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# Synthesis of enantiopure trisubstituted piperidines from a chiral epoxyaziridine and $\alpha$ -amino esters

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## Abstract

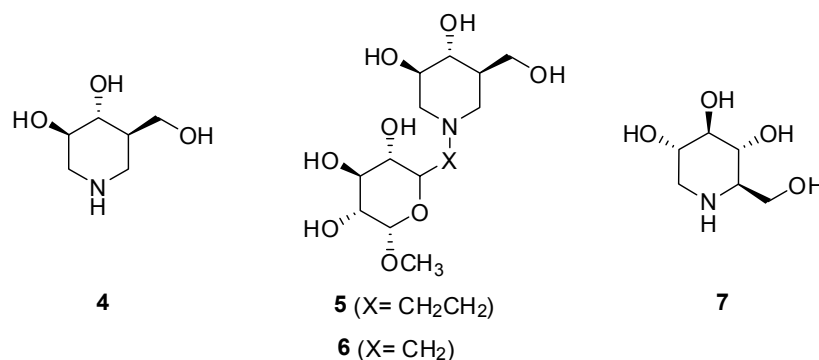
A new method to obtain enantiopure trisubstituted piperidines **1** by reaction of chiral epoxyaziridine **2** with  $\alpha$ -amino esters **3** in the presence of a Lewis acid is reported. This synthesis took place through the successive opening of both oxirane and aziridine rings of **2** by the amino group of the corresponding  $\alpha$ -amino ester **3** with total chemo- and regioselectivity. The time of reaction depended on the  $\alpha$ -amino ester employed. Moreover, lithium and ytterbium salts were tested to catalyze the reaction, obtaining the best results with ytterbium triflate in comparison with lithium perchlorate.

**Keywords:** Enantiopure piperidines,  $\alpha$ -amino esters

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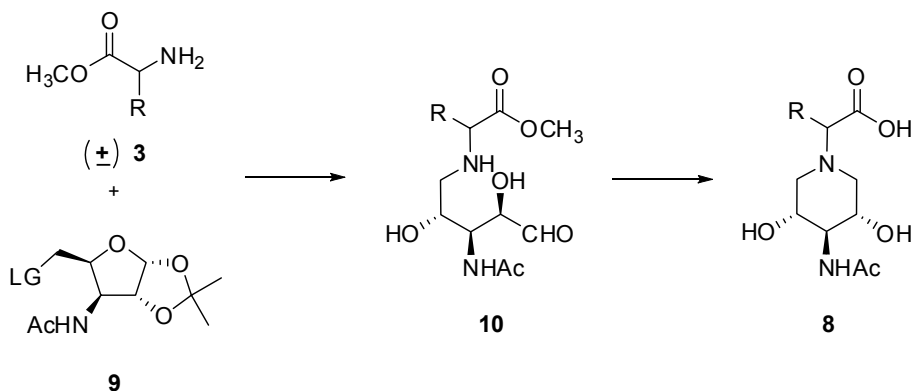
## Introduction

Polyhydroxylated piperidines are organic compounds with interesting therapeutical properties as antibiotics, anticarcinogenics and anticonvulsants,<sup>1</sup> and the participation of these compounds in biosynthesis or its use as reagent in the synthesis of other biological active compounds have been also reported.<sup>2</sup> In addition, during the last few years, a new interesting research area has been developed regarding the study of polyhydroxylated piperidines as enzymatic inhibitors, especially with glycosidases and sialidases or neuraminidases. Thus, isofagomine (**4**) is a potent  $\beta$ -D-glycosidase inhibitor and some of their glycolic derivatives, by example **5** and **6** (Figure 1), shown higher inhibitory activity against glycoamilases, sucrases, maltases, glycomaltases and isomaltases. Other polyhydroxylated piperidine, deoxynojirimycin (**7**), also shows inhibitory activity against  $\alpha$  and  $\beta$ -glycosidases.<sup>3</sup>



