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Efficient synthesis of (-)-clausenamide

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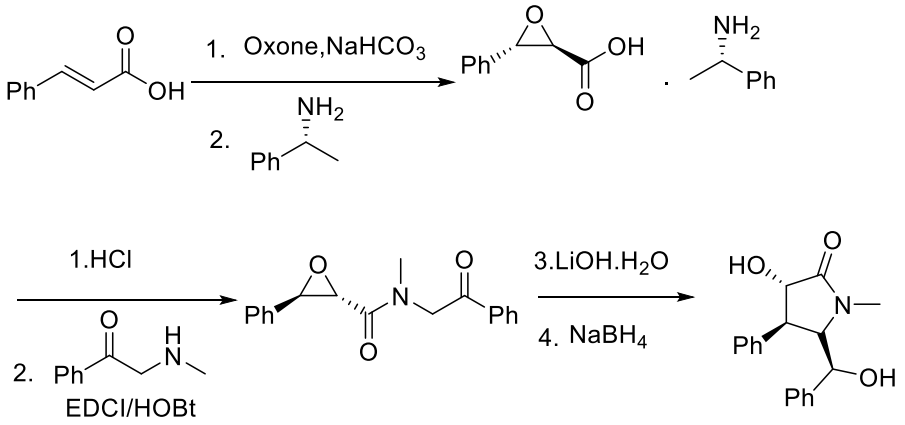
Abstract

A new method for the synthesis of (-)-clausenamide was reported. (-)-clausenamide was obtained from the inexpensive material of *trans*-cinnamic acid within five steps with overall yields of 8.9% and ee 99.5%. Compared with the multi-step asymmetric synthesis methods reported in literature, the raw materials used in this method are extremely inexpensive, and the operation of each experimental step is convenient. Furthermore, the reaction takes place under very mild reaction conditions (25 °C) to avoid the reaction conditions of anhydrous and very-low temperature (-78 °C), and each step of reaction does not need column chromatography separation, which is more suitable for large-scale preparation of (-)-clausenamide. The structures were confirmed by ^{1}H NMR, ^{13}C NMR and MS.

