N-Selective Alkylation of Norepinephrine by Reductive Amination

[1]Linming Zuo, [1]Han Lin, [2]Xianheng Wang* and [1]Changkuo Zhao**

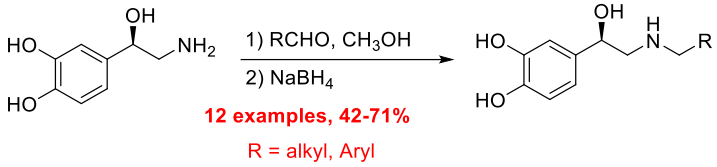
[1]*School of Pharmacy, Zunyi Medical University, No.6 Xue Fu West Road, Zunyi, 563003, China.*

[2]*Key Laboratory of Basic Pharmacology of Ministry of Education and Joint International Research Laboratory of Ethnomedicine of Ministry of Education, Zunyi Medical University, Zunyi Guizhou 563099, China.*

zck7103@hotmail.com*

(Received on 28th Feb 2024, accepted in revised form 24th December 2024)

Summary: A facile direct alkylation of norepinephrine has been developed by reductive amination. This method has several advantages, including a one-step procedure, ease of execution, moderate yields and broad substrates feasibility.



Keywords: N-alkylation; Norepinephrine; Selectivity; Synthesis; Structure modification

Introduction

L-noradrenaline is a naturally occurring catecholamine derivative (Fig 1). Noradrenaline mobilizes the brain and body for action. Pharmacologically, it acts as a sympathomimetic, affecting both alpha and beta receptors. This makes noradrenaline a primary neurotransmitter of the sympathetic nerves not only in the cardiovascular system, but also can be used for the treatment of hypotension. It has therefore attracted much attention from many medicinal chemists.

Alkyl or Aryl is an important lipophilic group, and the introduction of such group may modify bioavailability obviously. After perusal of literature, there are a few reports on the synthesis of N-Aryl norepinephrine. However, the existing synthetic routes (Schemes 1 and 2) are tedious, uneconomical, and unsuitable for commercialization

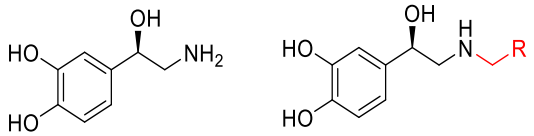
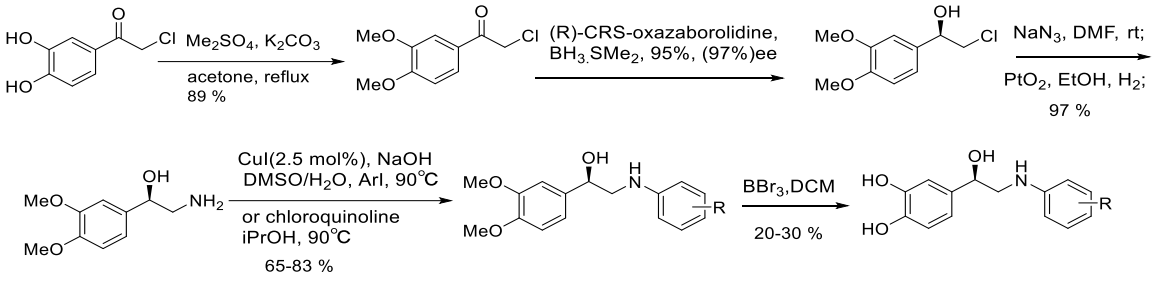


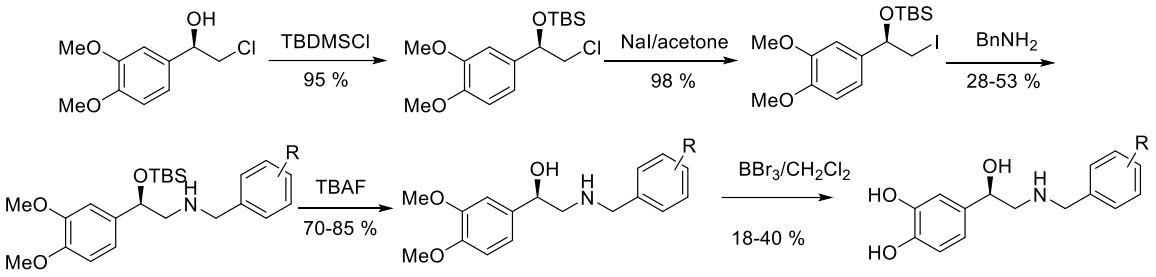
Fig. 1: Structure of L-norepinephrine and analogs.

