European Journal of Medicinal Chemistry 45 (2010) 5531–5538

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Laboratory note

Synthesis of N-substituted Clausenamide analogues

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ARTICLE INFO

Article history:
Received 24 February 2010
Received in revised form
14 August 2010
Accepted 16 August 2010
Available online 24 August 2010

Keywords:
Nootropic agents
N-substituted Clausenamide
Metabolites
Pyrrolidin-2-one

ABSTRACT

A practical synthesis of N-substituted Clausenamide analogues, including (−) and (+) CM1, Piracetam analogue **1** and Nefiracetam analogue **2**, have been developed.

1. Introduction

The pyrrolidin-2-one family of cognition-enhancers, often referred to as nootropics and exemplified by Piracetam and Nefiracetam (Fig. 1), has been the subject of studies for almost four decades. Several members are in use in several countries to control cognition impairment, to afford neuroprotection after stroke and to treat epilepsy [1]. Racemic Clausenamide (Fig. 1) is a pyrrolidin-2-one derivative isolated from *Clausena lansium* (*lour.*), a Chinese folk medicine [2]. Its two optical isomers, namely (+) and (−) Clausenamide, had been synthesized by our group [3,4]. (−)-Clausenamide showed potent nootropic activity in many behavioral experiments, and is developed as a promising antidementia drug now. While, (+)-Clausenamide does not possess such effects [5].

The structure of Clausenamide is quite different from that of Piracetam and Nefiracetam. In Clausenamide, there are four stereogenic centers resulted from three substituents at 3, 4, 5 positions of the central pyrrolidin-2-one. While, in Piracetam or Nefiracetam, there is only one, but larger, substituent. These substituents are suggested to be closely related to their respectively nootropic activities. Therefore, demethyl-Clausenamide derivatives with the side chain of Piracetam and Nefiracetam (Compounds **1** and **2**, Fig. 1) are designed with the aim of finding novel nootropic agents.

CM1 (Fig. 1), the hydroxylation product of Clausenamide, is one of the major metabolites of both (−)-Clausenamide and (+)-Clausenamide. The synthesis of (−)-CM1 is required to support the preclinical studies of (−)-Clausenamide. *In vivo* and *in vitro* metabolic studies also revealed that the content of CM1 in the metabolites of (−)-Clausenamide is significantly higher than that of (+)-Clausenamide [6]. It seems that there may be some correlation between the different physiological roles of (+) and (−) Clausenamide and their different metabolic behavior. If so, (−)-CM1 may also be a nootropic agent and may enhance and prolong the nootropic effect of (−)-CM1 *in vivo*.

To acquire novel compounds with nootropic activities and to support the preclinical studies of (−)-Clausenamide, the synthesis of Piracetam analogue **1**, Nefiracetam analogue **2** and CM1 as well as its optical isomers, has been conducted. An elegant method was devised to construct the γ-lactam skeleton and establish the relative configuration of the substituents, especially the 4/5 syn-configuration, which is essential to keep the nootropic activities [7]. The present report describes our efforts in this field.

1.1. Synthesis of racemic demethyl-Clausenamide

In our strategy, 4/5 syn-demethyl-Clausenamidone **9a** was chosen as the key intermediate for the synthesis of desired compounds. Our group has successfully fulfilled the total syntheses of Clausenamidone **9d** by an elegant base induced cyclization of compound **8d** (Scheme 1) [8]. Thus, the synthetic route of demethyl-Clausenamidone **9a** was designed following the same strategy. The key to the success of this strategy is conversion of **8a** to γ-lactam **9a** through intramolecular cyclization, Cyclization to 5-numbered ring from such structural type as **8a** is against Baldwin's rule [9]. But

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doi:10.1016/j.ejmech.2010.08.041