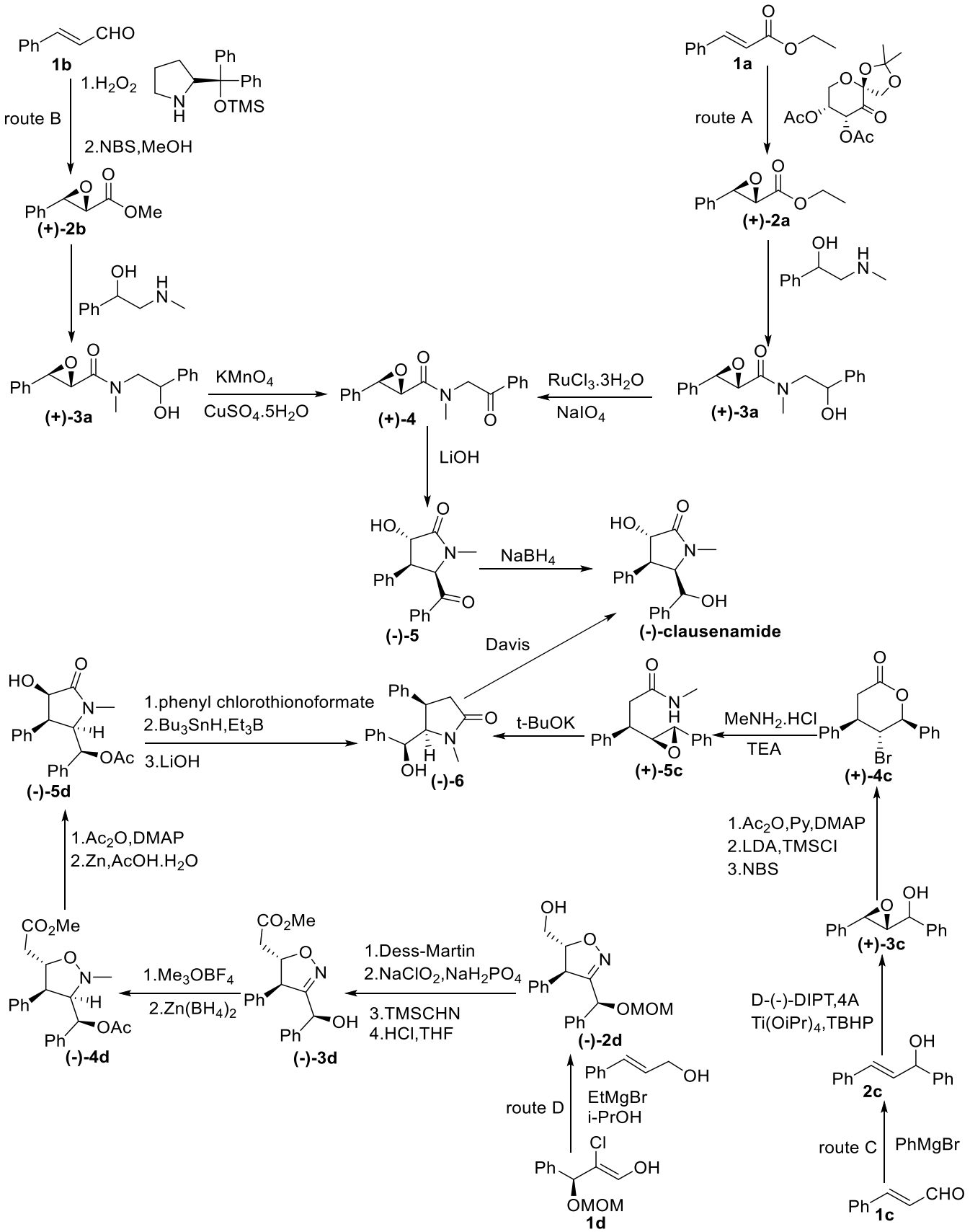


Keywords: (-)-Clausenamidone, (-)-clausenamide, chemical resolution, synthesis

Introduction

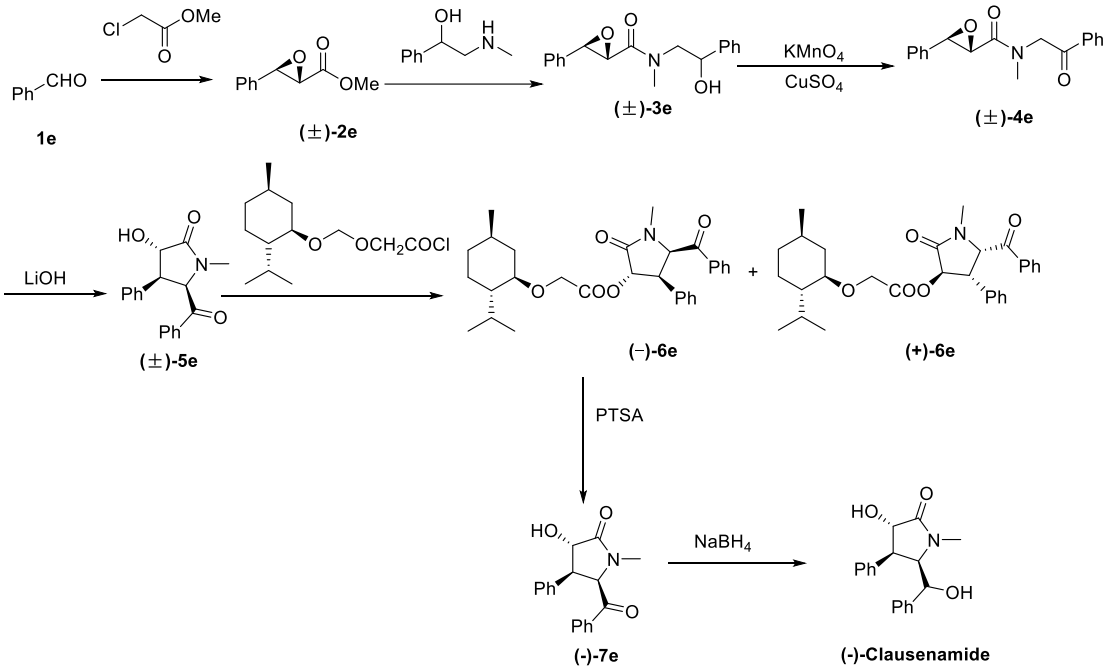
Racemic clausenamide is a pyrrolidone natural product first isolated from the aqueous extract of the leaves of clausenalansium,[1] and it exhibited nootropic and anti-acute cerebral ischemia in biological tests.[2] However, it has been shown that (-)-clausenamide was the real nootropic active ingredient, which possessed significant biological activities.[3-6] For instance, (-)-clausenamide could protect markedly against the neurotoxicity induced by okadaic acid and abeta25-35,[7] enhance the synaptic transmission in the dentate gyrus, protect the cerebrum in hypoxia and ischemia damage.[8-10] Therefore, (-)-clausenamide is considered to be a promising drug candidate for treatment of Alzheimer's disease and other neurodegenerative disorders.