.



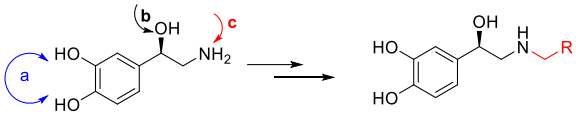
Scheme-1: Synthetic route starting from 3, 4-dihydroxy α-chloroacetophenone.

*To whom all correspondence should be addressed.



Scheme-2: Synthetic route starting from 3, 4-dihydroxy chlormethyl benzyldalcohol.

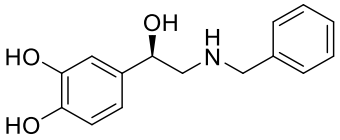
Based on the above study, we envisioned that a facile N-alkylation synthetic protocol by direct reductive amination is required indeed (Scheme 3), and the resulting N-alkylation norepinephrine derivatives will have a wide application in the field of pharmaceuticals. In this article, we herein described our synthesis research result.



Scheme-3: Retrosynthetic route of N-alkylation of norepinephrine

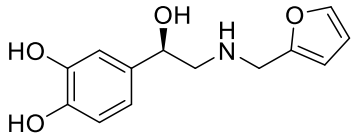
Experimental

(S)-4-(2-(benzylamino)-1-hydroxyethyl)benzene-1,2-diol **(4a)**



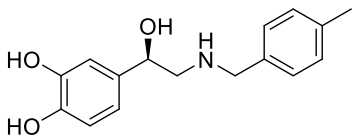
To a Schenk flask was added L-Norepinephrine (100 mg, 0.59 mmol), benzaldehyde (72 µL, 0.7 mmol), molecular sieve 4Å, and methanol (4 mL). The suspension was stirred at room temperature overnight. The reaction mixture was then colled to 0°C, followed by the addition of $NaBH_4$ (45 mg, 1.18 mmol). The mixture was then warmed to room temperature for 8 h. The mixture was then neutralized to pH =7 with the addition of dilute HCl (1N). After removal of the solvent, the residue was the purified by flash column chromatography, eluting with DCM: MeOH = 10: 1 to afford the title compound (**4h**, 97 mg, 64%) as brown oil. R_f= 0.26 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$ = **-16.59** (c=5x10^{-3} g/mL, CH_3OH), ^1H NMR (400 MHz, CD_3OD) δ 7.52 – 7.36 (m, 5H), 6.83 (s, 1H), 6.79 – 6.66 (m, 2H), 4.82 (dt, *J* = 9.6, 4.5 Hz, 1H), 4.17 (s, 2H), 3.01 (d, *J* = 10.0 Hz, 2H).^{13}C NMR (101 MHz, CD_3OD) δ 145.15, 145.02, 132.68, 132.26, 129.54, 128.89, 128.76, 117.14, 115.00, 112.75, 69.00, 53.52, 50.98. HRMS-ESI (m/z): calcd for $C_{15}H_{17}NO_3$ $[M+H]^+$: 260.1281, found 260.1284. No: LH230816

(S)-4-(2-((furan-2-ylmethyl)amino)-1-hydroxyethyl)benzene-1,2-diol **(4b)**



Yield 43%, brown oil, R_f = 0.41 (DCM: MeOH = 5: 1). $[\alpha]_D^{25}$ = **-9.92** (c=5x10^{-3} g/mL, CH_3OH), ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.48 (m, 1H), 6.68 (d, *J* = 1.6 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.51 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (d, *J* = 3.1 Hz, 1H), 4.42 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.71 (s, 2H), 2.61 – 2.50 (m, 2H). ^{13}C NMR (101 MHz, cd_3od) δ 148.12, 145.14, 144.92, 143.41, 133.14, 117.12, 114.93, 112.78, 110.40, 69.79, 53.98, 43.50.HRMS-ESI (m/z): calcd for $C_{13}H_{15}NO_4$ $[M+Na]^+$: 272.0893, found 272.0895. No: LH220830