**Figure 1.** Polyhydroxylated piperidines as enzymatic inhibitors.

In 1997, Parr and Horestein reported the synthesis of 2-(4-acetylamino-3,5-dihydroxypiperidin-1-yl)-propionic acids **8** from racemic alanine and phenylalanine methyl esters. The former compounds have shown inhibitory activity against sialidase or neuraminidase enzymes.<sup>4</sup> The synthesis of these compounds was performed by the coupling reaction of the xylofuranose derivative **9** (LG: leaving group) with the corresponding racemic  $\alpha$ -amino ester to obtain the  $\delta$ -amino aldehydes **10**, which undergo a reductive cyclization process to obtain, after fourteen steps, the piperidine rings derived from alanine and phenylalanine methyl esters in 8.7% and 7.9% overall yields, respectively (Scheme 1). The inhibitory activity of these compounds was explained by the formation of a zwitterion structure which mimetize an oxocarbenium ion in the transition state for sialidas.<sup>5</sup>



**Scheme 1.** Synthesis of propionic acids **8**.

Diverse methods for the syntheses of hydroxylated piperidines were reported, in some of them a high number of reaction steps were necessary, or the overall yields of these preparations were very low.<sup>6</sup> Based on these antecedents, the development of alternative general methods to obtain enantiopure piperidines in high yields and most direct form would be desirable. In this sense, the ring-opening with further aminocyclization reaction of bis(epoxides) is one of the

most useful methods for the preparation of heterocyclic amines.<sup>7</sup> Recently, we reported the synthesis of trisubstituted enantiopure piperidines through the chemo- and regioselective opening reaction of both epoxide and aziridine heterocycles of the enantiopure epoxyaziridine **2** with primary amines.<sup>8</sup>

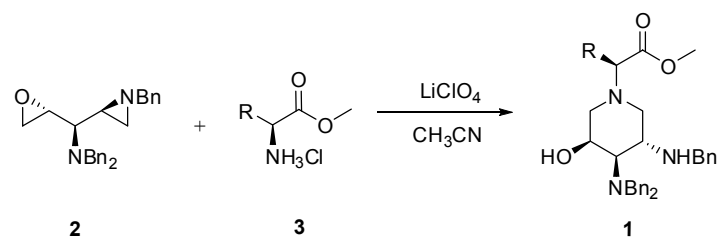
Herein we report the synthesis of enantiopure trisubstituted piperidines **1**, as precursors of biological active compounds, by reaction of the chiral epoxyaziridine **2** with  $\alpha$ -amino esters **3**, derived from natural  $\alpha$ -amino acids. In addition, lithium and ytterbium salts were tested to catalyze this process; the best results were obtained when the opening reaction of **2** was carried out in the presence of ytterbium triflate.

## Results and Discussion

The synthesis of trisubstituted piperidines **1** was achieved using enantiopure methyl esters **3**, derived from the natural  $\alpha$ -amino acids, L-alanine (**a**), L-phenylalanine (**b**), L-leucine (**c**), L-valine (**d**) and L-aspartic acid (**e**). Thus, the reaction of a solution of one equivalent of the epoxyaziridine **2** in acetonitrile with one equivalent of the corresponding methyl  $\alpha$ -amino ester **3** in the presence of one equivalent of lithium perchlorate at room temperature afforded the corresponding piperidines **1**.

The course of the reaction was monitored by high performance liquid chromatography (HPLC) and electrospray ionization mass spectrometry (ESI-MS) detection to establish the reaction time necessary to obtain the total conversion in each synthesis, the crude reaction products were analyzed by HPLC using a MeOH-H<sub>2</sub>O mixture as eluent and 0.8 mL/min flow rate in a reverse phase chromatographic column. Thus, after 72 hours of reaction with the amino ester **3d**, the complete disappearance of the starting epoxyaziridine **2** and formation of two new products at 7.6 min (peak A) and 11.2 min (peak B) retention time with a 30:70 relative abundance ratio, were observed. Both peaks showed correlation with a quasimolecular ion  $[M + H]^+$  of 516 amu. However, the analysis of the crude product of the same reaction obtained after 192 h shown the presence of peak A and peak B in a 9:91 relative abundance ratio (Table 1, entry 4).