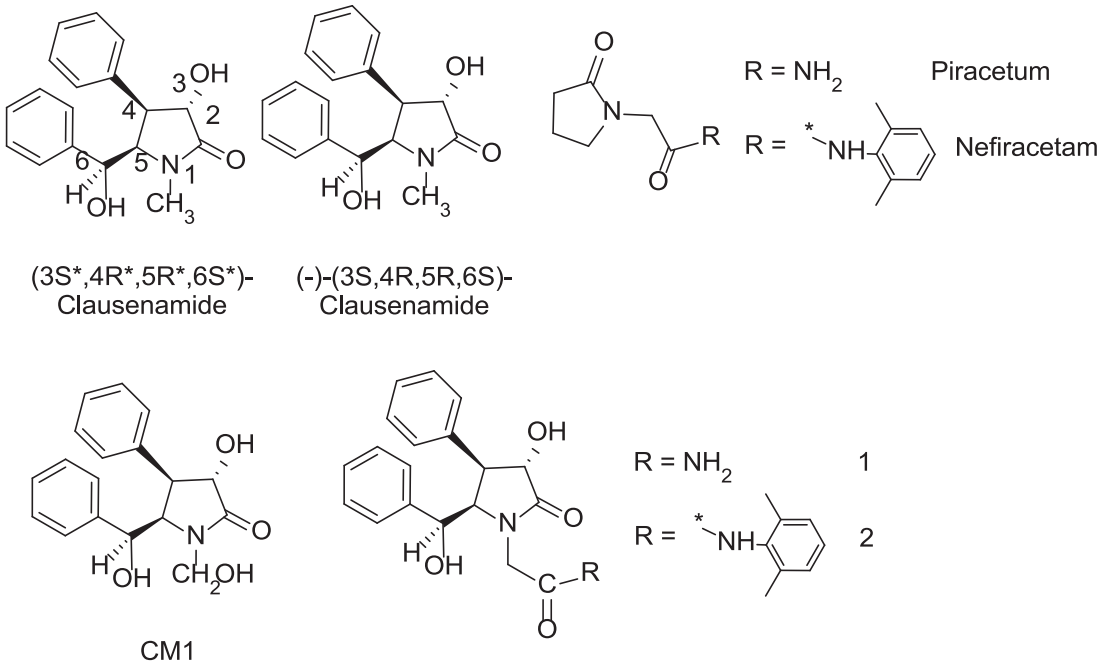
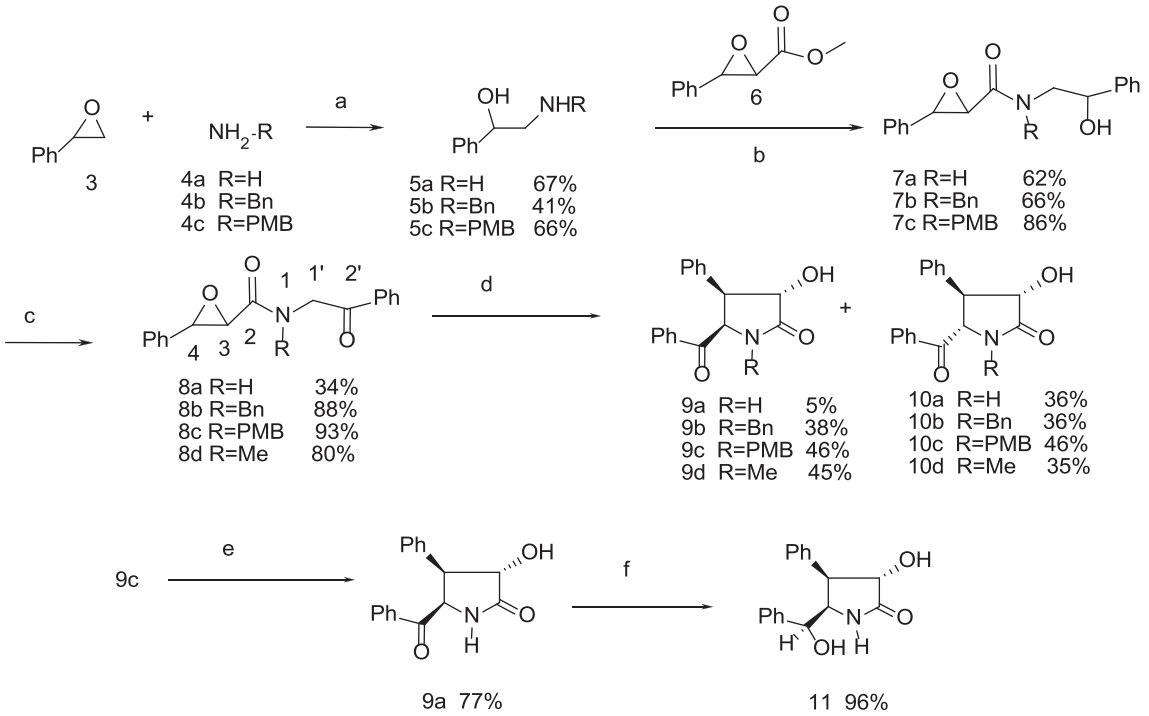