In the literature, there were two methods for the synthesis of (-)-clausenamide: asymmetric synthesis and resolution intermediate synthesis. To the best of our knowledge, resolution of the starting material to synthesize (-)-clausenamide has not yet been reported. Among asymmetric synthesis methods, there were two pathways to access (-)-clausenamide. One method for the synthesis of (-)-clausenamide was by synthesizing the key intermediate amide (**+**)-**4**, followed by the cyclization of (**+**)-**4** to afford (-)-clausenamidone **(-)-5** in the presence of LiOH, and reduction of **(-)-5** with sodium borohydride to obtain the target product. Shi Yi'an[11] reported the synthesis of (-)-clausenamide using trans cinnamate (**1a**) as the starting material within five steps with overall yield of 18.9% and 99% e e (Scheme1, 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 chiral catalyst fructose derivatives synthesis was low, and its cost was high. In addition, ruthenium trichloride trihydrate sodium periodate was used in the oxidation step, after the reaction is filtered by diatomaceous earth, leading to poor yields. Xuan Yi-ning started their synthesis from cinnamaldehyde (**1b**) (Scheme 1, route B)[12] to afford (-)-clausenamide in 6.2% yield over six steps and 99% e e. However, the esterification product and the intermediate epoxy cinnamaldehyde required column chromatography separation with low yields in the first step. The chiral catalyst prolinol silyl ether derivative was unstable and needed to be prepared freshly. In addition, potassium permanganate-copper sulfate pentahydrate was applied to the oxidation step as the oxidation system. A viscous manganese dioxide was produced during the reaction, which was filtered with difficultly and therefore is not desirable for large-scale preparation of (-)-clausenamide. The other strategy for constructing (-)-clausenamide was from (-)-3-deshydroxyxanthoenamide **(-)-6** as the common intermediate and subsequent treatment with Davis reagent to obtain (-)-clausenamide under alkaline conditions. Starting from cinnamic aldehyde (**1d**), Liu Di and workers described their synthesis of (-)-clausenamide (Scheme 1, route C).[13] The overall yield of this eight-step synthesis of (-)-clausenamide was 11.5% and 99% ee. This method, however, is limited by the Sharpless asymmetric epoxidation of (**2c**) which needs harsh conditions of anhydrous and long-term low temperature. Moreover, column chromatography must be used in purifying the multi-step reactions, and the Davis oxidant was used in the last step, making this process costly and not suitable for large-scale preparation of (-)-clausenamide. Subsequently, Tanda and coworkers have reported the synthesis of (-)-3-deshydroxyxanthoenamide **(-)-6** starting with phenylpropanhydroxime chloride **1d** to synthesize **(-)-6** in 6.5% over twelve steps and 99% e e.[14] However, the preparation of the starting material **1d** needed a multi-step sequence. Furthermore, this material is unstable, and can only be stored at room temperature for a few days. At the same time, reaction of **(-)-3d** with zinc borohydride required low temperature (-78 °C).



