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PII: S0960-894X(20)30309-7
DOI: https://doi.org/10.1016/j.bmcl.2020.127209
Reference: BMCL 127209

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 7 February 2020
Revised Date: 20 April 2020
Accepted Date: 23 April 2020

Please cite this article as: Du, J., Chu, W., Zhang, M., Ma, C., Feng, W., A novel method for preparing Eligulstat through chiral resolution, *Bioorganic & Medicinal Chemistry Letters* (2020), doi: https://doi.org/10.1016/j.bmcl.2020.127209

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A novel method for preparing Eligulstat through chiral resolution

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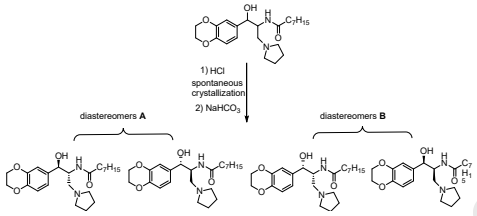

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A novel method for preparing Eligulstat through chiral resolution

Jianxun Du,‡ Weiming Chu,‡ Mengmeng Zhang , Chunying Ma, * and Wenhua Feng*

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Eligustat
Rare disease
Gaucher disease
Chiral resolution

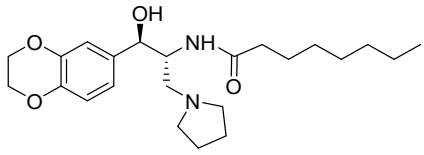
ABSTRACT

Eliglustat is a ceramide glucosyltransferase inhibitor work as first line oral therapy for adults with Gaucher disease type 1 (a rare disease) at present. Although the eliglustat in enantiomerically pure forms is obtained by asymmetric syntheses, the reported methods suffer from many limits when it comes to industrial applications. Therefore, the preparation of a racemic mixture followed by resolution can still be a viable and straightforward alternative, especially when it could be adapted to large scale. Herein, we developed an effective and practical synthetic route to prepare stereoisomers mixture of eliglustat, and a novel chiral resolution method to prepare eliglustat. Using 1,1'-Binaphthyl-2,2'-diyl -hydrogenphosphate (BNDHP) as resolution reagent, optical pure eliglustat (e.e. > 99%, 13.97% total yield) could be obtained after recrystallization.

1. Introduction

Eliglustat, a small-molecule oral glucosylceramide analogue, is approved for first-line use in patients with Gaucher disease type 1, a rare autosomal recessive lysosomal storage disorder in which the lipid glucosylceramide accumulates in Gaucher cells in organs including the spleen, liver and bone marrow caused by enzyme glucosylceramidase deficiency[1](**Figure 1**). Despite the fascinating biological activity, the price of Eliglustat is rather high (more than 300 thousands dollars one year). Herein, more attention has been paid to develop a concise and efficient synthesis of eliglustat.

The stereocontrolled construction of two contiguous stereogenic tertiary carbons is the greatest challenge in the synthesis of Eliglustat. To date, several asymmetric synthetic methods *via* introduction of different chiral sources have been documented. As one of the pioneering works, Genzyme corporation reported a seven-step synthesis route in which (s)-(+)-2-phenylglycinol was employed as a chiral source[2]. Subsequently, Husain and Ganem developed a route toward the key intermediate of eliglustat by utilizing a selective syn-addition of aryl Grignard reagents to the Garner aldehyde[3]. In 2015, another two asymmetric synthesis of eliglustat with high enantioselectivity were reported by Van den Berg[4] and Xu[5], respectively. In 2018, Xie and co-authors achieved the synthesis of eliglustat in six linear steps with 28.4% overall yield by utilizing Crimmins aldol reaction[6]. Recently, the team of Jiancun Zhang and Zhongqing Wang developed an asymmetric synthesis with 56.8% overall yield in nine steps[7]. Although asymmetric syntheses are preferred for obtaining eliglustat in enantiomerically pure forms, these methods encounter with many limits when they are applied in industry, including complicated operations, high cost of chiral reagent, and harsh reaction conditions, such as non-scalable microwave equipment, extremely high or low temperature and the use of heavy-metal catalysts (Cu, Ti, etc). Therefore, the preparation of a racemic mixture followed by resolution can still be a viable and straightforward alternative, especially when it could be adapted to large scale. For example, mass production of bedaquiline, an antituberculosis drug developed by Johnson& Johnson, has been successfully industrialized by utilizing resolution methods[7]. In addition, chiral resolution was also demonstrated to be practical and effective in the preparation of tramadol and ephedrine[8, 9]. However, as well as we known, the synthesis of eliglustat via chiral resolution has never been reported before.