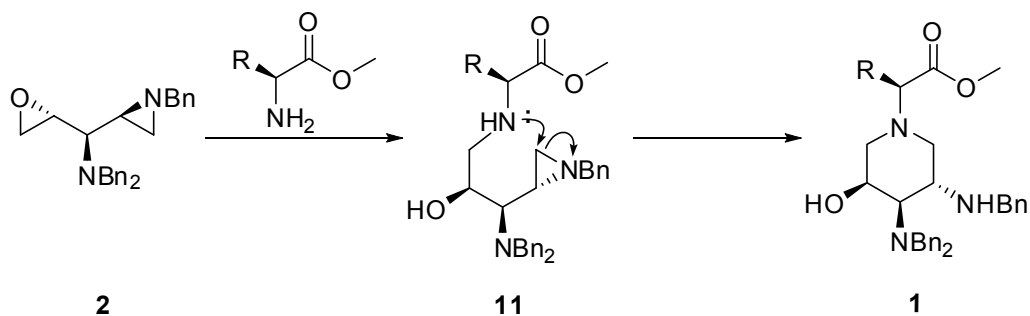
The presence of the two peaks, with the same quasimolecular ion, was an indirect evidence of the formation of the intermediate amino alcohol **11d** (peak A), which has the same molecular weight as piperidine **1d**. This intermediate would undergo the amino cyclization process to give the piperidine **1d** (peak B) in the course of the reaction. For piperidine **1b** (Table 1, entry 2) was found a similar behavior than piperidine **1d**. The formation of piperidine **1a** was achieved at 72 h (Table 1, entry 1), and for piperidines **1c** and **1e** was at 24 h (Table 1, entries 3 and 5). High purity and yields were obtained with all compounds.

**Table 1.** Synthesis of trisubstituted piperidines **1** catalyzed with LiClO<sub>4</sub>

Entry	Product	R	Time(h)	Yield (%) <sup>a</sup>
1	<b>1a</b>	Me	72	93
2	<b>1b</b>	Bn	168	77
3	<b>1c</b>	<i>i</i> -Bu	24	90
4	<b>1d</b>	<i>i</i> -Pr	192	91
5	<b>1e</b>	MeO <sub>2</sub> CCH <sub>2</sub>	24	75

<sup>a</sup>Measured by HPLC on based of the starting epoxyziridine **2**.

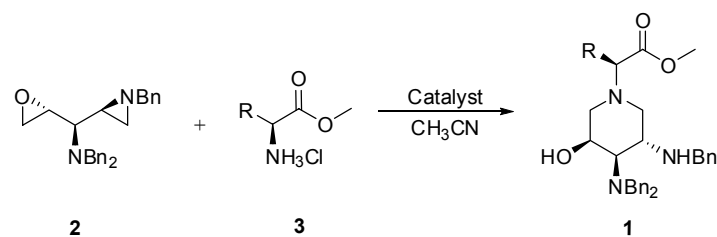
To explain the synthesis of piperidines **1** we propose the mechanism depicted in Scheme 2. After activation of the epoxide with the catalyst, a ring opening at C-2 of the oxirane ring by nucleophilic attack of the amino group of the corresponding  $\alpha$ -amino ester **3**, would afford the intermediate **11**. An alternative ring-opening of the aziridine by  $\alpha$ -amino esters **3** would be ruled out due to no ring activation has been observed in amino aziridines with lithium perchlorate in ring-opening reactions.<sup>9</sup> An intramolecular ring opening at less hindered position of the aziridine ring of intermediate **11** by the nucleophilic attack of the secondary amino group of the starting amino ester would afford the piperidine **1**. This mechanism is also in agreement with the assignment of the stereochemistry of piperidines **1**, based on their NMR data and is supported on the result of the HPLC analysis of the crude products obtained in the synthesis of piperidines **1**.

**Scheme 2.** Proposed mechanism for the synthesis of piperidines **1**.

The epoxide ring opening process occurs during the first 24 h with quantitative conversion of the epoxyaziridine **2** into the amino alcohol **11**. In addition, the detection of only one chromatographic peak, when the intermediate was formed could be a direct evidence of the complete selectivity of the ring-opening reaction.

