

## Efficient synthesis of (-)-clausenamide

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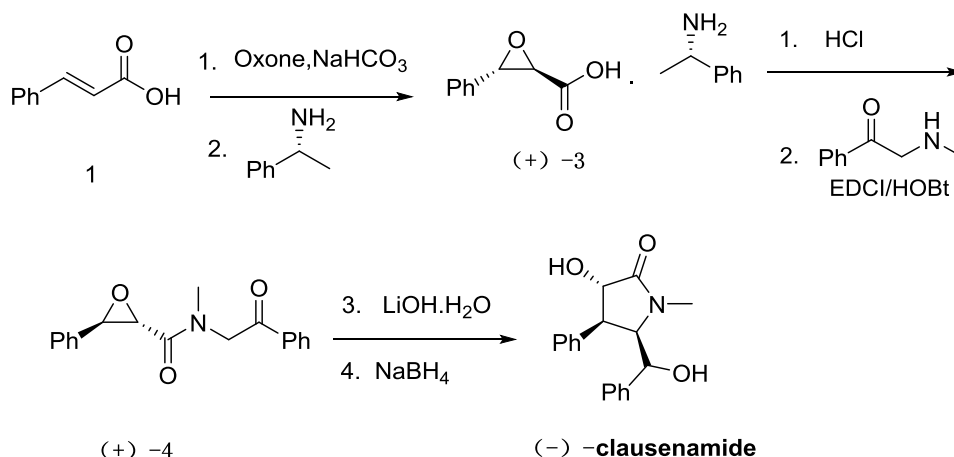
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### Abstract

A new method for the synthesis of (-)-clausenamide was reported. (-)-Clausenamide was synthesized starting from the inexpensive trans-cinnamic acid. The synthesis was carried out over five steps, and the overall yields were 8.9% (99.9% ee). Compared with the multi-step asymmetric synthesis methods reported in the literature, the raw materials used in this method are inexpensive. The overall method is easy to carry out. Furthermore, the reaction takes place under very mild reaction conditions (25 °C). Anhydrous and very low temperature (-78 °C) conditions can be avoided. The column chromatography technique need not be conducted after each reaction step. Hence, this is a suitable method to carry out the large-scale synthesis of (-)-clausenamide. The structures were confirmed using the <sup>1</sup>H NMR, <sup>13</sup>C NMR, and MS techniques.