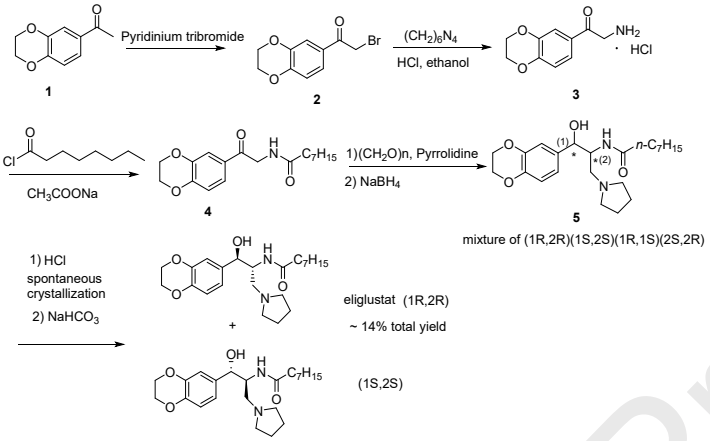
eliglustat

Figure 1. the structure of eliglustat

Herein, we would like to introduce our efforts which developed a new and practical procedure for optical resolution of (±)-eliglustat with chiral (R)-1,1'-binaphthalene-2,2'-diyl hydrogenphosphate as resolution agents. Instead of chromatography, crystallization can be used in the separation and purification of the synthetic intermediates, which makes it possible to operate on a large, commercial scale.

2. R

According to the retrosynthetic analysis, a mixture of eliglustat and its stereoisomers (**5**) can be obtained in four steps (Scheme 1). The synthesis commenced with a commercially available 1,4-benzodioxan-6-yl methyl ketone (**1**) which was subjected to sequentially bromination, amination, and acylation to produce the intermediate **4** with 93% yield. Mannich reaction of **4** with paraformaldehyde and pyrrolidine, and then reduction with $NaBH_4$ led to the formation of mixture **5.** The ratio of diastereosiomers A/B was about 1:1 which was determined by HPLC. However, direct separation of diastereosiomers A from crude **5** via chromatography was found to be a challeng due to the little polarity differences. Further optimization lent an interesting twist that treatment of crude **5** with HCl in water led to the spontaneous crystallization of diastereomer A (Eligustat and its enantiomer) hydrochloride salt which can get nearly 50% total free diastereomer A by further alkalizing with $NaHCO_3$.



Scheme 1. The preparation of rac-eliglustat with four isomers

To get monobrominated 2-bromine-3',4'-(ethylenedioxy)-acetophenone, we firstly used bromine as bromide reagent at room temperature, however it only generated a mixture which contained 57.5% monobrominated, 20% dibrominated and some multibrominated product, monitored by LC-MS. And the mixture can be purified by crystallization in ethyl acetate. Some experiments have been made to promote the yield such as adding different equivalent HOAc and reacting at a lower temperature but they all failed without any meaningful results. Furthermore, we tried different bromination reagents. NBS had a low activity of the bromination with trace product. Pyridinium tribromide showed an almost perfect behavior in this bromination process with 98% yield (**Table 1**).

Table 1.The bromination of 3',4'-(ethylenedioxy)-acetophenone

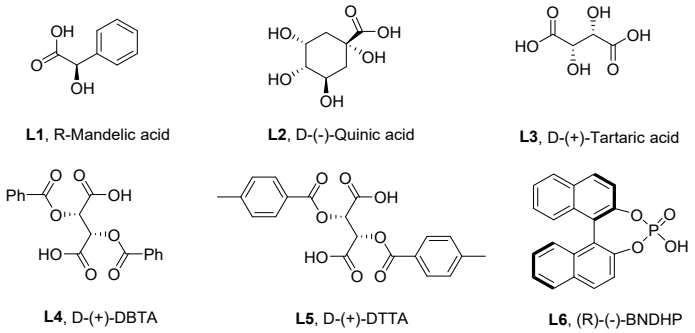
Entry	Reagent[a]	T °C	HOAc	Solvent	Yield %
1	Br_2	25	-	DCM	57.5%
2	Br_2	0	-	DCM	59.1%
3	Br_2	0	0.1 eq	DCM	63.0%
4	Br_2	0	1 eq	DCM	61.2%
5	Br_2	0	-	DCM+HOAc[b]	5.2%
6	NBS	25	-	DCM	1.2%
	NBS	25		Acetonitrile	5%
7	$C_5H_6Br_3N$	25	-	MeOH+DCM[c]	98.1%

[a] The reagent equilvalent is 1.05eq.
[b] HOAc is used to dissolve the sub strate 3',4'-(ethylenedioxy)-acetophenone. DCM is dichloromethane. HOAc is acetic acid
[c] Pyridinium tribromide(C5H6Br3N) can be dissolved well in MeOH(methanol).