On the other hand, lithium triflate<sup>10</sup> and ytterbium triflate<sup>11</sup> were tested as catalysts in the reaction between epoxyaziridine **2** and L-valine methyl ester **3d**. The effect of these catalysts in comparison with the use of lithium perchlorate<sup>12</sup> was performed monitoring the course of the reaction with HPLC and ESI-MS detection. The use of ytterbium triflate afforded the best result. Thus, after 96 h of reaction in the presence of ytterbium triflate, conversion of the epoxyaziridine **2** and intermediate **11d** into the piperidine **1d** was complete (Table 2, entry 3). Moreover, only the chromatographic peak for piperidine **1d** was detected during the first hours of the reaction. On the contrary, when the reaction was carried out with lithium perchlorate and lithium triflate, a conversion of 48% and 52% was obtained, respectively (Table 2, entries 1 and 2). These results suggested that ytterbium triflate not only catalyzes the epoxide ring opening reaction, but also catalyzes the aziridine ring opening reaction and consequently the amino cyclization process.<sup>13</sup> Also, when L-aspartate methyl ester **3e** and ytterbium triflate were used to form piperidine **1e** (Table 2, entry 4), the reaction was complete in 96 hours with quantitative yield. Finally, the ytterbium catalyst was used in 10% molar amount to form piperidine **1d** at the same reaction time obtaining 98% yield of the desired product.

**Table 2.** Catalyst effect on the amino cyclization process



Entry	Product	R	Catalyst (equiv) <sup>a</sup>	Time(h)	Yield (%) <sup>b</sup>
1	<b>1d</b>	<i>i</i> -Pr	LiClO <sub>4</sub> (1.0)	96	48
2	<b>1d</b>	<i>i</i> -Pr	LiOTf (1.0)	96	52
3	<b>1d</b>	<i>i</i> -Pr	Yb(OTf) <sub>3</sub> (1.0)	96	100
4	<b>1e</b>	MeO <sub>2</sub> CCH <sub>2</sub>	Yb(OTf) <sub>3</sub> (1.0)	96	100
5	<b>1d</b>	<i>i</i> -Pr	Yb(OTf) <sub>3</sub> (0.1)	96	98

<sup>a</sup>Molar equivalents of catalyst. <sup>b</sup>Measured by HPLC on based of the starting epoxyaziridine **2**.

The structure and absolute configuration of piperidines **1** were established by  $^1\text{H}$  NMR coupling constants analysis, COSY and NOESY experiments. In COSY experiments of piperidine **1d**, the C3-H hydrogen (4.17 ppm) presented coupling constants with hydrogen C4-H (3.19 ppm) and hydrogen C2 $_{\alpha}$ -H (2.57 ppm) of  $J = 9.4, 3.0$  Hz, respectively. In addition, strong correlations were observed between geminal hydrogens of methylenes C-2 and C-6 in COSY and NOESY experiments. This correlation is observed in six-member cyclic molecules, due to a conformational equilibrium which produces an exchange of the environment of methylene protons.<sup>14</sup> Therefore, and since the original asymmetric center in epoxyaziridine **2** (C-4 in **1**) had an *R* absolute configuration and had not been involved in any process, the absolute configuration of **1** was established as 2*S*, 3'*S*, 4'*R*, 5'*S*.

## Conclusions

In summary, we have developed a new attractive methodology for the synthesis of enantiopure trisubstituted piperidines, which are precursors of potential biological active compounds. Enantiopure trisubstituted piperidines **1** were prepared by the sequential opening reactions of the epoxide and aziridine rings of epoxyaziridine **2** by the amino group of chiral  $\alpha$ -amino esters. The reactions shown complete chemo- and regioselectivity. The reaction times were different depending on the starting  $\alpha$ -amino ester. Moreover, the comparative study about the use of lithium triflate or ytterbium triflate as catalysts respect to those results obtained with  $\text{LiClO}_4$  was performed. Ytterbium catalyst activates both epoxide and aziridine ring opening processes and the corresponding piperidines were obtained in quantitative yields in shorter reaction time even when it was used in catalytic amount.