Scheme1. Asymmetric Synthesis of (-)-clausenamide

(-)-Clausenamide was able to be prepared in another way: the intermediate (±)-clausenamidone（±）-**5e** (Scheme2) was resolved using menthol oxyacetic acid to obtain menthoxyacetyclausenamidone ((-)-**6e**). This compound was subjected to hydrolysis to furnish (-)-**7e**, which was reduced with $NaBH_4$ to give (-)-clausenamide in 11.5% and 98% e e.[15] Because the diastereoisomeric products (-)-**6e** and (+)-**6e** need to be separated by column chromatography, and its enantiomer (+)-clausenamidone was discarded, the process did not conform to the atom economy. Furthermore, the preparation of the resolving agent (-)-menthyloxyacetic acid required a large amount of sodium metal, with toluene reactions carried out at reflux for 60-70 hours , which is not conducive to large-scale preparation.

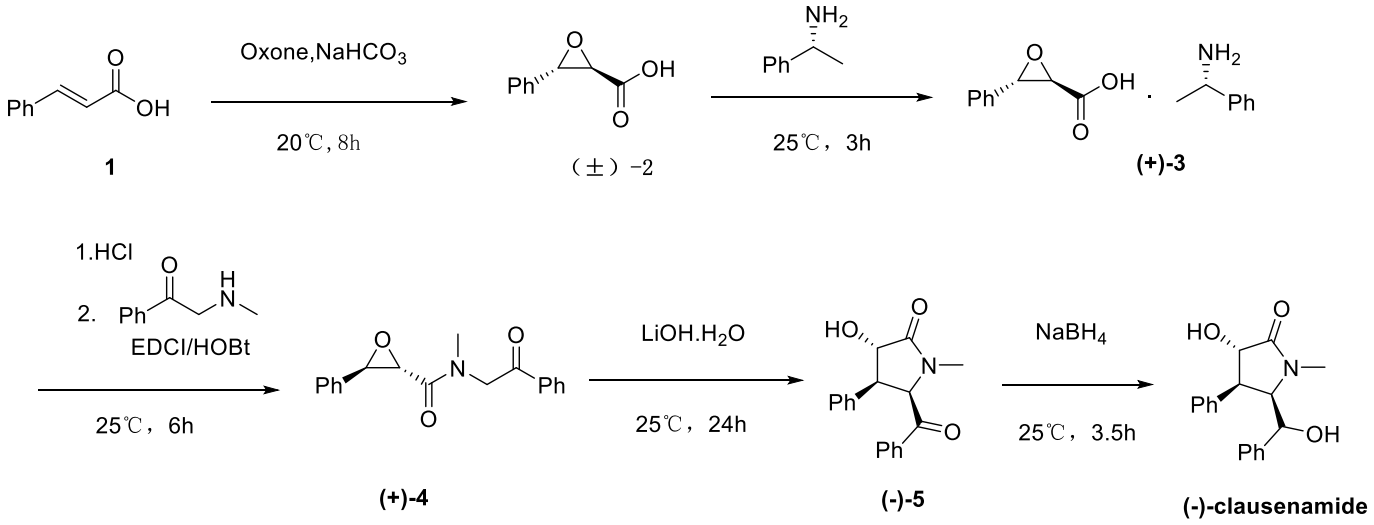


Scheme 2. Chiral resolution of (±)-clausenamidone

Results and Discussion

In this paper, we designed the cheap *trans*-cinnamic acid (**1**) as starting material (Scheme 3). First, treatment of *trans*-cinnamic acid (1) with potassium persulfate allow to obtain racemic epoxy cinnamic acid **(±)-2**, followed by resolution of **(±)-2** with (R)-(+)-α-methylbenzylamine, yielded (2S,3R)-epoxycinnamic acid(R)-α-methylbenzylamine salt **(+)-3**. The latter was treated with 1M H Cl in dichloromethane to give **(+)-2**, which was directly used without further purification，and was converted to the amide **(+)-4** using 2-methylamino-1-phenyl-ethanol. Subsequent treatment with Li OH afforded lactam **(-)-5**. Finally, reduction of **(-)-5** with $NaBH_4$ furnished (-)-clausenamide in a total yield of 8.9% over five steps and 99.5% e e. Compared with the synthetic methods reported in the literature, the operation of each experimental step is convenient. Moreover, the reaction takes place under very mild reaction conditions (25 °C) to avoid the reaction conditions of anhydrous and very low temperature (-78 °C), and each step of reaction does not need column chromatographic separation. The reaction products of each step can be purified by recrystallization. The raw materials and

solvents used in the reaction are low in cost, use expensive chiral catalysts is not needed, and the solvent is a relatively safe third type organic solvent, which is more suitable for large-scale preparation.



Scheme3. Synthesis of (-)-clausenamide

Conclusions

