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AN IMPROVED AND ECONOMICAL PROCESS FOR PREPARATION OF PREGABALIN, AN ANTICONVULSANT

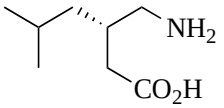
Fei Xiong,[1,3,#,*] Bin Yang,[2,#,*] Wei-Xiang Wang,[1] Yue-Feng Zhao,[1] Qing-Gang Tan,[1] Shang-Wu Gu,[1] Jia-Min Huo,[1] Yao Xie,[1] Jun-Zhe Yan,[1] Xi-Lin Feng,[1] and Ju Li[1]

[1] Department of Chemistry, University of Shanghai for Science and Technology, Shanghai 200093, *P. R.* China;
[2] School of Energy and Power Engineering, University of Shanghai for Science and Technology, Shanghai 200093, *P. R.* China;
[3] Department of Chemistry, Fudan University, Shanghai 200043, *P. R.* China
[#] These authors contributed equally to this work.
e-mail: feixiong09@fudan.edu.cn; yangbin@usst.edu.cn

Abstract – An improved, practical, economical and efficient process for the preparation of highly enantiomerically pure pregabalin (**1**) involving chemical resolution through diastereomeric crystallization is described herein. 3-Isobutylpentanedioic acid (**2**) is subjected to dehydration to afford 3-isobutylglutaric anhydride (**3**), followed by a ring-opening esterification with cinnamyl alcohol to form the racemic hemiester ***rac*-4**, which is, in turn, salified with an inexpensive organic base (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol (**CHA**) to form diastereomeric salts mixture. Then subsequently chemical resolution through diastereomeric crystallization to produce the desired enantiopure hemiester **4**, which is the key chiral synthetic intermediate of pregabalin (**1**).

Pregabalin (**1**) is an important anticonvulsant drug used for epilepsy, neuropathic pain, anxiety and social phobia treatment,[1-4] which is chemically known as (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**) (**Figure 1**). Thus, a fundamental challenge in the preparation of **1** was control of chirality and a great number of reports are available in the literature related to the various synthetic strategy for the preparation of pregabalin.[5-6] In recent years, many studies have reported tremendous achievements in the catalytic asymmetric desymmetrizations of *meso* compounds with the chemical and enzymatic catalyst via

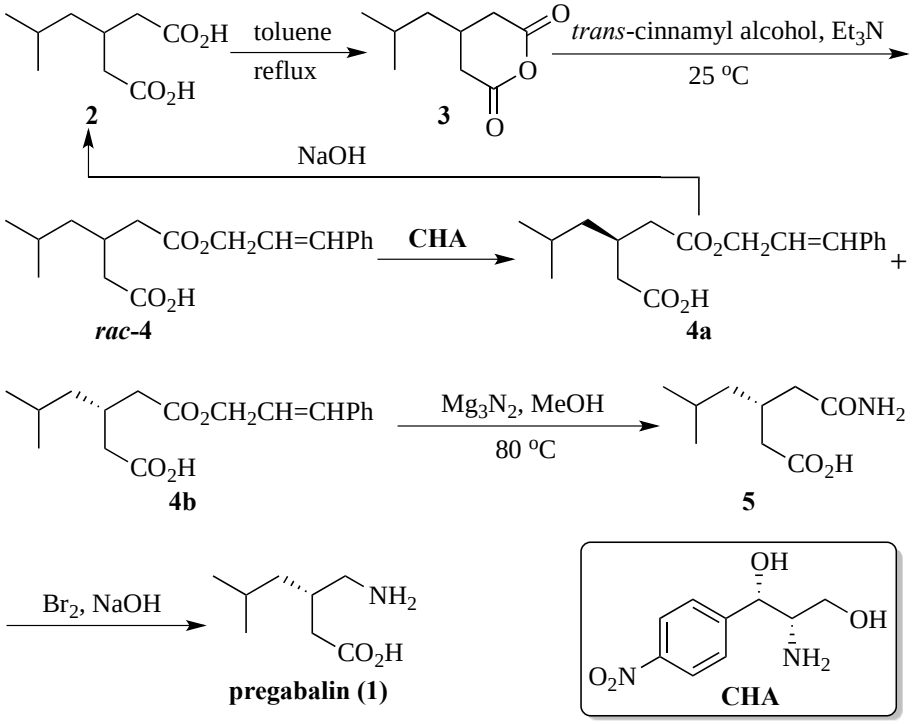
enantioselective alcoholysis of 3-isobutylpentanedioic acid (**2**) or its anhydride **3**.[7-11] However, these processes have restricted application on manufacturing-scale because of the cost intensive reagents required for the preparation of chiral organocatalyst and the complexity of the chemical process itself. Therefore, it was useful and desirable to develop a practical and economical process.