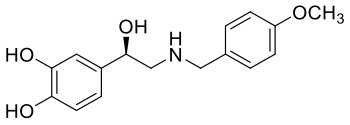
(S)-4-(1-hydroxy-2-((4-methylbenzyl)amino)ethyl)benzene-1,2-diol (**4c**)



Yield 46%, brown oil, R_f = 0.23 (DCM : MeOH = 10 : 1), $[\alpha]_D^{25}$ = **-15.19** (c=5x10^{-3} g/mL, CH_3OH), ^1H NMR (400 MHz, CD_3OD) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 6.82 (d, *J* = 2.0

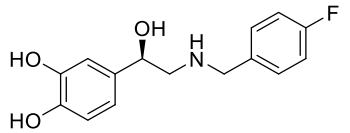
Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.81 (dd, *J* = 9.6, 3.8 Hz, 1H), 4.18 (s, 2H), 3.11 – 2.96 (m, 2H), 2.35 (s, 3H).^{13}C NMR (101 MHz, CD_3OD) δ 145.17, 145.08, 139.36, 132.38, 129.66, 129.40, 128.17, 117.04, 114.96, 112.66, 68.54, 53.01, 50.43, 19.86, HRMS-ESI (m/z): calcd for $C_{16}H_{19}NO_3$ $[M+H]^+$: 274.1438, found 274.1443. No: LH220919

(S)-4-(1-hydroxy-2-((4-methoxybenzyl)amino)ethyl)benzene-1,2-diol **(4d)**



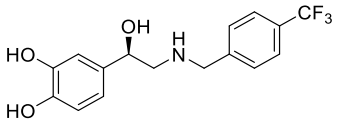
Yield 57%, brown oil, R_f = 0.18 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$= **-16.99** (c=5x10^{-3} g/mL, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.83 (dd, *J* = 5.5, 2.5 Hz, 1H), 6.76 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.82 (td, *J* = 8.3, 4.0 Hz, 1H), 4.13 (s, 2H), 3.78 (s, 3H), 3.09 – 2.86 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 160.51, 145.16, 145.05, 132.54, 131.20, 123.41, 117.10, 114.99, 114.05, 112.71, 68.76, 54.46, 53.06, 50.34.HRMS-ESI (m/z): calcd for $C_{16}H_{19}NO_4$ $[M+Na]^+$: 312.1206, found 312.1211. No: LH230726

(S)-4-(2-((4-fluorobenzyl)amino)-1-hydroxyethyl)benzene-1,2-diol **(4e)**



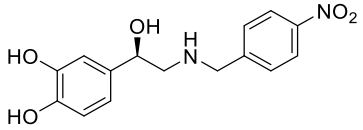
Yield 59%, brown oil, R_f = 0.16 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$= **-14.52** (c=5x10^{-3} g/mL, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.15 (t, *J* = 8.5 Hz, 2H), 6.84 (s, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.70 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.83 (dd, *J* = 9.5, 3.9 Hz, 1H), 4.19 (s, 2H), 3.11 – 2.96 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 164.44, 161.98, 145.16, 145.05, 132.55, 131.98, 128.06, 117.11, 115.62, 115.40, 114.97, 112.72, 68.83, 53.44, 50.09, HRMS-ESI (m/z): calcd for $C_{15}H_{16}FNO_3$ $[M+H]^+$: 278.1187, found 278.1190. No: LH230730B

*(S)-4-(1-hydroxy-2-((4-(trifluoromethyl)benzyl)amino)ethyl)benzene-1,2-diol***(4f)**