## Experimental Section

**General Procedures.** All reagents were purchased in the higher quality available and were used without further purification. The solvents used in column chromatography were obtained from commercial suppliers and used without further distillation. Infrared spectra (FTIR) were recorded on a Perkin Elmer FT-IR 1600 spectrophotometer. Nuclear magnetic resonance  $^1\text{H}$  (at 200 MHz) and  $^{13}\text{C}$  (at 50 MHz) spectra were recorded on a Varian Mercury 200 MHz Spectrometer in  $\text{CDCl}_3$  with TMS as internal standard. Liquid chromatograms were obtained on an Agilent 1100 Series LC with a reverse phase ZORBAX  $\text{s}\beta\text{-C18}$  column (5 mm, 3 x 150 mm) and MSD Trap. Electrospray ionization mass spectra (ESI-MS) were obtained with an ion trap, and the intensities are reported as a percentage relative to the base peak after the corresponding  $m/z$  value. HR-MS were obtained in an Agilent LCTOF (2006), a high resolution TOF analyzer with Windows XP based OS and APCI/ESI ionization. Melting points were obtained on an Electrothermal 88629

apparatus and are uncorrected. Optical rotations were determined using an Autopol III polarimeter.

### General procedure for the synthesis of trisubstituted piperidines 1

The epoxyaziridine **2**<sup>8</sup> (0.30 g, 0.78 mmol), NaHCO<sub>3</sub> (3.9 mmol) and the catalyst (0.78 mmol) were dissolved in 20 mL of anhydrous acetonitrile. Then, the corresponding  $\alpha$ -amino ester **3** (0.78 mmol) was added to the solution under argon atmosphere. The reaction mixture was stirred at room temperature until the reaction was completed. Water was added (30 mL) to the mixture and then was extracted with dichloromethane (3 x 20 mL), the organic phase was recovered and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated to give an amber liquid pure product.

#### Methyl 2S-(3S-benzylamino-4R-dibenzylamino-5S-hydroxypiperidin-1-yl) propionate (**1a**).

Colorless oil. Yield 93%. *R<sub>f</sub>* 0.3 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 97/3); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -5.6 (*c* 0.39, MeOH). FTIR (NaCl): 3316 (br), 3026 (m), 2917 (m), 2810 (m), 1736 (vs), 1452 (s), 1204 (m) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  7.25 (m, 15H), 4.19 (br s, 1H), 3.87-3.47 (m, 9H), 3.71 (s, 3H), 3.18 (br s, 1H), 3.17 (br s, 1H), 3.05 (d, *J* = 9.8 Hz, 1H), 2.88 (d, *J* = 12.4 Hz, 1H), 2.62 (dd, *J* = 9.8, 3.2 Hz, 1H), 2.09 (d, *J* = 12.4 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz):  $\delta$  175.1 (s), 138.9 (s), 137.3 (2 x s), 129.1 (4 x d), 128.4 (2 x d), 128.0 (2 x d), 127.9 (4 x d), 127.0 (d), 126.5 (2 x d), 70.2 (d), 64.7 (d), 63.8 (d), 60.6 (t), 59.8 (t), 57.3 (d), 53.4 (2 x t), 51.7 (q), 45.5 (t), 18.4 (q). HPLC: *t<sub>R</sub>* 7.4 min, 0.8 mL/min; 80:20 MeOH/H<sub>2</sub>O. ESIMS *m/z*: 488 [M+H]<sup>+</sup>; MS/MS *m/z* (rel. int.): 385(100), 294(10), 222(20). HRMS calculated for [C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>3</sub>+H]<sup>+</sup>: 488.2913. Found: 488.2907.