pregabalin (1)

Figure 1. The chemical structure of pregabalin

In the course of our group's synthetic studies on industrial total synthesis of (+)-biotin,[12] a novel chiral resolution technology has been successfully developed for the manufacture of optically pure monoester, the synthetic precursor for *Roche* lactone intermediate,[13-17] involving the crystallization resolution of the diastereomeric mixture formed by the reaction of racemic monoester with commercially available (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol (**CHA**), an organic base by-product in the industrial production of chloramphenicol. Therefore, this promising work of our group came into our specific attention due to the parallels with our ongoing research concerning the preparation of optically pure pregabalin via a chiral resolution of racemic monoester intermediate strategy. Here we report an improved and economical process for the production of pregabalin via the chemical resolution synthetic strategy.



Scheme 1

Our improved chemical process for the total synthesis of pregabalin (**1**) also commenced with the generation of *meso*-cyclic anhydride **3** using commercially available material 3-isobutylpentanedioic acid (**2**) and the proposed synthetic route is depicted in **Scheme 1**. It is known from the literature that diacid **2** can be converted into the corresponding *meso*-cyclic anhydride **3** upon the intramolecular dehydration reaction using acetic anhydride as dehydrant.[7] In our preliminary repeated experiments, treatment of diacid **2** with acetic anhydride generated *meso*-cyclic anhydride **3** in only 50% isolated yield and 91% purity due to the desired product **3** is a high boiling point oily material and unavoidable mixed with a small amount of unreacted acetic anhydride during the purification process of vacuum distillation. To address these issues, an improved dehydration procedure to prepare **3** was developed and the typical procedure is as follows: treatment of diacid **2** in refluxing toluene in the presence of a catalytic amount of concentrated sulfuric acid with azeotropic removal of water for 4 h led to the desired *meso*-cyclic anhydride **3**. To our delight, we further observed that the diacid **2** reacted very well in refluxing toluene with azeotropic removal of water leading to the product **3** in almost quantitatively yield after 6 h in the absence of acidic catalyst. A particularly attractive feature of this alternative approach was the resulting reaction mixture could be used for the next step directly without any further isolation or purification while overcoming tedious operation and consequently brings more benefits to the industrial development.

To one-pot alcoholysis and ring-opening procedure transform the *meso*-cyclic anhydride **3** into the corresponding racemic monoester ***rac*-4**, a solution of the former **3** in toluene was treated with cinnamyl alcohol and trimethylamine. After 5 min, racemic monoester ***rac*-4** was formed in 100% isolated yield by evaporation of the reaction mixture. With the racemic monoester ***rac*-4** in hand, our attention was then turned to obtain the optically active (*S*)-monoester **4b** and the suggestion on how to chemical resolution of ***rac*-4** came from our recent studies on (+)-biotin through the process of a racemic synthesis followed by a resolution separation of enantiomers.[12] Treatment of racemic monoester ***rac*-4** with a slight excess of **CHA** in isopropanol at reflux for 30 min gave the **CHA** salts of (*S*)-monoester **4b** as white solid, which was isolated in 27% yield by simple filtration of the reaction mixture at room temperature. And the enantiopure monoester **4b** was then easily recovered by acidified carefully with 2M HCl and concentrated. The $[\alpha]_D^{25}$ value indicating that the absolute stereochemistry of **4b** was the desired (*S*)-enantiomer and the enantiomeric purity of **4b** was further confirmed by chiral HPLC analysis.[7]

As seen from **Table 1**, the optimization of other reaction conditions (solvent and concentration) for this chemical resolution process was also undertaken. It was observed that amongst three different solvents examined (**Table 1**, entries 1-3), the optimum solvent in terms of isolated yield was ethanol. Further diluting the concentration to 0.6 M resulted in a detrimental effect on the isolated yield (**Table 1**, entries 2, 5-6). In contrast, it was found that the enantiomeric excess of **4b** generally decreased on raising the concentration of the substrate from 1 mol/L to 1.2 mol/L (**Table 1**, entries 2, 4). Furthermore, the other

enantiomer, (*R*)-monoester **4a**, could be transformed into the synthetic precursor diacid **2** upon alkaline hydrolysis of the carboxylic ester of **4a**.

Table 1. Optimization of the reaction conditions in the chemical resolution of ***rac*-4**

Entry	solvent	T (°C)	Concn.[a] (M)	Yield[b] (%)	ee[c] (%)
1	2-PrOH	25	1	27	99
2	EtOH	25	1	43	99
3	H_2O	25	1	19	99
4	EtOH	25	1.2	45	93
5	EtOH	25	0.8	41	99
6	EtOH	25	0.6	39	99

[a] Refers to the concentration of ***rac*-4** in the solvent.
[b] Yield of isolated product (*S*)-monoester **4b**.
[c] The enantiomeric purity of **4b** were determined by chiral HPLC analysis.