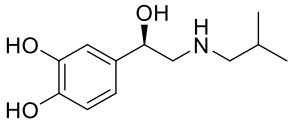
Yield 48%, brown oil, R_f = 0.19 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$ = **-17.72** (c=5x10^{-3} g/mL, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (q, *J* = 8.0 Hz, 4H), 6.85 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.80 (s, 1H), 4.12 (s, 2H), 2.96 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 145.08, 144.87, 138.97, 133.24, 129.75, 125.48, 125.34, 122.78, 117.25, 115.00, 112.87, 69.91, 54.51, 50.91. HRMS-ESI (m/z): calcd for $C_{16}H_{16}F_3NO_3$ $[M+H]^+$: 328.1155, found 328.1155. No: LH230802

(S)-4-(1-hydroxy-2-((4-nitrobenzyl)amino)ethyl)benzene-1,2-diol **(4g)**



Yield 52%, yellow solid, M.p.178.8~180.0℃, R_f = 0.33 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$= **-14.26** (c=5x10^{-3} g/mL, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.65 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.65 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.94 (s, 2H), 2.85 – 2.69 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 147.21, 146.37, 144.95, 144.55, 134.28, 129.12, 123.16, 117.18, 114.75, 112.81, 71.62, 55.65, 51.71.HRMS-ESI (m/z): calcd for $C_{15}H_{16}N_2O_5$ $[M+Na]^+$: 327.0951, found 327.0947. No: LH230810

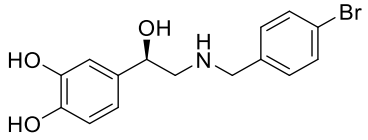
(S)-4-(1-hydroxy-2-(isobutylamino)ethyl)benzene-1,2-diol **(4h)**



Yield 23%, brown oil, R_f = 0.36 (DCM: MeOH = 5:1). $[\alpha]_D^{25}$= **-5.86** (c=5x10^{-3} g/mL, CH_3OH),

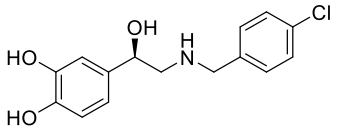
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 2H), 6.76 (s, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 4.77 (s, 1H), 3.79 – 3.59 (m, 1H), 3.43 (q, *J* = 7.0 Hz, 2H), 2.82 (d, *J* = 10.2 Hz, 1H), 2.71 (s, 2H), 1.96 (s, 1H), 0.90 (t, *J* = 6.2 Hz, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 145.55, 145.20, 133.45, 117.08, 115.80, 113.86, 68.49, 55.16, 54.69, 25.88, 20.74, 20.61. HRMS-ESI (m/z): calcd for $C_{12}H_{19}NO_3$ $[M+H]^+$: 226.1438, found 226.1441. No: LH220827

(S)-4-(2-((4-bromobenzyl)amino)-1-hydroxyethyl)benzene-1,2-diol **(4i)**



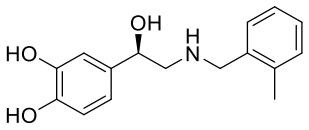
Yield 45%, brown solid, M.p. 129.6~131.2℃, , R_f = 0.28 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$= **-10.72** (c=5x10^{-3} g/mL, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.70 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.82 (dd, *J* = 9.6, 3.7 Hz, 1H), 4.19 (s, 2H), 3.12 – 2.99 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 145.20, 145.11, 132.37, 131.92, 131.65, 130.73, 123.21, 117.06, 114.95, 112.67, 68.68, 53.41, 50.02.HRMS-ESI (m/z): calcd for $C_{15}H_{16}BrNO_3$ $[M+H]^+$: 338.0387, found 338.0384. No: LH230817

(S)-4-(2-((4-chlorobenzyl)amino)-1-hydroxyethyl)benzene-1,2-diol **(4j)**



Yield 56%, brown oil, R_f = 0.23 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$= **-16.99** (c = 5x10^{-3} g/mL, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.83 (s, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.70 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.83 (dd, *J* = 9.6, 3.9 Hz, 1H), 4.18 (s, 2H), 3.09 – 2.98 (m, 2H).^{13}C NMR (101 MHz, CD_3OD) δ 145.16, 145.05, 134.93, 132.54, 131.34, 130.79, 128.82, 117.08, 114.93, 112.68, 68.83, 53.54, 50.07. HRMS-ESI (m/z): calcd for $C_{15}H_{16}ClNO_3$ $[M+H]^+$: 294.0892, found294.0891. No: LH230825