, we tried to utilize Gabriel Synthesis with potassium phthalimide transforming **2** to an intermediate. Although this progress was available and effective, unfortunately, it was hard to cleavage the intermediate to get product **3** regardless of the acid condition or base condition and the cleavaged part had a large proportion of racemization. Delepine reaction is another method which is usually used for this reaction. The Delepine reaction between **2** and hexamethylenetetramine made a success with 97% yield and easy separation.

The main byproduct of the synthesis presents to be the byproduct of Mannich reation transforming compound **4** to compound **5** by self-elimination of mannich base and hydroxymethylated elimination of compound **4** (see **Scheme S3,** in the supporting information). Because the Mannich base is hard to separate, we reduct it directly without purification. The byproduct of Mannich reaction can be also reduced by sodium borohydride and it is easy to separate from the main product.

With the successful preparation of diastereomer **A** (*rac*-eliglustat), we further studied the chiral resolution of the desired (1R, 2R) enantiomer eliglustat. Obviously, a suitable chiral resolving reagent is supposed to be crucial to this separation. Classical resolution procedures involving the use of well-known resolving agents such as chiral camphor-10-sulphonic acid, tartaric acid, and mandelic acid have been available for a long time. Rene Imhof *etal* previously described the use of binaphthyl phosphoric acids in the resolution of 7-phenylquinolizidines.[10] In 2002, Periasamy *etal* reviewed many novel methods of resolving racemic diols and amino alcohols.[11] Inspired by these encouraging works, a series of commercially available and commonly methods used acidic resolving agents **L1-L6** (Table 2) were screened for the enantiomer resolution. Firstly, diastereomers A and resolving agents were mixed and dissolved in acetone or ethanol for crystallization (Table 2, entries 1-8). **L1-L2** could not yield any precipitated products both in acetone and ethanol. As for **L3**, no resolution effect was detected. While, upon further optimization, a good enantioselectivity (88.5:11.5 dr) and moderate yield of eliglustat salt was obtained by using bulky **L4** as the resolution regent. To our delight, the yield of product could be increased to 78% with 95.6:4.3 dr when sterically bulkier **L5** was employed. These results indicated that steric hinderance effect may be favorable for the resolution of diastereomers A. Indeed, further optimization with **L6** as resolution regent in acetone showed an excellent resolution effect



(95:5). Upon switching to mixed solvents acetone/dimethyl sulphoxide(2:1), the yield was increased to 65.2%, but a slightly diminished enantioselectivity was obtained (7.6:92.4). Pleasingly, the enantioselectivity and yield could be further improved to 97.7:2.3 and 78.7%, respectively, when ethanol was used as solvent. Changing the amount of **L6** to 0.75 equiv or 1.5 equiv led to lower enantioselectivity and yield both in ethanol or acetone.

Table 2. Resolution of racemic eliglustat with resolving agents[a]

Entry	agent (equiv)	Solvents (mL)	d.r. value of salt [b]	eliglustat salt[c]
1	L1 (1)	acetone (15)	–[e]	–[e]
2	L1 (1)	ethanol (15)	–[e]	–[e]
3	L2 (1)	acetone (15)	–[e]	–[e]
4	L2 (1)	ethanol (15)	–[e]	–[e]
5	L3 (1)	acetone (15)	55:45	–[e]
6	L4(1)	acetone (25)	11.8:88.2	60.1%
7	L5 (1)	acetone (25)	4.3:95.6	70.6%
8	L6 (1)	acetone (15)	5.0:95.0[d]	57.6%
9	L6 (1)	acetone/DMSO (2:1, 15)	7.6:92.4	65.2%
10[d]	L6 (1)	ethanol (15)	2.3:97.7 (0.4:99.6)[f]	78.7% (65%)[f]
11[d]	L6 (0.75)	ethanol (20)	9.3:90.7	70.1%
12	L6 (0.75)	acetone (15)	19.3:80.7	44.5%
13[d]	L6 (1.5)	ethanol (20)	2.7:97.3	50.1%
14	L6 (1.5)	acetone (15)	10.4:89.6	65.5%

[a] The amount of racemic eliglustat is 2.5 mmol.
[b] The ratio is determined by chiral HPLC analysis.
[c] Isolated yield calculated based on theoretical yield.
[d] The reaction was allowed to heat to complete dissolution and cool to room temperature.
[e] No crystallization.
[f] The yield and purity of eliglustat • L6 salt after recrystallization were given in parenthesis.