The corresponding amide **5** was, in turn, obtained in 94% yield by treatment of (*S*)-monoester **4b** with Mg_3N_2 in methanol. Finally, a Hoffmann rearrangement of amide **5** furnish the enantiomeric pure pregabalin (**1**) in 84% yield, which is identical in all respects with previous reported values.

In the present article we reported an improved synthetic process for the preparation of pregabalin (**1**) via the chemical resolution strategy, which is not only cost competitive to current industrial processes but also leaves a significantly smaller environmental footprint.

EXPERIMENTAL

Melting points were determined with a *WRS*-1B digital melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance 400 spectrometer using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. Optical rotations were measured with a *JASCO* P1020 digital automatic polarimeter. HPLC analysis of the enantiomeric excesses of monoester **4b** was performed using chiralpak AS column (n-hexane/EtOH/TFA=95/5/0.2). Mass spectra were recorded on a Waters Quattro-Micromass instrument by using electrospray ionization (ESI) techniques. Unless otherwise noted, all the reagents were obtained from commercial sources and used as received.

3-Isobutylglutaric anhydride (3). A mixture of **2** (20 g, 106 mmol) in toluene (320 mL) was refluxed under stirring with a water separator for 6 h. The resulting reaction mixture was then cooled to room temperature and used for the next step directly without isolation and purification of product **3.**

^{1}H NMR ($CDCl_3$): δ 2.85 (dd, 2H, J_1 = 17 Hz, J_2 = 4.1 Hz), 2.12-2.50 (m, 3H), 1.61-1.75 (m, 1H), 1.27 (t,

2H, *J* = 7.1 Hz), 0.91 (d, 6H, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 166.5, 43.1, 35.4, 25.9, 24.2, 21.8. MS (ESI): *m/z* 193.1 ($M+Na^+$).

(*S*)-3-Isobutylpentanedioic acid mono-(3-phenylallyl) ester (4b). A mixture of Et_3N (0.1 g, 1 mol%), *trans*-cinnamyl alcohol (14.2 g, 106 mmol), **3** (106 mmol) in toluene (300 mL) was stirred at 25 °C for 5 min. The resulting mixture was then concentrated under reduced pressure to give the racemic monoester ***rac*-4**. A suspension of ***rac*-4** (106 mmol) and (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol (22.7 g, 107 mmol) in EtOH (106 mL) was stirred at reflux for 30 min. The resulting mixture was cooled to room temperature and then filtered. The filter residue was acidified by 2M HCl and the organic phase was extracted by CH_2Cl_2 (3 × 30 mL). The combined organic layers were then washed with H_2O (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the product **4b** (13.98 g, 43%). $[\alpha]_D^{25}$ 0.53 (neat) (lit.[7] $[\alpha]_D^{25}$ 0.53 (neat)).

^{1}H NMR ($CDCl_3$): δ 7.22-7.40 (m, 5H), 6.65 (d, 1H, *J* = 15.8 Hz), 6.27 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.5 Hz), 4.73 (dd, 2H, J_1 = 6.5 Hz, J_2 = 1.2 Hz), 2.38-2.48 (m, 5H), 1.56-1.7 (m, 1H), 1.21-1.27 (m, 2H), 0.87 (d, 6H, *J* = 6.5 Hz). IR (KBr): 2956, 2927, 2871, 1734, 1707, 1168, 966, 745, 692 cm^{-1}. MS (ESI): *m/z* 327.1 ($M+Na^+$).

(*R*)-3-(2-Amino-2-oxoethyl)-5-methylhexanoic acid (5). Mg_3N_2 (22.5 g, 225 mmol) was added into the suspension of **4b** (13.68 g, 45 mmol) in MeOH (200 mL) at 25 °C. After being allowed to warm up to 80 °C for 18 h, the resulting mixture was acidified to pH = 3 with 2M HCl and extracted with EtOAc (3 × 50 mL). After phase separation, the combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from Et_2O to afford **5** (7.94 g, 94%) as a white solid. mp 132.1-132.8 °C (lit.[18] mp 131-135 °C).

^{1}H NMR (DMSO-d_6): δ 6.77 (s, 1H), 6.37 (s, 1H), 1.97-2.21 (m, 5H), 1.57 (m, 1H), 1.07 (t, 2H, *J* = 6.4 Hz), 0.8 (d, 6H, *J* = 6.4 Hz). IR (KBr): 3434.6, 3332.4, 3224.4, 2958.3, 2931.3, 2873.4, 1712.5, 1643.1, 1592.9, 1411.6, 1294, 1236.1, 1207.2, 1168.7, 954.6, 624.8 cm^{-1}. MS (ESI): *m/z* 209.9 ($M+Na^+$).