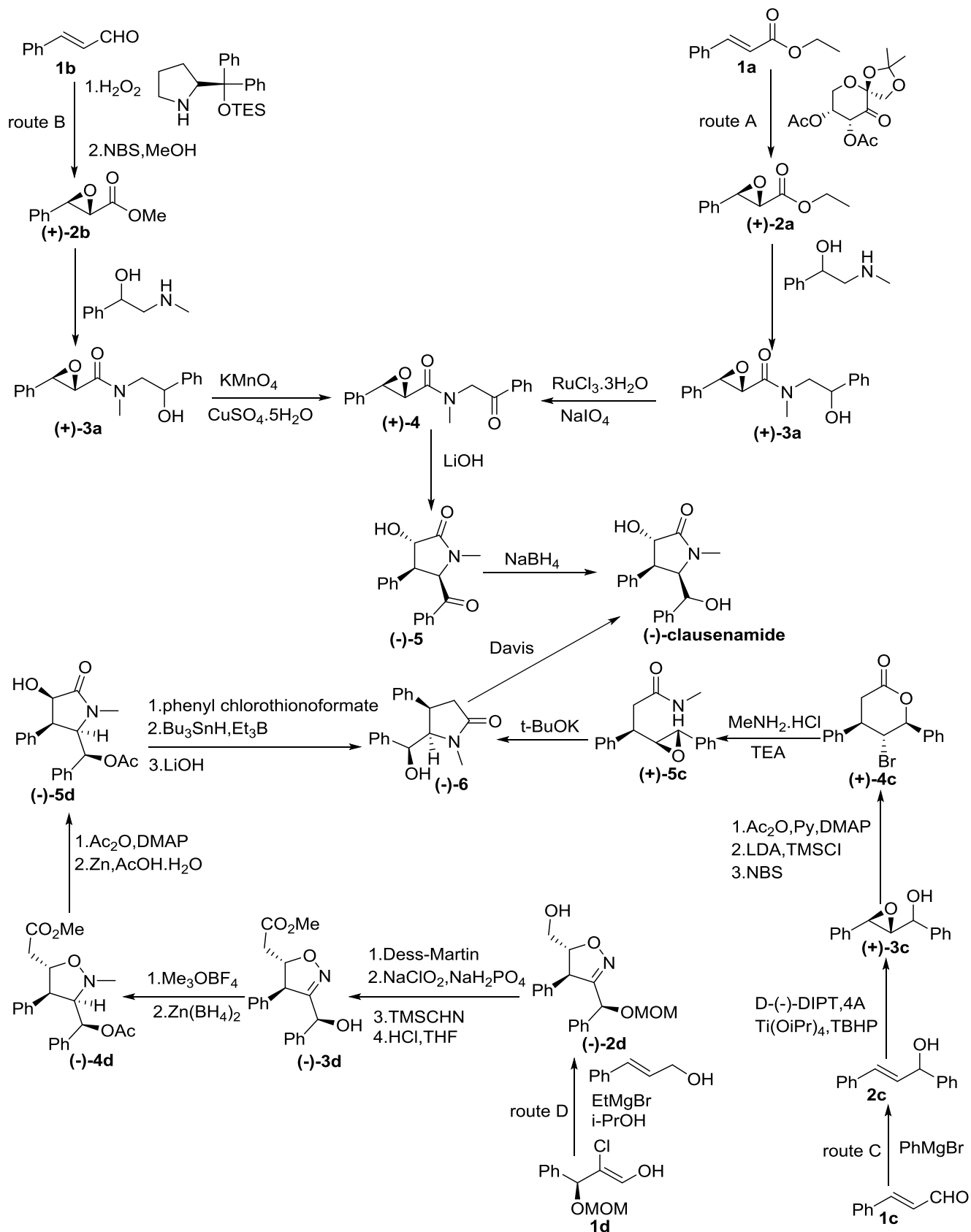


**Keywords:** (-)-Clausenamidone, (-)-clausenamide, chemical resolution, synthesis

## Introduction

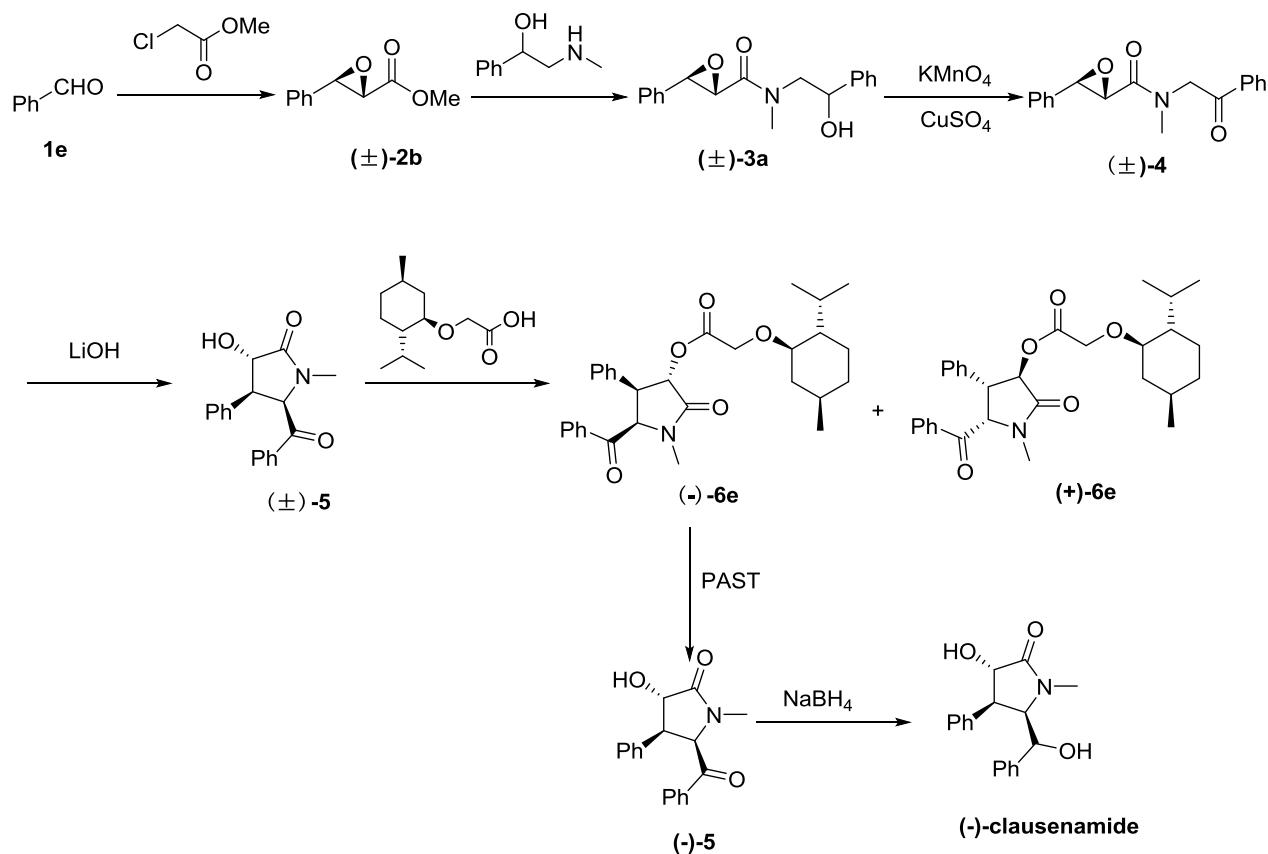
Racemic clausenamide is a pyrrolidone-derived natural product first isolated from the aqueous extract of the leaves of clausenalanisium.<sup>1</sup> This compound exhibited the properties of nootropic and anti-acute cerebral ischemia in biological tests.<sup>2</sup> However, it has been reported that (-)-clausenamide was the primary nootropic active ingredient, which possessed significant biological activities.<sup>3–6</sup> (-)-Clausenamide could significantly inhibit neurotoxicity induced by okadaic acid and abeta25–35,<sup>7</sup> enhance the synaptic transmission in the dentate gyrus, protect the cerebrum in hypoxia and ischemia damage.<sup>8–10</sup> Therefore, (-)-clausenamide is considered a promising drug candidate for treating Alzheimer's disease and other neurodegenerative disorders.