Fig. 1. The structure of Clausenamide, CM_1, Piracetam and Nefiracetam, Piracetam analogue **1** and Nefiracetam analogue **2**.

previous study had showed that the intramolecular cyclization of compound **8d** under the catalyst of LiOH worked nice to give a mixture of **9d** and **10d**. The electronic effect induced by phenyl group at β-carbon of the epoxy group may be favorable factor for the nucleophilic attack at β-carbon to form the γ-lactam.

The β-phenyl-ethanol amine **5a** was prepared from styrene oxide **3** and aqueous ammonia. **5a** took place amine-ester exchange reaction with methyl β-phenyl-glycidate **6** giving the straight-chain amide **7a**. Oxidation of **7a** with potassium permanganate and copper sulfate furnished amide **8a** in good yield. However the cyclization of compound **8a** did not take place under catalytic amount or stoichiometric amount of base (LiOH) at room temperature. It proceeded when the reaction mixture was heated to 60 °C, but produced a complex mixture of products. Only a small quantity of **9a** (5% yield) and **10a** (36% yield) was obtained through careful separation. We proposed that it is the amide hydrogen atom of **8a**, which can also dissociate to generate anion other than the proton at the α position of carbonyl group (1′ position) under the alkaline



Scheme 1. Reagents and conditions: a: room temperature, 10days; b: sodium methoxide/methanol, a week; c: $KMnO_4/CuSO_4$, CH_2Cl_2, d: LiOH/MeOH, H_2O; e: $(NH_4)_2Ce(NO_3)_6$/CH_3CN, H_2O; f: $NaBH_4/CH_3OH$.

reaction condition, handicap and complicate the reaction, and changing the amide hydrogen atom to an inert group, for example benzyl, may facilitate the reaction. Thus N-Bn amide **8b** was prepared following the method for the preparation of **8a** from benzylamine **4b** and styrene oxide **3**. **8b** underwent cyclization smoothly to give **9b** and **10b** as the main components of the reaction products. Unfortunately, the debenzylation of **9b** failed with various methods, such as catalytic hydrogenolysis, acidic solvolysis [10], Li/NH_3 reduction [11] and *t*-BuLi/O_2 oxidation [12]. N-*p*-methoxybenzyl (PMB) substituted amide **8c** was thus prepared, considering the *p*-methoxybenzyl group was easier to be stripped off than benzyl group. The intramolecular cyclization of compound **8c** gave a mixture of γ-lactam **9c** and **10c**. The desired 4/5-cis compound **9c** was separated by silica gel column chromatography. The debenzylation of **9c** by CAN oxidation [13] worked well to give the key intermediate demethyl-Clausenamidone **9a**, which yielded racemic demethyl-Clausenamide **11** by subsequent reduction of the ketone group with sodium borohydride.

1.2. Synthesis of Piracetam analogue 1, Nefiracetam analogue 2

The synthesis of compounds **1** and **2** is illustrated in Scheme 2. The two hydroxyl groups of demethyl-Clausenamide **11** were protected with 3,4-2*H*-dihydropyran to give 3,6-di-O-tetrahydropyran-demethyl-Clausenamide **12**. Condensation of compound **12** with ethyl bromoacetate or 2-bromo-N-(2,6-dimethylphenyl) acetamide in the presence of sodium hydride [14] and subsequent deprotection yielded N-(ethoxycarbonyl-methyl)-demethyl-Clausenamide **13** or Nefiracetam analogue **2** respectively. Incubation of compound **13** in NH_3/CH_3OH overnight gave the Piracetam analogue **1**.