3. Materials and Methods

Typical experimental procedure for the preparation of key compounds.

2-bromine-3',4'-(ethylenedioxy)-acetophenone (2)

Pyridinium tribromide (63 mmol,20.15 g) in 100 ml MeOH was added dropwise over 30 min to a stirred solution of 3',4'-(ethylenedioxy)-acetophone (60 mmol,10.69 g) in 100 ml dichloromethane.The mixture was reacted at room temperature for about 10 hours.After completion of the reaction ,the solvent is removed in vacuo, the product is dissolved with 100 ml dichloromethane and washed with water for 3 times. After washing with saturated sodium chloride solution, the organic phase is dried by anhydrous sodium sulfate and then be removed in vacuo.The crude product can be purified by crystallization from ethyl acetate(12.77 g, 98%).^{1}H NMR (400 MHz, Chloroform-d) δ 7.52 (d, J = 8.1 Hz, 2H), 6.93(d, J = 8.2 Hz, 1H),4.33 (dd, J = 5.8, 2.6 Hz, 2H), 4.29 (dd , J = 5.6, 2.8 Hz, 2H).^{13}C NMR (126 MHz, Chloroform-d) δ 196.71, 148.05, 143.32 131.20, 122.52, 117.88, 117.23, 64.74, 64.18, 26.42. HRMS (ESI): calcd for $C_{10}H_{12}NO_3$ ([M + H]+) 257.0807, found 257.0842.

2-amino-3',4'-(ethylenedioxy)-acetophenone·HCl (3)

Hexamethylenetetramine(8.41g,60mmol)was added dropwise into the methane solution of 2-bromine-3',4'-(ethylenedioxy)-acetophenone(15.42g, 60mmol). 30 mins later, crystalline adduct was filtered and wished with chlorobenzene. The product was dried and transferred to 500 mL round-bottom flask with 100 mL ethanol, and then, 20 mL concentrated hydrochloric acid was added and the mixture was stirred for 2 hours at 35-40 ℃. After salt was collected by vacuum filtration (12.77 g, 97%). ^{1}H NMR (400 MHz, D_2O) δ 7.57 (dt, J = 8.6, 1.8 Hz, 1H), 7.53 (t, J = 1.7 Hz, 1H), 7.05 (dd, J = 8.5, 1.3 Hz, 1H), 4.65 – 4.60 (m, 2H), 4.43 – 4.38 (m, 2H), 4.36 (dt, J = 5.7, 1.9 Hz, 2H).^{13}C NMR (100 MHz, D_2O) δ 192.10, 149.56, 143.34, 126.81, 122.96, 117.80, 117.39, 65.08, 64.35, 44.85. HRMS (ESI): calcd for $C_{10}H_{12}NO_3$ ([M + H]+) 194.0812, found 194.0804.

N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-oxoethyl)octanamide (4)

Sodium acetate (90 mmol, 50% in water) was added in three portions to a stirred solution of 2-amino-3',4'-(ethylenedioxy)-acetophenone·HCl 7.69 g in tetrahydrofuran (150 mL). Then octanoyl chloride (60 mmol, 9.76 g) was added dropwise over 30min at -5℃. The reaction was allowed to warm to room temperature and stirred for 1 hour. After vacuum filtration, the filtrate was concentrated and purified by recrystallization (DCM:hexane = 1:20) to give 4 10.5 g as a white solids total yielded 98%.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.52 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 4.5 Hz, 1H), 4.68 (d, J = 4.1 Hz, 2H), 4.35 – 4.27 (m, 4H), 2.29 (t, J = 7.7 Hz, 2H), 1.68 (p, J = 7.5 Hz, 2H), 1.31 (ddd, J = 23.8, 8.6, 4.4 Hz, 8H), 0.88 (t, J = 6.6 Hz, 3H).^{13}C NMR (126 MHz, Chloroform-d) δ 192.68, 173.47, 148.94, 143.66, 128.15, 122.10, 117.61, 117.43, 64.75, 64.09, 46.12, 36.60, 31.68, 29.27, 29.01, 25.74, 22.61, 14.06. HRMS (ESI): calcd for $C_{18}H_{26}NO_4$ ([M + H]+) 320.1856, found 320.1842.