In the literature, two methods have been reported for the synthesis of (-)-clausenamide: asymmetric synthesis and resolution intermediate synthesis. To the best of our knowledge, the resolution of the starting material to synthesize (-)-clausenamide has not yet been reported. Two pathways can be followed to access (-)-clausenamide, following the asymmetric synthesis methods. One method involves the synthesis of the key intermediate amide (+)-**4**, followed by the cyclization of (+)-**4** to afford (-)-clausenamidone (-)-**5** in the presence of LiOH. The process also involves the reduction of (-)-**5** with sodium borohydride to obtain the target product. Shi Yi'an<sup>11</sup> reported the synthesis of (-)-clausenamide using trans cinnamate (**1a**) as the starting material. The synthesis could be conducted over five steps. The overall yield was 18.9% (99% ee; Scheme 1, route A). The disadvantage of this method was that the raw materials and chiral catalyst fructose derivatives need to be prepared by themselves. The yield of the chiral catalyst fructose derivatives was low, and its cost was high. In addition, ruthenium trichloride trihydrate sodium periodate was used during oxidation. The reaction mixture was filtered using diatomaceous earth prior to conducting the oxidation step. This resulted in the poor yields of the products. Xuan Yi-ning used cinnamaldehyde (**1b**) (Scheme 1, route B)<sup>12</sup> as the starting material during the synthesis of (-)-clausenamide. The yield of the product was 6.2% over six steps (99% ee). However, the esterification product and the intermediate epoxy cinnamaldehyde required needed to be separated by column chromatography. The yield of the product obtained after the first step was low. The chiral catalyst prolinol silyl ether derivative was unstable and needed to be prepared each time freshly. In addition, potassium permanganate-copper sulfate pentahydrate was used for oxidation. A viscous manganese dioxide was produced during the reaction, which was difficult to filter. This makes the large-scale synthesis of (-)-clausenamide difficult. (-)-Clausenamide can also be synthesized starting from (-)-3-deshydroxyxanthoenamide (-)-**6** as the common intermediate. The subsequent steps involve the treatment with Davis reagent to obtain (-)-clausenamide under alkaline conditions. Liu Di and workers synthesized (-)-clausenamide starting from cinnamic aldehyde (**1d**) (Scheme 1, route C).<sup>13</sup> The overall yield of the eight-step synthesis of (-)-clausenamide was 11.5% (99% ee). This method is limited by the Sharpless asymmetric epoxidation of (**2c**), which needs harsh conditions (anhydrous environment and long-term low temperature). The column chromatography technique must be used to purify the compounds obtained at each step of the multi-step reactions. The Davis oxidant was used in the last step, making this process costly and unsuitable for the large-scale preparation of (-)-clausenamide. Tanda reported the synthesis of (-)-3-deshydroxyxanthoenamide (-)-**6** starting from phenylpropanhydroxime chloride **1d**. (-)-**6** was synthesized in 6.5% yield over twelve steps (99% ee).<sup>14</sup> The synthesis of the starting material **1d** was completed over multiple steps. Furthermore, this material is unstable and can only be stored at room temperature for a few days. At the same time, the reaction of (-)-**3d** with zinc borohydride could be conducted under low reaction temperature (-78 °C).



Scheme 1. Asymmetric Synthesis of (-)-clausenamide.

(-)-Clausenamide can also be prepared following a second pathway: the intermediate ( $\pm$ )-clausenamidone (**( $\pm$ )-5**) (Scheme 2) was resolved using menthol oxyacetic acid to obtain menthoxyacetyclausenamidone (-)-**6e**. This compound was subjected to hydrolysis to furnish (-)-**5**, which was reduced with  $\text{NaBH}_4$  to give (-)-clausenamide in 11.5% yield (98% ee).<sup>15</sup> As the diastereoisomeric products (-)-**6e** and (+)-**6e** need to be separated by column chromatography, and the enantiomer (+)-clausenamidone is not used for further reactions; the process does not conform to the concept of atom economy. Furthermore, the preparation of the resolving agent (-)-menthyloxyacetic acid requires the use of a large amount of sodium metal (solvent: toluene). The reaction mixture is refluxed for 60–70 h. Hence, the reaction conditions are not suitable for large-scale synthesis.

