8, 1H), 4.72–4.56 (m, 3H), 4.10 (d, J = 9.1, 1H), 2.83 (t, J = 8.6, 1H), 2.51–2.39 (m, 1H), 2.25 (d, J = 13.3, 1H), 2.00 (s, 3H), 1.78 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.26, 174.78, 171.16, 170.86, 135.70, 135.23, 129.20, 128.92, 128.83, 128.70, 128.59, 128.35, 127.93, 127.85, 63.08, 54.29, 53.62, 42.88, 39.40, 30.62, 23.51, 20.88. HRMS (ESI): calcd. for $C_{24}H_{24}N_2NaO_5$(M + Na): 443.1577; found: 443.1574.

*(4aS,7aS)-octahydro-1H-pyrrolo[3,4-b]pyridine (**14**)*

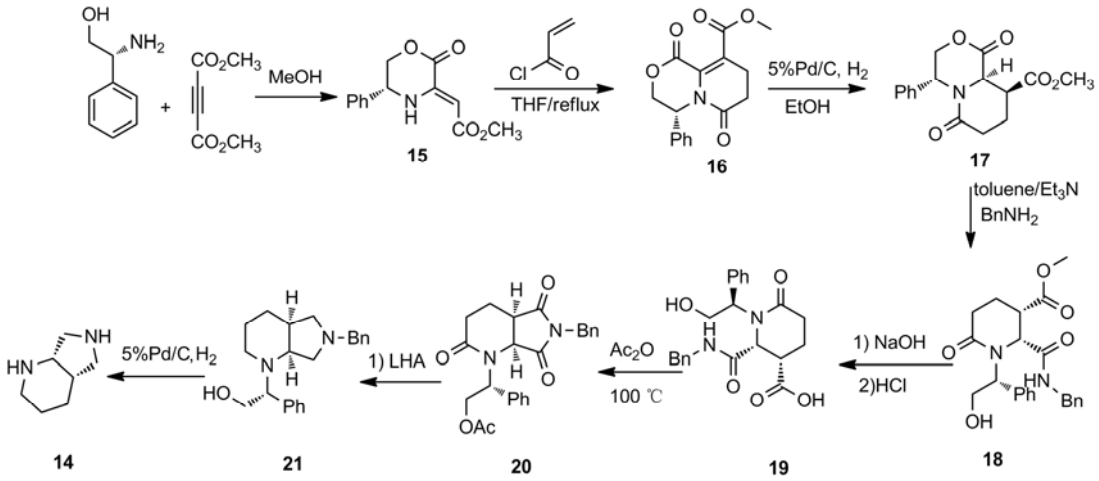
To a solution of **20** (2.1 g, 5 mmol) dissolved in 30 mL anhydrous THF was added 285 mg LAH slowly. The mixture was stirred at 50 °C over 10 h. Then the mixture was cooled to 0 °C and sodium sulfafe decahydrate was added slowly with strong stirring until no bubbles. Then sodium hydroxide (2 mol L^{-1}, 50 mL) was added into the above mixture and the product was extracted with EtOAc (100 × 2). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give intermediate **21** as brown oil which was used directly without further purification. HRMS (ESI): calcd. for $C_{22}H_{29}N_2O$(M+H): 337.2274; found: 337.2276.

To the above brown oil in 20 mL methanol was added Pd/C (10%, 500 mg) and the mixture was stirred under hydrogen atmosphere (90 °C/9 MPa) over 20 h. Then the mixture was filtered through celite and concentrated in vacuo to give brown residue. Then the residue was dissolved in 50 mL water and extracted the byproduct with cyclohexane (50 × 2) which was washed again with water (20 × 2). The aqueous solution was combined and the pH was adjusted to 12 by adding sodium hydroxide. Then the resulting solution was extracted with chloroform (100 × 2). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give pale yellow oil. The yield of the two combination steps was 60%. $[\alpha]_D^{20}$: −2.46 (c = 1.0, H_2O). ^{1}H NMR (600M, $CDCl_3$) δ = 1.40 (m, 1H), 1.51 (m, 1H), 1.62 (m, 2H), 2.21 (br, 2H), 2.49 (m, 1H), 2.57(td, 1H), 2.74 (d, 1H), 2.93 (m, 4H), 3.13 (t, 1H) [6].

3 Results and discussion

In planning the synthesis of **14**, the key factor is how to construct the two chiral centers. Interestingly, Claude Agami had used (*R*)-2-amino-2-phenyl-ethanol as chiral inductor to efficiently create two new stereogenic centers similar to our target [13, 14]. Meanwhile, (*R*)-2-amino-2-phenyl-ethanol was used as chiral induction reagent for preparation of aspartic acid derivatives and alanine derivatives by Kaoru Harada due to its cheap and easy to take off properties [12]. As a result, we wish to construct the two chiral centers by chiral induction with (*R*)-2-amino-2-phenyl-ethanol. Based on their synthetic protocols, we put forward our synthetic strategy (Scheme 2).

To begin our research, oxazinone **15** was prepared through Michael addition/esterification tandem reaction described by Kagan and Horeau, during their classical asymmetric synthesis of aspartic acid [15]. We optimized their method by strictly controlling the reaction condition. We found the dropping rate should keep slowly or the reaction solution would become very dark. What's more, the concentration process should be done in vacuo below 35 °C. After usual work up, the crude product was used directly in the next step without further purifications. Then, bicyclic product **16** was prepared by condensation of **15** with acryloyl chloride, following the Paulvannan and Stille procedure [16]. In the purification process, we found that product **16** could be purified through recrystallization from ether-petroleum ether without column chromatography. Then, bicyclic product **16** was hydrogenated in dry ethanol and intermediate **17** was received as off white solid after usual workup without column chromatography. As a result, we could get product **17** after three steps with yield of 69% with simple purification workup. Deserve to be mentioned, the diastereomer formed by adding Na_2CO_3 as additive during the hydrogenation process. So we could get the other diastereomer with the same method.