In this work, a new method is applied to the synthesis of (-)-clausenamide, which provides access to the target compound in five steps from the cheap starting material *trans*-cinnamic acid. First, *trans*-cinnamic acid was oxidized using potassium persulfate to give racemic epoxycinnamic acid **2**, followed by resolution with (*R*)-(+)-α-methylbenzylamine to gain (+)-(2*S*,3*R*)-epoxycinnamic acid-(*R*)-α-methylbenzylamine salt (**3**),
Then, **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 to obtain (-)-clausenamide in yield of 8.9% and 99.5% ee. The advantage of this approach is that raw materials are extremely cheap, the reaction takes place under moderate reaction conditions, whilst also avoiding the anhydrous reaction conditions and ultra-low temperature, all reactions were carried out at room temperature, and only recrystallization purification is needed to obtain the pure products, which are more suitable for large-scale preparation.

Experimental Section

General. Melting points were determined on laboratory devices X-5 melting point apparatus. Optical rotation was performed with P8000 automatic polarimeter. ^{1}HNMR and ^{13}CNMR spectra were recorded on a 500 MHz/300MHz spectrometer (AVANCE) with TMS as the internal standard. Chemical shifts are expressed in (δ) are given in ppm, whereas J-values for ^{1}H–^{1}H coupling constants are given in Hertz. The apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad). High-resolution mass spectra (HRMS) were obtained (in positive/or negative ion mode) using electron spray ion trap (ESI) technique with a 6210ESI/TOF instrument. Enantiomeric excess (ee) was determined by Agilent 1200 high performance

liquid chromatography, AD-H, OJ-H Chiral column. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification

Racemic epoxy cinnamic acid(±)-2. To a stirred solution of trans cinnamic acid (148.20g, 1mol) in acetone (650ml) was added slowly $NaHCO_3$ (380.0g, 4.5mol) till dissolve at room temperature, whereupon EDTA-2Na (650mL, 4 ×10-4mol/L) aqueous solution was added at 0 °C, with further added potassium hydrogen persulfate (620.0g, 2mol) in EDTA-2Na(1250mL, 4 ×10-4mol/L) aqueous solution at below 20 °C for one hour. The solution was stirred at room temperature for 8h. TLC (Petroleum ether: Ethyl acetate=3:1)was monitored until starting materials disappear. The reaction solution was filtered to remove insoluble salts, and the filtrate was stirred with 1.0L ethyl acetate under ice bath. The solution was acidified to pH2～3 at 0 °C with HCl and separated the organic layers, the aqueous solution was extracted with ethyl acetate (3×500mL). The pooled organics were washed with distilled water (1L), saturated brine (1L), dried (Na_2SO_4), and concentrated in vacuo to a volume of 750mL at below 40 °C.