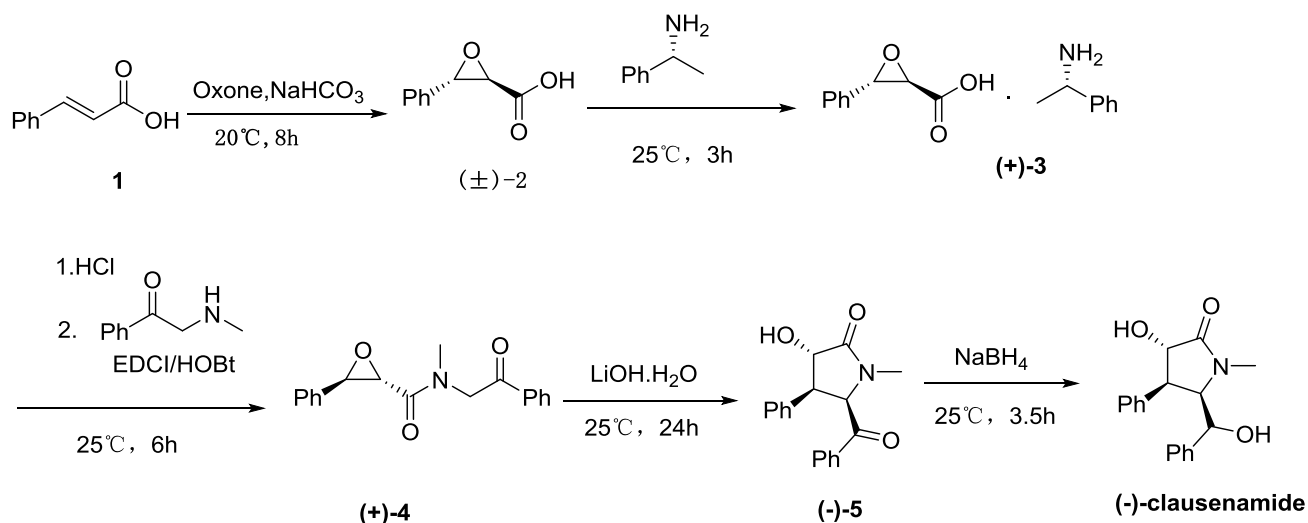


**Scheme 2.** Chiral resolution of ( $\pm$ )-clausenamidone.

## Results and Discussion

We designed a cost-effective method to synthesize the starting material, trans-cinnamic acid (**1**) (Scheme 3). First, trans-cinnamic acid (**1**) was treated with potassium persulfate to obtain the racemic epoxy cinnamic acid ( $\pm$ )-**2**. Following this, the resolution of ( $\pm$ )-**2** was achieved using (R)-(+)- $\alpha$ -methylbenzylamine. (2S,3R)-epoxycinnamic acid(R)- $\alpha$ -methylbenzylamine salt (+)-**3** was obtained. The latter was treated with HCl (1M) in dichloromethane to give (+)-**2**, which was directly used in the next step without further purification. This compound was converted to the amide (+)-**4** using 2-methylamino-1-phenyl-ethanol. Subsequent treatment with  $\text{LiOH}$  afforded lactam (-)-**5**. Finally, the reduction of (-)-**5** with  $\text{NaBH}_4$  furnished (-)-clausenamide in 8.9% yield over five steps (99.9% ee). Compared with the synthetic methods reported in the literature, the

operational steps followed in the described procedure are simpler. Moreover, the reaction takes place under mild reaction conditions (25 °C). Anhydrous reaction conditions and very low-temperature temperature (-78 °C) can be avoided. The products obtained after each step need not be separated using the column chromatography technique. The reaction products obtained at each step can be purified by the process of recrystallization. The raw materials and solvents used in the reaction are cost-effective. The use of expensive chiral catalysts can be avoided. The solvent used is relatively safe (third-type organic solvent) and can be efficiently used in large-scale synthesis processes.



**Scheme 3.** Synthesis of (-)-clausenamide.

## Conclusions

In this work, a new method has been reported for the synthesis of (-)-clausenamide. The target compound can be synthesized over five steps starting from the cheap starting material (trans-cinnamic acid). First, trans-cinnamic acid was oxidized using potassium persulfate to yield the racemic epoxy cinnamic acid **2**. This was followed by the process of resolution in the presence of (R)-(+)-α-methylbenzylamine. (+)-(2S,3R)-epoxycinnamic acid-(R)-α-methylbenzylamine salt (**3**) was obtained.

Following this, **3** was converted to the amide **4** using 2-methylamino-1-phenyl-1-ethanone. Base-catalyzed cyclization of **4** furnished lactam **5**. Finally, reduction of **5** with sodium borohydride yielded (-)-clausenamide in 8.9% yield (99.9% ee). The advantage of this approach is that cheap raw materials can be used, and the reaction takes place under moderate reaction conditions (anhydrous reaction conditions and ultra-low reaction temperatures can be avoided). All reactions were carried out at room temperature, and the products were purified using the process of recrystallization. This method is suitable to carry out the large-scale synthesis of natural products.