(S)-4-(1-hydroxy-2-((2-methylbenzyl)amino)ethyl)benzene-1,2-diol **(4k)**



Yield 63%, brown oil, R_f = 0.35 (DCM: MeOH = 10: 1), $[\alpha]_D^{25}$= **-17.26** (c = 5x10^{-3} g/mL, CH_3OH),^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, *J* = 7.1 Hz, 1H), 7.25 (td, *J* = 7.0, 3.7 Hz, 3H), 6.86 (s, 1H), 6.74 (q, *J* = 8.1 Hz, 2H), 4.85 (dd, *J* = 9.2, 4.2 Hz, 1H), 4.19 (s, 2H), 3.19 – 2.99 (m, 2H), 2.40 (s, 3H). HRMS-ESI (m/z): calcd for $C_{16}H_{19}NO_3$ $[M+H]^+$: 274.1438, found 274.1440. No: LH230901

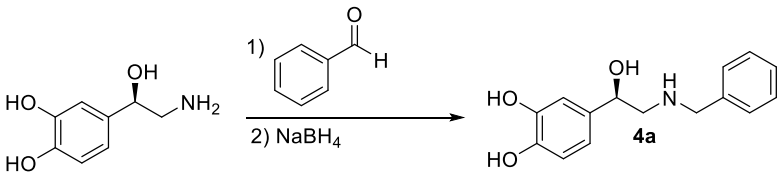
Results and Discussion

Considering the several possible reaction positions, direct alkylation of L-norepinephrine resulted in a mixture of products, with no desired compound formed.

Reductive amination of aldehydes and ketones is a very convenient method for the preparation of secondary and tertiary amines. Therefore, using naturally occurring L-norepinephrine as a chiral starting material in a reductive amination reaction is a reasonable choice to prepare N-alkylated L-norepinephrine derivatives. And benzaldehyde was then chosen as an example to explore this reaction (Table-1). Different temperatures, reaction times and molar ratios were tried to optimize this reaction. It was found that the desired N-alkylation product (**4a**) can be prepared in 64% yield (Entry 3).

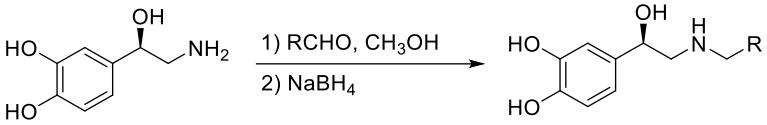
Based on the above finding, different aldehydes were then tested for this reaction to extend substrate range. All the aromatic aldehydes will give the desired reductive amination product in a moderate yield correspondly. But for aliphatic aldehydes, the reaction will become complicated, and the yield will be decreased (**Entry 4h**). The results were shown in the following Table-2.

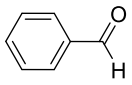
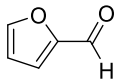
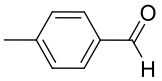
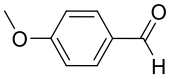
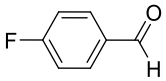
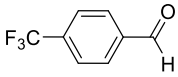
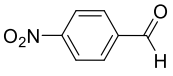
Table-1: Optimization of reductive amination reaction.

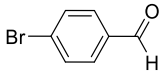
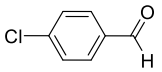
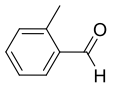


Entry	Benzaldehyde (mol/mol)	$NaBH_4$ (mol/mol)	Solvent	Temp/Time	Yield
1	1.1	2	CH_3OH	1)overnight 2)rt, 4 h	39%
2	1.1	2	CH_3OH	1)overnight 2)rt, 14 h	22%
3	1.1	2	CH_3OH	1)overnight 2)8 h	64%
4	1.1	1	CH_3OH	1)overnight 2)rt, 8 h	26%
5	2	2	CH_3OH	1)overnight 2)rt, 8 h	32%
6	1.1	2	CH_3OH	1)overnight 2)40℃, 8 h	44%

Table-2: Reductive amination of L-norepinephrine.