(2*S*,3*R*)-Epoxycinnamate-(*R*)-α -methylbenzylamine salt (+)-3. To the above solution of **(±)-2** (750mL) was added (R)-(+)-α -methylbenzylamine (121.18g, 1.0mol). The solution was stirred vigorously at room temperature，while a large amount of white solid appeared in the reaction solution, precipitation did not increase significantly after 3 hours . The white solid that formed was collected by filtration in vacuo and dried under vacuum to give the (2S,3R)-epoxycinnamate-(R)-α-methylbenzylamine salt **(+)-3** as a white solid (116.91g), recrystallization with absolute ethanol gave **(+)-3** as white crystals (104.08g) in 36.5%[16]. mp:159.3-160.5℃, $[\alpha]_D^{20}$+126.7 (c1, EtOH) [lit:[16]$[\alpha]_D^{24}$+113 (c0.5, EtOH)]; ^{1}H NMR (300MHz, Chloroform-d) δ 7.50-7.25 (m, 10H), 4.33-4.29 (q, *J* 0.3Hz, 1H), 3.76-3.74 (d, *J* 0.9Hz, 1H), 3.16 (d, *J* 1.2Hz, 1H), 2.50 (t, *J* 0.9Hz, 2H), 1.48-1.47 (d, *J* 3.6Hz, 3H). The enantiomeric excess was determined to be 98.9% by HPLC with a Daicel Chiralcel AD-H column (4.6 mm × 25 cm) (n-hexane/IPA =80/20, λ = 254 nm, 1mL/min), t = 4.990 min.

***N*-Methyl-*N*-benzoylmethyl-α, β-epoxy-β-phenylpropionamide (+)-4.** To a stirred solution of **(+)-3** (114.06g, 0.4mol) in distilled water (1.2L) was added dichloromethane (1L), the mixture was acidified to pH 3-4 at 0 °C with HCl (1M） and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×500mL). The pooled organics were washed with a saturated sodium chloride solution, dried ($NaSO_4$), and filtered in vacuo. Subsequently, to the solution was added EDCI (84.36g, 0.44mol), HOBt (59.46g, 0.44mol), *N*-methylmorpholine (101.2g, 1mol), followed by 2-(methyl amino)-1-phenyl-1-ethanone hydrochloride (74.02g, 0.4mol)within 0.5h.TLC (petroleum ether:ethyl acetate 2:1) was monitored untill starting materials disappeared. The reaction mixture was then poured onto distilled water (1.5L) and stirred for 0.5h. The organic layer was separated, washed with saturated sodium bicarbonate solution, brine, dried (Na_2SO_4) successively, and the solvent was removed under reduced pressure to give *N*-methyl-*N*-benzoyl methyl-α, β -epoxy- β -phenyl propionamide **(+)-4** as a light yellow oil[11].$[\alpha]_D^{20}$ +161.4 (c1,CH_3OH) [lit:[11]$[\alpha]_D^{20}$ -145(c1.0,$CHCl_3$)]; ^{1}H NMR (600MHz, Chloroform-d) δ7.97-7.3 (m,10H), 5.03(s,0.4H), 5.01-4.9 (d, *J* 5.4Hz, 0.65H), 4.79 (s,0.5H),4.76 (s,0.4H), 4.13-4.11 (d, *J* 2.4Hz,1H), 3.79-3.77(d, *J* 1.8Hz,1H), 3.21 (s,3H).^{13}C NMR(600MHz, Chloroformd) δ 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 $[M+1]^+$ calcd for $C_{18}H_{17}NO_3$ 295.12; found， 296.1281. The enantiomeric excess was determined to be 99.9% by HPLC with a Daicel Chiralcel AD-H column (4.6 mm × 25cm) (n-hexane/i-PrOH = 85/15, λ = 254 nm, 1 mL/min), t = 16.348min.