## Experimental Section

**General.** The melting points of the compounds were determined using laboratory devices (apparatus: X-5 melting point). Optical rotation was determined using the P8000 automatic polarimeter.  $^1\text{H}$ NMR and  $^{13}\text{C}$ NMR spectra were recorded on a 500 MHz/300MHz spectrometer (AVANCE) with trimethylsilane (TMS) as the internal standard. Chemical shifts expressed in ( $\delta$ ) are given in ppm, whereas J-values for  $^1\text{H}$ – $^1\text{H}$  coupling constants are represented in Hertz (Hz). The apparent multiplicity has been reported (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad). High-resolution mass spectra (HRMS) were recorded (in positive/or negative ion mode) using the electron spray ion trap (ESI) technique on a 6210ESI/TOF instrument. Enantiomeric excess (ee) was determined by Agilent 1200 high-performance liquid chromatography (HPLC) system using AD-H, OJ-H Chiral columns. Unless otherwise indicated, all reagents and solvents were purchased from commercial sources and were used without further purification.

**Racemic epoxy cinnamic acid( $\pm$ )-2.** To a stirred solution of trans-cinnamic acid (148.20 g, 1 mol) in acetone (650 mL),  $\text{NaHCO}_3$  (380.0 g, 4.5 mol) was slowly added till the reagents dissolved in the solvent at room temperature. Subsequently, an aqueous solution of EDTA-2Na (650 mL,  $4 \times 10^{-4}$  mol/L) was added at 0 °C. This was followed by the addition of an aqueous solution containing potassium hydrogen persulfate (620.0 g, 2 mol) and EDTA-2Na (1250 mL,  $4 \times 10^{-4}$  mol/L) at <20 °C. The addition was completed over one hour. The solution was stirred at room temperature for 8 h. The thin layer chromatography (TLC) technique was used (Petroleum ether: Ethyl acetate = 3:1) to monitor the progress of the reaction. The reaction was allowed to proceed until signals corresponding to the starting materials stopped appearing on the TLC plates. The reaction solution was filtered to remove insoluble salts, and the filtrate was dissolved in ethyl acetate (1.0 L). The mixture was stirred in an ice bath. The solution was acidified to a pH in the range of 2–3 at 0 °C using HCl. The organic layers were separated and collected. The aqueous solution was extracted with ethyl acetate (3  $\times$  500 mL). The pooled organics were washed with distilled water (1 L) and saturated brine (1 L). It was dried using  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated in vacuo to a volume of 750 mL (< 40 °C).

**(2S,3R)-epoxycinnamate-(R)- $\alpha$ -methylbenzylamine salt (+)-3.** (R)-(+)- $\alpha$ -methylbenzylamine (121.18 g, 1.0 mol) was added to a solution of ( $\pm$ )-2 (750 mL). The solution was stirred vigorously at room temperature. A large amount of white solid was produced in the reaction solution. The amount of precipitate did not increase significantly after 3 h. The white solid that formed was collected by filtration and dried in vacuo to yield (2S,3R)-epoxycinnamate-(R)- $\alpha$ -methylbenzylamine salt (+)-3 as a white solid (116.91 g). Recrystallization with absolute ethanol gave (+)-3 as white crystals (104.08 g) in 36.5% yield<sup>16</sup>. mp:159.3–160.5 °C,  $[\alpha]_D^{20} +126.7$  (c1, EtOH) [lit:<sup>16</sup>  $[\alpha]_D^{24} +113$ (c0.5, EtOH)];  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.53–7.50 (d, J 9 Hz, 2H), 7.44–7.40 (t, J 7.2 Hz, 2H), 7.39–7.35 (t, J 7.2 Hz, 3H), 7.35–7.32 (dt, J 7.2 Hz, 6.6Hz, 1H), 7.31–7.29 (d, J 6.8 Hz, 2H), 4.33–4.29 (q, J 6.18 Hz, 1 H), 3.76–3.74 (d, J 1.89 Hz, 1 H), 3.16 (d, J 1.96 Hz, 1 H), 1.48–1.47 (d, J 6.8 Hz, 3H). The enantiomeric excess was determined to be 97% using an HPLC system equipped with a Daicel Chiralcel AD-H column (4.6 mm  $\times$  25 cm) (n-hexane/isopropanol = 80/20,  $\lambda$  = 254 nm, 1 mL/min, t = 4.990 min).