Entry	RCHO	Time	Yield
4a		1)overnight 2)8 h	64%
4b		1)overnight 2)8 h	43%
4c		1)overnight 2)8 h	46%
4d		1)overnight 2)8 h	57%
4e		1)overnight 2)8 h	59%
4f		1)overnight 2)8 h	48%
4g		1)overnight 2)8 h	52%

4h	**$(CH_3)_2CHCHO$**	**1)overnight 2)12 h**	**23%**
4i		**1)overnight 2)8 h**	**45%**
4j		**1)overnight 2)8 h**	**56%**
4k		**1)overnight 2)8 h**	**63%**

Conclusion

We present a systematic study culminating in a general and straightforward method for the synthesis of N-alkylated L-norepinephrine with moderate yields. The ^{1}H NMR, ^{13}C NMR and HR-MS spectra of these L-norepinephrine derivatives were consistent with their structures and were listed in Supporting Information. The biological evaluation of these molecules are undergoing at present.

Acknowledgments

Dr. Xianheng Wang designed the study and Dr. Changkuo Zhao was responsible for the synthetic route design. Mr. Han Lin and Lingming Zuo prepared the sample. All authors gave the approval for the final submission. We thank for the financial support from Science and Technology Foundation of Guizhou Province (QianKeHe ZhiCheng [2022]293), Guizhou Provincial Administration of Traditional Chinese Medicine (GZWKJ2023-238), Key Project of Guizhou Provincial Administration of Traditional Chinese Medicine (QZYY-2021-086), Science and Technology Foundation of Zunyi City (ZunyiKeHe HZ [2022]417), and we are also grateful Dr. Jianyong Zhang's useful explanation on HPLC and LC/MS spectra data. The authors declare that they have no conflict of interest.

Reference

1. Francesco Scorzelli, Giusy Tassone, Daniele Padula, and Matteo Zacchè 1Mechanistic Aspects of the AsymmetricTransfer Hydrogenation in the Manufacture of Noradrenaline. *European Journal of Organic Chemistry*, **36**, e202200490 (2022).
2. Kershaw NM, Wright GSA, Sharma R, Antonyuk SV, Strange RW, Berry NG, O'Neill PM and Hasnain SS. X-ray crystallography and computational docking for the detection and development of protein-ligand interactions. *Current Medicinal Chemistry*, **20**, 569 (2013).
3. Matteo Zacche, Pier Andrea Gatti, Fulvio Gerli, Davide Sbarbada, Fabio Rondina. A process for the preparation of enantiomerically pure norepinephrine via enantioselective transfer hydrogenation of the novel intermediates 2-benzylamino-3',4'-dihydroxyacetophenone acetate or formate, WO 2020212157.
4. Dalvi MB, Kenny RS, Kawle GR. Process for preparation of (DL)-norepinephrine acid addition salt, a key intermediate of (R) - (-) - norepinephrine.WO2013008247
5. Maxim E, Bernard D, Geneviève A, Thierry C, Maria CGA, Pascal C and Christian M. A concise formation of N-substituted 3, 4-diarylpyrroles – synthesis and cytotoxic activity. *Org. Bio Chem*, **12**, 1518 (2014).
6. Jinhong P, Taotao Z, Kai P, Wei Z, Jun D, Qi Z.A method for the preparation of norepinephrine. CN108069863
7. Hemalata DL and Manickam S. An improved synthesis of 1, 2-dehydro-N-acetyldopamine, Organic Preparations and Procedures International, **20,** 191 (1988).
8. Kureshy RI, Khan NUH, Abdi SHR, Bajaj HC, Roy T, Das A. Recyclable chiral catalyst for asymmetric nitroaldol reaction and process for the preparation thereof, WO 2014118799
9. Seonki H, Jihoon K, Yun Suk N, Junghong P, Sunjin K, Kaushik S, Gun-Il I, Dong-Keun H, Won Jong K, and Haeshin L. Poly(norepinephrine): Ultrasmooth Material-Independent Surface Chemistry and Nanodepot for Nitric Oxide , Angewandte Chemie, International Edition, **52**, 9187 (2013).