#### Methyl 2S-(3S-benzylamino-4R-dibenzylamino-5S-hydroxypiperidin-1-yl)-3-phenylpropionate (**1b**).

Colorless oil. Yield 77%. *R<sub>f</sub>* 0.38 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 97/3); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -11.9 (*c* 0.71, MeOH). FTIR(NaCl): 3168 (br), 3026 (m), 2922 (m), 2813 (m), 1737 (vs), 1452 (m), 1200 (s) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  7.26 (m, 20H), 4.23 (br s, 1H), 3.86-3.46 (m, 9H), 3.64 (s, 3H), 3.16 (br s, 1H), 3.15 (br s, 1H), 3.09 (d, *J* = 6.2 Hz, 2H), 3.07 (d, *J* = 9.8 Hz, 1H), 2.89 (d, *J* = 12.8 Hz, 1H), 2.63 (dd, *J* = 9.8, 3.2 Hz, 1H), 2.00 (d, *J* = 12.8 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz):  $\delta$  173.6 (s), 138.8 (s), 137.2 (2 x s), 136.4 (s), 129.1 (6 x d), 128.4 (2 x d), 128.2 (2 x d), 128.0 (2 x d), 127.8 (4 x d), 126.7 (d), 126.6 (d), 126.5 (2 x d), 70.4 (d), 64.7 (d), 63.7 (d), 63.6 (d), 60.7 (t), 59.8 (t), 53.4 (2 x t), 51.5 (q), 46.1 (t), 39.0 (t). HPLC: *t<sub>R</sub>* 13.4 min, 0.8 mL/min, 80:20 MeOH/H<sub>2</sub>O. ESIMS *m/z*: 564 [M+H]<sup>+</sup>; MS/MS *m/z* (rel. int.): 385(100), 367(10), 294(15), 222(20). HRMS calculated for [C<sub>36</sub>H<sub>41</sub>N<sub>3</sub>O<sub>3</sub>+H]<sup>+</sup>: 564.3226. Found: 564.3214.

#### Methyl 2S-(3S-benzylamino-4R-dibenzylamino-5S-hydroxypiperidin-1-yl)-4-methylpentanoate (**1c**).

Colorless oil. Yield 90%. *R<sub>f</sub>* 0.43 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 97/3); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -4.5 (*c* 1.86, MeOH). FTIR(NaCl): 3290 (br), 3050 (m), 2950 (m), 1736 (vs), 1452 (m) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  7.25 (m, 15H), 4.18 (br s, 1H), 3.90-3.51 (m, 8H), 3.70 (s, 3H), 3.45 (t, *J* = 6.8 Hz, 1H), 3.19 (br s, 2H), 3.04 (d, *J* = 9.6 Hz, 1H), 2.95 (d, *J* = 12.4 Hz, 1H), 2.60 (dd, *J* = 9.6, 3.2 Hz, 1H), 2.09 (d, *J* = 12.4 Hz, 1H), 1.76 (sxt, *J* = 6.6 Hz, 1H), 1.60 (m, 2H), 1.37 (d, *J* = 7.0 Hz, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz):  $\delta$  175.1 (s), 138.9 (s), 137.3 (2 x s), 129.1 (4 x d), 128.4 (2 x d), 128.0 (2 x d), 127.8 (4 x d), 126.7 (d), 126.5 (2 x d), 70.4 (d), 65.1 (d), 63.9 (d),



61.0 (d), 60.3 (t), 59.6 (t), 53.7 (2 × t), 51.5 (q), 46.4 (t), 42.2 (t), 24.9 (d), 22.6 (q), 22.4 (q). HPLC:  $t_R$  14.1 min, 0.8 mL/min, 80:20 MeOH/H<sub>2</sub>O. ESIMS  $m/z$ : 530 [M+H]<sup>+</sup>; MS/MS  $m/z$  (rel. int.): 385(100), 294(20), 222(20). HRMS calculated for [C<sub>33</sub>H<sub>43</sub>N<sub>3</sub>O<sub>3</sub>+H]<sup>+</sup>: 530.3383. Found: 530.3374.