(-)-Clausenamidone (-)-5. To the light yellow oil （+）**-4** was added LiOH (16.80g, 0.4mol) in H_2O (1.5L) and stirred at room temperature for 24h. TLC (Petroleum ether: Ethyl acetate 2:1) was monitored untill starting materials disappeared. The white solid that formed was collected by vacuum filtration and dried under vacuum to give **5**, and recrystallized with ethyl acetate to give (-)-clausenamidone **(-)-5** as white crystal

(42.672g, 35.3%)[11]. mp 196.6-198.4 °C. $[\alpha]_D^{20}$-340.2 (c 0.5, CH_3OH); [lit:[11]$[\alpha]_D^{20}$-355(c 0.29, Me OH)]; ^{1}H NMR (600MHz, Chloroform-d) δ 7.55-7.50 (m, 2H), 7.44-7.38 (m,1H), 7.26-7.21 (m, 2H), 7.14-7.09 (m, 2H), 7.08-7.03 (m, 2H), 7.03-6.98 (m, 1H), 5.38 (d, *J* 8.9Hz, 1H), 4.90 (d d, *J* 10.0, 2.2Hz 1H), 3.85 (t, *J* 9.4Hz, 1H), 2.92 (d, *J* 2.4Hz, 1H), 2.89 (s, 3H). ^{13}C NMR(151MHz, Chloroform-d) δ 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* $[M+1]^+$ Calcd for $C_{18}H_{17}NO_3$, 296.1281 Found 296.1271. The enantiomeric excess was determined to be 99.9% by HPLC with a Daicel Chiralcel OJ-H column (4.6 mm×25cm) (n-hexane/i-PrOH =80/20, λ=254nm, 1mL/min), t = 6.605min.

(-)-Clausenamide. To a solution of (-)-clausenamidone（-）**- 5** (0.3g, 0.001mol) in anhydrous methanol (30mL) at 0～10 °C, $NaBH_4$ (0.19g, 0.005mol) was added slowly. The solution was stirred at room temperature for 3.5h, TLC (Petroleum ether: Ethyl acetate=1:2) was monitored untill materials disappeared. The reaction was quenched by the addition of saturated aqueous NH_4Cl (30mL) and stirred 10min.The reaction mixture was extracted with EtOAc (3x30mL). The organic layers were washed with water (50mL), saturated aqueous $NaHCO_3$ (30mL), brine (30mL), dried (Na_2SO_4) successively, and evaporated under reduced pressure to give white solid. Recrystallization from acetonitrile gave (-)-clausenamide as white crystal (0.21g, 69%) [13] mp 159~161.5°C. $[\alpha]_D^{20}$-100 (c0.01 , CH_3OH)[lit:[13]$[\alpha]_D^{20}$-144.2(c0.55,CH_3OH)]; ^{1}H NMR (600MHz, CH_3OH) δ: 7.29-7.19（m, 5H）,7.16-7.07(m,3H),6.70-6.75 (d, *J* 7.8Hz, 2H), 4.41-4.36 (d d, *J* 8.4Hz,3Hz,1H), 4.05-3.99 (d, *J* 11.4Hz, 1H), 3.70-3.61 (t, *J* 10.2Hz, 1H), 3.32-3.30(d d, *J* 3.6Hz,1.8Hz,1H),3.18 (s,3H); ^{13}C NMR (600MHz, CH_3OH) δ: 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* $[M+1]^+$calcd for $C_{18}H_{19}NO_3$,298.14; found,298.1438; The enantiomeric excess was determined to be 99.9% by HPLC with a Daicel Chiralcel OJ-H column (4.6mm × 25 cm)(n-hexane/i-PrOH = 70/30, λ = 220nm, 1mL/min), t =9.641min.

Supplementary Material

Characterization data (for all new products), copies of ^{1}H and ^{13}C NMR, HRMS and IR spectra associated with this paper

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