**N-methyl-N-benzoylmethyl- $\alpha$ ,  $\beta$ -epoxy- $\beta$ -phenylpropionamide(+)-4.** To a stirred solution of (+)-3 (114.06 g, 0.4 mol) in distilled water (1.2 L), was added dichloromethane (1 L). The mixture was acidified to reach a pH in the range of 3–4 with HCl (1M) at 0 °C, and the organic layer was collected. The aqueous layer was extracted with dichloromethane (3  $\times$  500 mL). The pooled organics were washed with a saturated solution of sodium chloride, dried over  $\text{NaSO}_4$ , and filtered in vacuo. Subsequently, EDCI (84.36 g, 0.44 mol), HOBT (59.46 g, 0.44 mol), N-methyl morpholine (101.2 g, 1 mol) were added to the residue. This was followed by the addition of 2-(methyl amino)-1-phenyl-1-ethanone hydrochloride (74.02 g, 0.4 mol) within 0.5 h of the start of the reaction.

The progress of the reaction was monitored using the TLC technique (Petroleum ether: Ethyl acetate = 2:1) until the signals corresponding to the starting materials stopped appearing on the TLC plate. The reaction mixture was then poured into a container containing distilled water (1.5 L), and the mixture was stirred for 0.5 h. The organic layer was separated, washed with saturated sodium bicarbonate solution, brine, and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure to give N-methyl-N-benzoyl methyl- $\alpha,\beta$ -epoxy- $\beta$ -phenyl propionamide **(+)-4** as a light yellow oil <sup>11</sup>.  $[\alpha]_{\text{D}}^{20} +161.4$  (c1,  $\text{CH}_3\text{OH}$ ) [lit:<sup>11</sup> $[\alpha]_{\text{D}}^{20} -145$  (c1.0,  $\text{CHCl}_3$ )]; <sup>1</sup>H NMR (600 MHz, Chloroform-d)  $\delta$  8.0-7.99(d, J 7.2 Hz, 2 H), 7.91-7.88 (d, J 8.4 Hz, 2H), 7.712-7.67 (t, J 7.8 Hz, 1H), 7.66-7.62 (t, J 7.8 Hz, 1H), 7.59 7.55 (t, J 7.6 Hz, 2H), 7.52-7.49 (t, J 7.8 Hz, 2H), 5.18 (s, 0.44 H), 5.13 (s, 0.34 H), 4.23-4.22(d, J 2.4 Hz, 1 H), 4.023-4.013 (d, J 2.4 Hz, 1 H), 3.93-3.92(d, J 1.8 Hz, 1 H), 3.15 (s, 3H). <sup>13</sup>C NMR (600 MHz, Chloroform-d)  $\delta$  193.65, 167.46, 135.70, 135.07, 133.97, 128.97, 128.82, 128.62, 128.11, 125.91, 57.96, 57.32, 54.49, 36.01. HRMS (ESI):  $m/z$   $[\text{M}+1]^+$  calcd. for  $\text{C}_{18}\text{H}_{17}\text{NO}_3$  295.12; found, 296.1281. The enantiomeric excess was determined to be 100% using an HPLC system equipped with a Daicel Chiralcel AD-H column (4.6 mm  $\times$  25 cm) (n-hexane/isobutanol = 75/25  $\lambda$  = 254 nm, 1 mL/min, t = 16.777min).