Preparation of racemic eliglustat

To a solution of 4 (3.19 g, 10 mmol) in anhydrous ethanol (50 mL) was added paraformaldehyde (0.45 g, 15 mmol), pyrrolidine (1.25 mL, 15 mmol) and concentrated hydrochloric acid (0.5 mL,6 mmol) under nitrogen atmosphere. The mixture was stirred at reflux for 3 hours. After the reaction was completed by TLC monitoring, the reaction mixture was cooled to room temperature and 1.25 mL pyrrolidine (15 mmol) was added. The mixture was stirred for additional 40 min. After that, sodium borohydride (3.78 g, 100 mmol) was added in three portions to the reaction mixture at 0 ℃ and stirred for 5 hours. After the reaction was completed by TLC monitoring, solvent was removed by rotary evaporator. The residue was resolved in 150ml dichloromethane and washed with water (150 mL*2) and adjusted pH to 4.0 with 1M hydrochloric acid. The organic phase was separated and concentrated by rotary evaporator to give crude eliglustat and its isomers.To this crude product was added water (30 mL), ethyl acetate (30 mL) and concentrated hydrochloric (6 mL). After stirring for 40 min, white precipitate were formed and were collected by vacuum filtration to give racemic eliglustat·HCl salts 2.64 g (60% yield).

Characterization of racemic eliglustat·HCl salts : ^{1}H NMR (400 MHz, Chloroform-d) δ 11.17 (s, 1H), 6.90 (d, J = 1.9 Hz, 1H), 6.83 – 6.77 (m, 2H), 5.18 (d, J = 2.9 Hz, 1H), 4.39 (d, J = 7.3 Hz, 1H), 4.23 (s, 4H), 3.83 (d, J = 15.3 Hz, 2H), 3.52 – 3.42

(m, 4H), 2.27 – 1.99 (m, 6H), 1.53 – 1.43 (m, 2H), 1.22 (m, 8H), 0.90 – 0.84 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 174.8, 143.42, 143.02, 133.41, 118.82, 117.17, 114.94, 70.69, 64.32, 55.39, 54.62, 54.45, 52.22, 36.45, 31.65, 29.04, 25.51, 23.25, 22.63, 14.08. HRMS (ESI): calcd for $C_{23}H_{37}N_2O_4$ ([M + H]+) 405.2748, found 405.2729.

The above racemic eliglustat·HCl salts were transferred to a round bottom flask (200 mL) with 150 mL water. Saturated $NaHCO_3$ solution (15 mL) was added dropwise and stirred for 30min during which racemic eliglustat was formed. Vacuum filtration and drying provided 2.56 g racemic eliglustat as white solid.

Characterization of racemic eliglustat : ^{1}H NMR (500 MHz, Chloroform-d) δ 6.87 – 6.75 (m, 3H), 5.84 (d, J = 7.5 Hz, 1H), 4.91 (d, J = 3.1 Hz, 1H), 4.24 (s, 5H), 2.85 – 2.72 (m, 2H), 2.65 (h, J = 7.4, 5.3 Hz, 4H), 2.10 (t, J = 7.6 Hz, 2H), 1.78 (d, J = 6.2 Hz, 4H), 1.52 (t, J = 7.3 Hz, 2H), 1.24 (tt, J = 12.7, 6.5 Hz, 9H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 173.44, 143.44, 142.82, 134.53, 118.93, 117.02, 115.08, 75.48, 64.35, 57.87, 55.21, 52.29, 36.86, 31.66, 29.11, 29.01, 25.67, 23.68, 22.63, 14.08. HRMS (ESI): calcd for $C_{23}H_{37}N_2O_4$ ([M + H]+) 405.2748, found 405.2729.