(*S*)-3-Aminomethyl-5-methylhexanoic acid (1). Bromine (15.3 g, 96.8 mmol) was added dropwise into a solution of **5** (14.96 g, 15 mmol) and 50% NaOH (32.8 g) in H_2O (57 mL) at 5 °C. The reaction mixture was then cooled to 45 °C and quenched into concentrated hydrochloric acid (21 g). The mixture was warm up to 80 °C for 2 h and then cooled to 0 °C. The precipitated crystals were collected and recrystallized from *i*-PrOH/water (1:1) to give pure pregabalin (**1**) (2.01 g, 84%) as colorless crystals, mp 178.1-179.0 °C, $[\alpha]_D^{25}$ +10.2 (*c* 1.0, H_2O) (lit.[5] mp 177-179 °C, $[\alpha]_D^{25}$ +10.1 (*c* 1.0, H_2O)).

^{1}H NMR (D_2O): δ 2.93-3.05 (m, 2H), 2.31-2.36 (m, 1H), 2.14-2.27 (m, 2H), 1.67 (sep, 1H, *J* = 6.8 Hz), 1.23 (t, 2H, *J* = 7.0 Hz), 0.84-0.92 (m, 6H). ^{13}C NMR (D_2O): δ 181.19, 43.75, 40.81, 40.64, 31.72, 24.42, 22.04, 21.56. MS (ESI): *m/z* 181.9 ($M+Na^+$).

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REFERENCES

1. I. Selak, *Curr. Opin. Invest. Drugs*, 2001, **2**, 828.
2. B. A. Lauria-Horner and R. B. Pohl, *Expert Opin. Invest. Drugs*, 2003, **12**, 663.
3. J. H. Jung, D. H. Yoon, P. Kang, W. K. Lee, H. Eum, and H. J. Ha, *Org. Biomol. Chem.*, 2013, **11**, 3635.
4. S. Debarge, P. McDaid, P. O. Neill, J. Frahill, J. W. Wong, D. Carr, A. Burrell, S. Davies, M. Karmilowicz, and J. Steflik, *Org. Process Res. Dev.*, 2014, **18**, 109.
5. M. S. Hoekstra, D. M. Sobieray, M. A. Schwindt, T. A. Mulhern, T. M. Grote, B. K. Huckabee, V. S. Hendrickson, L. C. Franklin, E. J. Granger, and G. L. Karrick, *Org. Process Res. Dev.*, 1997, **1**, 26.
6. M. Ordonez and C. Cativiela, *Tetrahedron: Asymmetry*, 2007, **18**, 3.
7. Z. Hamersak, I. Stipetic, and A. Avdagic, *Tetrahedron: Asymmetry*, 2007, **18**, 1481.
8. T. Ivsic and Z. Hamersak, *Tetrahedron: Asymmetry*, 2009, **20**, 1095.
9. E. P. Sang, E. H. Nam, H. B. Jang, J. S. Oh, S. Some, Y. S. Lee, and C. E. Song, *Adv. Synth. Catal.*, 2010, **352**, 2211.
10. T. Ivsic, J. Novak, N. Doslic, and Z. Hamersak, *Tetrahedron*, 2012, **68**, 8311.
11. H. J. Yang, F. J. Xiong, X. F. Chen, and F. E. Chen, *Eur. J. Org. Chem.*, 2013, **21**, 4495.
12. F. E. Chen, X. H. Ling, Y. X. Lu, X. Y. Zhang, and X. H. Peng, *Chem. J. Chinese U.*, 2001, **22**, 1141.
13. F. Xiong, X. X. Chen, and F. E. Chen, *Tetrahedron: Asymmetry*, 2010, **21**, 665.
14. X. X. Chen, F. Xiong, H. Fu, Z. Q. Liu, and F. E. Chen, *Chem. Pharm. Bull.*, 2011, **59**, 488.
15. F. Xiong, F. J. Xiong, W. X. Chen, H. Q. Jia, and F. E. Chen, *J. Heterocycl. Chem.*, 2013, **50**, 1078.
16. F. Xiong, Z. Y. Shen, X. K. Li, Y. N. Peng, H. Y. Zhu, S. P. Zhang, Y. Y. Song, and J. L. Du, *Org. Prep. Proced. Int.*, 2015, **47**, 242.
17. F. Xiong, J. Li, G. Li, B. Song, Y. X. Zhou, F. E. Chen, and D. Li, *Heterocycles*, 2016, **92**, 544.
18. J. H. Jung, D. H. Yoon, P. Kang, W. K. Lee, H. Eum, and H. J. Ha, *Org. Biomol. Chem.*, 2013, **11**, 3635.