**(-)-Clausenamidone (-)-5.** To the light yellow oil **(+)-4** was added LiOH (16.80 g, 0.4 mol) in  $\text{H}_2\text{O}$  (1.5 L). The mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored using the TLC technique (Petroleum ether: Ethyl acetate = 2:1) until the signals corresponding to the starting materials stopped appearing on the TLC plate. The white solid that formed during the reaction was collected by vacuum filtration and dried under vacuum to give **5**. The product was recrystallized from ethyl acetate to give (-)-clausenamidone **(-)-5** as white crystals (42.672 g, 35.3%) <sup>11</sup>. m.p 196.6-198.4 °C.  $[\alpha]_{\text{D}}^{20} -340.2$  (c 0.5,  $\text{CH}_3\text{OH}$ ); [lit:<sup>11</sup> $[\alpha]_{\text{D}}^{20} -355$  (c 0.29,  $\text{CH}_3\text{OH}$ )]; <sup>1</sup>H NMR (600 MHz, Chloroform-d)  $\delta$  7.55-7.50 (m, 2 H), 7.44-7.38 (m, 1H), 7.26-7.21 (m, 2 H), 7.14-7.09 (m, 2 H), 7.08-7.03 (m, 2 H), 7.03-6.98 (m, 1 H), 5.38 (d, J 8.9 Hz, 1 H), 4.90 (dd, J 10.0 Hz, 2.2 Hz, 1 H), 3.85 (t, J 9.4 Hz, 1 H), 2.92 (d, J 2.4 Hz, 1H), 2.89 (s, 3H). <sup>13</sup>C NMR (151 MHz, Chloroform-d)  $\delta$  197.28, 174.90, 136.29, 134.09, 133.52, 128.58, 128.49, 128.33, 128.13, 127.89, 71.87, 64.89, 51.39, 29.59. HRMS (ESI):  $m/z$   $[\text{M}+1]^+$  calcd. for  $\text{C}_{18}\text{H}_{17}\text{NO}_3$ , 296.1281; found, 296.1271. The enantiomeric excess was determined to be 100% using an HPLC system equipped with a Daicel Chiralcel OJ-H column (4.6 mm $\times$ 25cm) (n-hexane/ isopropanol = 80/20,  $\lambda$ = 254 nm, 1 mL/min, t = 9.956 min).

**(-)-Clausenamide.** To a solution of (-)-clausenamidone **(-)-5** (0.3 g, 0.001 mol) in anhydrous methanol (30 mL) at 0-10 °C,  $\text{NaBH}_4$  (0.19 g, 0.005 mol) was added slowly. The solution was stirred at room temperature for 3.5 h. The progress of the reaction was monitored using the TLC technique (Petroleum ether: Ethyl acetate = 1:2) until signals corresponding to the starting materials stopped appearing on the TLC plate. The reaction was quenched by adding a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (30 mL). The mixture was stirred for 10 min. The reaction mixture was extracted with EtOAc (3  $\times$  30 mL). The organic layers were washed with water (50 mL), saturated aqueous  $\text{NaHCO}_3$  (30 mL), and brine (30 mL). The layer was dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure to give the product as a white solid. Recrystallization from acetonitrile gave (-)-clausenamide as white crystals (0.21 g, 69%) <sup>13</sup>; m.p159–161.5 °C.  $[\alpha]_{\text{D}}^{20} -100$  (c0.01,  $\text{CH}_3\text{OH}$ ) [lit:<sup>13</sup> $[\alpha]_{\text{D}}^{20} -144.2$ (c0.55,  $\text{CH}_3\text{OH}$ )]; <sup>1</sup>H NMR (600 MHz,  $\text{CH}_3\text{OD}$ )  $\delta$ : 7.29-7.19 (m, 5H), 7.16-7.07 (m, 3H), 6.70-6.75 (d, J 7.8 Hz, 2H), 4.41-4.36 (dd, J 8.4 Hz, 3 Hz, 1 H), 4.05-3.99 (d, J 11.4 Hz, 1 H), 3.70–3.61 (t, J 10.2 Hz, 1 H), 3.32-3.30 (dd, J 3.6 Hz, 1.8 Hz, 1H), 3.18 (s, 3H); <sup>13</sup>C NMR (600 MHz,  $\text{CH}_3\text{OD}$ )  $\delta$ : 177.30, 141.27, 136.74, 129.88, 129.20, 128.80, 128.50, 128.43, 127.94, 74.15, 70.78, 67.46, 51.33, 31.53; HRMS(ESI):  $m/z$   $[\text{M}+1]^+$  calcd. for  $\text{C}_{18}\text{H}_{19}\text{NO}_3$ , 298.14; found, 298.1438; The enantiomeric excess was determined to be 100% using an HPLC system equipped with a Daicel Chiralcel OJ-H column (4.6 mm  $\times$  25 cm) (n-hexane/ isopropanol = 70/30,  $\lambda$  = 220 nm, 1 mL/min, t = 9.614 min).

## Supplementary Material

Characterization data (for all new products), copies of  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HRMS, and IR spectra associated with this paper have been provided.

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