Resolution of (±)-Eliglustat with (R)-(-)-BNDHP acid in ethanol

Racemic Eliglustat (1.0 g, 2.5 mmol) in ethanol (5 mL) and (R)-(-)-BNDHP (0.87 g, 2.5 mmol) in ethanol (20mL) were mixed in 50 mL round bottom flask. The mixture was heated at 70 ℃ for 20 min to give transparent solution. The solution was allowed to cool to room temperature, and then, the seed of eliglustat·(R)-(-)-BNDHP acid salt was added to promote crystallization. After stirring for about 3 h, the precipitate was collected by filtration and washed with cool ethanol to give 0.73 g eliglustat·(R)-(-)-BNDHP acid salt as white solid (d.r. = 2.3:97.7, 78.7% yield), which was further purified by recrystallization in methanol to give 0.61 g eliglustat·(R)-(-)-BNDHP acid salt (d.r. = 0.4:99.6 %, 65% yield). The white solid was suspended in toluene 20 mL, and 20 mL 10% K_2CO_3 solution was added. The mixture was heated to 80-85 ℃ with stirring for 30 minutes, then, the water phase was removed and another 10 mL 10% K_2CO_3 solution was added to organic phase. After stirring for 15 minutes, the organic layer was separated and washed with water (20 mL). The organic layer was concentrated to give 0.30 g eliglustat as a white solid (60% yield).

Resolution of (±)-Eliglustat with 2,3-Di-O-para-toluoyl-D-tartaric acid in ethanol

Racemic Eliglustat (1.0 g, 2.5 mmol) in ethanol (5 mL) and 2,3-Di-O-para-toluoyl-D-tartaric acid (0.966 g, 2.5 mmol) in ethanol (10 mL) were mixed in 50 mL round bottom flask and stirred at room temperature for 20 min during which precipitate was formed quickly. Filtration and recrystallization of the crude product in methanol provided 0.68 g eliglustat·D-(+)-DDTA (d.r. = 4.3:95.6) salt as white solid in 70.6% yield. The white solid was suspended in 50 mL CH_2Cl_2 and 50 mL saturated K_2CO_3 and another 10 mL 10% K_2CO_3 solution was added to organic phase. The mixture was stirred for 20 min, and then, the organic layer was separated and washed with water (50×2 mL). The organic phase was concentrated and purified by recrystallization (DCM/hexane) to give 0.28 g eliglustat (e.e. = 99.3%, 56%) as a white solid.

4. Conclusions

In summary, we have developed an easy handed and practical synthesis route to access the stereoisomers mixture of eliglustat. Using (R)-(-)-BNDHP as resolution reagent, optical pure eliglustat (e.e. > 99%) was obtained. Notably, instead of chromatography, crystallization could be used in the separation and purification of synthetic intermediates and eliglustat, which make it possible to operate on a large, commercial scale.

‡ These authors contributed equally to this work.

Acknowledgments

Financial support was provided by CAMS Innovation Fund for Medical Sciences (CAMS-2017-I2M-1-011) and the National Natural Science Foundation of China (No. 81903432).

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Supplementary Material

Supplementary data related to this article can be found at****

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Weiming Chu, Jianxun Du, Mengmeng Zhang, Chunyin Ma, Wenhua Feng

Graphical Abstract

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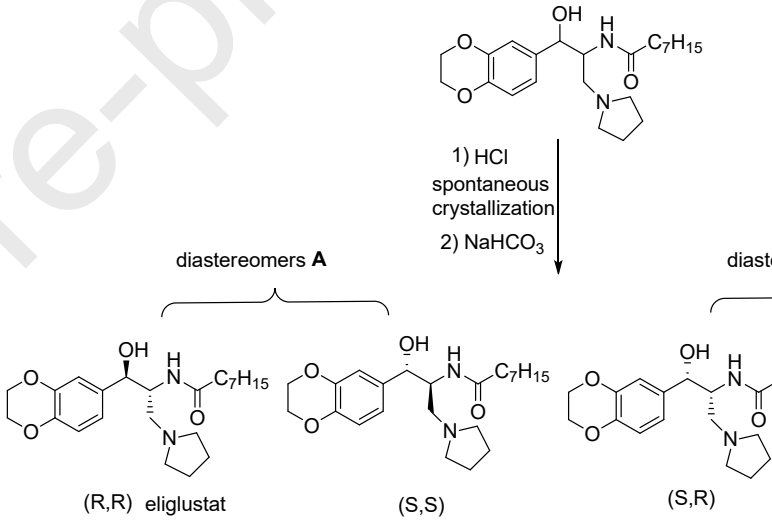

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In the large-scale production, Chiral resolution is still a viable, practical and straightforward alternative method to prepare Eliglustat, a ceramide glucosyltransferase inhibitor work as first line oral therapy for adults with Gaucher disease type 1 (a rare disease) at present. Herein we developed a six-step synthetic route with 22% total yield to produce optical pure eliglustat (e.e. > 99%, 13.97% total yield) with a novel chiral resolution method using 1,1'-Binaphthyl-2,2'-diyl -hydrogenphosphate (BNDHP) as resolution reagent.