**Methyl 2S-(3S-benzylamino-4R-dibenzylamino-5S-hydroxypiperidin-1-yl)-3-methylbutyrate (1d).** Colorless oil. Yield 91% (cat. LiClO<sub>4</sub>), 100% (cat. Yb(tfc)<sub>3</sub>).  $R_f$  0.45 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 97/3);  $[\alpha]_D^{20} = -4.4$  ( $c$  0.90, MeOH). FTIR(NaCl): 3290 (br), 3177 (m), 3027 (m), 2955 (m), 1734 (vs), 1452 (m), 1197 (s) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  7.27 (m, 15H), 4.17 (br s, 1H), 3.88 (d,  $J = 12.6$  Hz, 1H), 3.87 (d,  $J = 14.8$  Hz, 2H), 3.71 (d,  $J = 12.6$ , 1H), 3.70 (s, 3H), 3.70 (d,  $J = 14.8$  Hz, 2H), 3.19 (br s, 3H), 3.14 (d,  $J = 5.4$  Hz, 1H), 3.04 (d,  $J = 9.4$  Hz, 1H), 3.00 (d,  $J = 12.8$  Hz, 1H), 2.57 (dd,  $J = 9.4, 3.0$  Hz, 1H), 2.10 (d,  $J = 12.8$  Hz, 1H), 2.06 (m, 2H), 1.06 (d,  $J = 3.5$  Hz, 3H), 1.02 (d,  $J = 3.5$  Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz):  $\delta$  174.1 (s), 139.1 (s), 137.2 (2 × s), 129.2 (4 × d), 128.2 (2 × d), 128.1 (2 × d), 127.8 (4 × d), 126.7 (d), 126.5 (2 × d), 70.4 (d) 68.9 (d), 65.1 (d), 64.0 (d), 60.1 (t), 59.4 (t), 53.6 (2 × t), 51.3 (q), 47.8 (t), 31.3 (d), 19.1 (q) 18.9 (q). HPLC:  $t_R$  11.2 min, 0.8 mL/min, 80:20 MeOH/H<sub>2</sub>O. ESIMS  $m/z$ : 516 [M+H]<sup>+</sup>; MS/MS  $m/z$  (rel. int.): 385(100), 294(15), 264(10), 222(20). HRMS calculated for [C<sub>32</sub>H<sub>41</sub>N<sub>3</sub>O<sub>3</sub>+H]<sup>+</sup>: 516.3226. Found: 516.3214.

**Dimethyl 2-(3-Benzylamino-4-dibenzylamino-5-hydroxypiperidin-1-yl)succinate (1e).** Colorless oil. Yield 75% (cat. LiClO<sub>4</sub>), 100% (cat. Yb(tfc)<sub>3</sub>).  $R_f$  0.38 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 97/3);  $[\alpha]_D^{20} = -5.8$  ( $c$  1.10, MeOH). FTIR (NaCl): 3290 (br), 3177 (m), 3027 (m), 2955 (m), 1734 (vs), 1452 (m), 1197 (s) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  7.27 (m, 15H), 4.18 (br s, 1H), 3.91-3.66 (m, 6H), 3.73 (s, 3H), 3.70 (s, 3H), 3.44 (s, 2H), 3.19 (br s, 1H), 3.18 (br s, 1H), 3.06 (d,  $J = 9.8$  Hz, 1H), 2.93 (br s, 1H), 2.90 (d,  $J = 12.8$  Hz, 1H), 2.87 (br s, 1H), 2.84 (dd,  $J = 6.2, 2.6$  Hz, 1H), 2.63 (dd,  $J = 9.8, 3.2$  Hz, 1H), 2.16 (dd,  $J = 12.8, 3.0$  Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz):  $\delta$  172.8 (s), 170.9 (s), 138.9 (s), 137.2 (2 × s), 129.1 (4 × d), 128.4 (2 × d), 128.0 (2 × d), 127.8 (4 × d), 126.8 (d), 126.6 (2 × d), 70.3 (d), 64.7 (d), 63.7 (d), 60.7 (t), 59.9 (t), 58.2 (d), 53.5 (2 × t), 52.1 (q), 51.8 (q), 45.6 (t), 36.5 (t). HPLC:  $t_R$  5.8 min, 0.8 mL/min, 80:20 MeOH/H<sub>2</sub>O. ESIMS  $m/z$ : 546 [M+H]<sup>+</sup>; MS/MS  $m/z$  (rel. int.): 385(100), 294(15), 264(10), 222(20). HRMS calculated for [C<sub>32</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>+H]<sup>+</sup>: 546.2968. Found: 546.2967.

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