Scheme 2 Synthetic way for construction of target molecule.

Then, we hoped to form imide by amino-ester exchange. However, the reaction proceeded and only exchanged the lactone. We tried several base such as LDA, LHMDS, NaHMDS, KHMDS, and so on, nevertheless the yield was low and little racemization product was found. So we separate this transformation into two steps. Firstly, we hydrolyzed the methyl ester into acid with sodium hydroxide. The hydrolysis condition should be done below 20 ℃ and the equivalent load of sodium hydroxide should be strictly controlled in case of racemization. In this way, the acid intermediate was received quantitatively and was used in the ring closing step without further purifications. Then we closed the lactam ring with acetic anhydride. The lactam was received by simple crystallization from ethyl ether and methanol. As a result, the intermediate **20** was received after two simple steps with the yield of 70%.

Next, we reduced the three carbonyls with LHA in anhydrous THF under refluxing condition. Only 70% yield was received. We tried other reduction method such as $NaBH_4/TiCl_4$, $NaBH_4/BF_3.Et_2O$, $NaBH_4/I_2$, however, LHA was better than any of them. Finally, we chose LHA as reduction reagent. After usual workup, intermediate **21** was received as brown oil which was used in the next step directly without further purification. In the final step, we used high pressure hydrogenation condition to take off benzyl group and benzyl alcohol simultaneously. After usual workup, product **14** was received as palebrown oil. The yield of the final two steps was 60%.

4 Conclusion

In summary, we found a simple and economic way of synthesizing (*S*, *S*)-2, 8-diazobicyclo [4.3.0] nonane which is a valuable intermediate used for constructing quinolone and naphtyridine derivatives having antibacterial effectiveness such as moxifloxacin. The synthetic process included 8 steps and total yield was up to 29%. All the raw materials used were cheap and easy to buy, and what's more, during the entire process, all of the intermediate were easily purified by simple recrystallization or used in the next step directly without further purification. In all, this novel way is expected to be an alternative for traditional method after further scale-up experiment. Further experiment for optimizing the entire process and scale-up are underway in our group.

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1 Hoogkamp-Korstanje JAA, Roelofs-Willemse J. Comparative *in vitro* activity of moxifloxacin against Gram-positive clinical isolates. *J Antimicrob Chemother,* 2000, 45: 31–39
2 Petersen U, Krebs A, Schenke T, Schriewer M, Grohe K, Krebs A, Haller I, Metzger KG, Bremm KD, Endermann R, Zeiler HJ. Quinolone and naphthyridone carboxylic acid derivative. Japan Patent, 200304889, 2003-02-21
3 Takemura M, Kimura Y, Matlsuhashi N. Bicyclic amine derivatives. European Patent, 603887, 1994-06-29
4 Wang ZQ, Feng SS, Cheng YZ. A novel and economical process for preparing(*S*, *S*)-2, 8-diazabicyclo [4, 3, 0] nonane and its enantiomer. PCT patent, 2008085480, 2007-07-17
5 Klemm L, Johnson W, White D. Thieno (3, 4-b) pyridine and thieno (3, 4-c) pyridine. American patent, 3709894, 1973-01-09
6 Riccardo M, Giancarlo A, Elisabetta B, Andrea C, Stefano F, Marco G. Synthesis of (4aS, 7aS)-octahydro-1H-pyrolo [3, 4, b] pyridine. PCT patent, 100215, 2010-10-09
7 Uwe P, Andreas K, Thomas S. Eantiomerenreine chinolincarbonsă ure derivate. Germany patent, 4208792, 1993-09-23
8 Uwe P，Andreas K，Thomas S. Chinolon-und naph-thridon-carbons ău r derivatcals antibakterieUes mittel. European patent, 550903, l992-12-28
9 Wuppertal FP. Method for producing (*S*, *S*)-benzyl-2, 8-diazabicyclo [4, 3, 0] nonane. American patent, 6235908, 2001-03-22
10 Uwe P, Andreas K, Thomas S. Eantiomerenreine chinolincarbonsă ure derivate. Germany patent, 4208789, 1993-09-23

11 Dreisbach C. Method for racemic biochemical resolution of cis-and trans-pyrrolopiperidine. PCT patent, 9909200, 1999-02-25
12 Minoru T, Kaoru H. Asymmetric synthesis of aspartic acid by hydrogenation of optically active 1, 4-oxazine derivative. *Bull Chem Soc Jpn*, 1980, 53: 561–562
13 Agami C, Kadouri-Puchot C, Le Guen V, Vaissermann J. Neuromediator analogs: Synthesis of cis (2*R*, 3*S*) and trans (2*S*, 3*S*)-2, 3-piperidine dicarboxylic acids from (2*S*)-2-phenylglycinol. *Tetrahedron Lett*, 1995, 36: 1657–1660
14 Claude A, Louis H, Catherine KP, Valérie Le G. Enantioselective synthesis ofconformationally restricted analogs of NMDA: Cis- and trans-piperidine-2, 3-dicarboxylic acids and methylated derivatives. *J Org Chem*, 1996, 61: 5736–5742
15 Vigneron JP, Kagan H, Horeau A. Synthese asymetrique de l'acide aspartique optiquement pur. *Tetrahedron Lett*, 1968, 9: 5681–5683
16 Paulvannan K, Stille JR. Formation of 1, 2, 3, 4-tetrahydro-2-pyridones by aza-annulation of imines with acrylate derivatives. *J Org Chem,* 1992, 57: 5319–5328