1.3. Synthesis of racemic and optical active CM1

Hydroxymethylation [15] of **11** in acetone in the presence of K_2CO_3 using formaldehyde afforded the desired racemic CM1, which showed identical ^1H NMR, ^{13}C NMR and MS spectra to the sample obtained from metabolites of Clausenamide (Scheme 3).

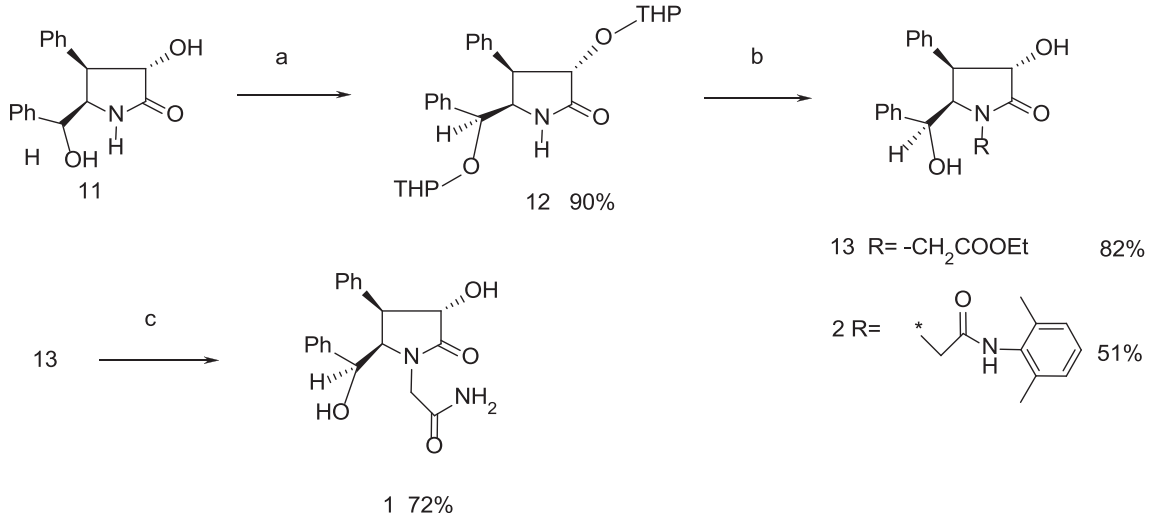
Enantiomers of CM1 were prepared by resolution of the intermediate (±) **9c** using phthalyl-L-alanine as the resolving agent (Scheme 3). Condensation of (±) **9c** with phthalyl-L-alanine gave a mixture of diastereoisomers **14a** and **14b**, which was difficult to be separated by chromatography. Therefore debenzylation of the mixture of **14a** and **14b** with CAN was carried out first, the mixture of **15a** and **15b** was easily separated by SiO_2 column chromatography. Reduction of the ketone of **15a** or **15b** with $NaBH_4$ followed by hydrolysis with aq. NaOH in one pot gave the enantiomerically pure demethyl-Clausenamidone (−)-**11** or (+)-**11** respectively. Hydroxymethylation of (−)-**11** and (+)-**11** yielded the corresponding (−)-CM1{$[\alpha]_D^{18} = -119^\circ$ (*c*,0.261, CH_3OH)} and (+)-CM1 {$[\alpha]_D^{18} = +117^\circ$ (*c*, 0.394, CH_3OH)} with ee >99% (determined by HPLC with chiral column). The retention time of (−)-CM1 is in line with that of CM1 obtained from the metabolism of (−)-Clausenamide. This result indicated that (−)-CM1 was the metabolite of (−)-Clausenamide and the absolute configuration of (−)-CM1 must be 3S,4R,5R,6S. Then the absolute configuration of (+)-CM1 must be 3R,4S,5S,6R.

1.4. Pharmacology

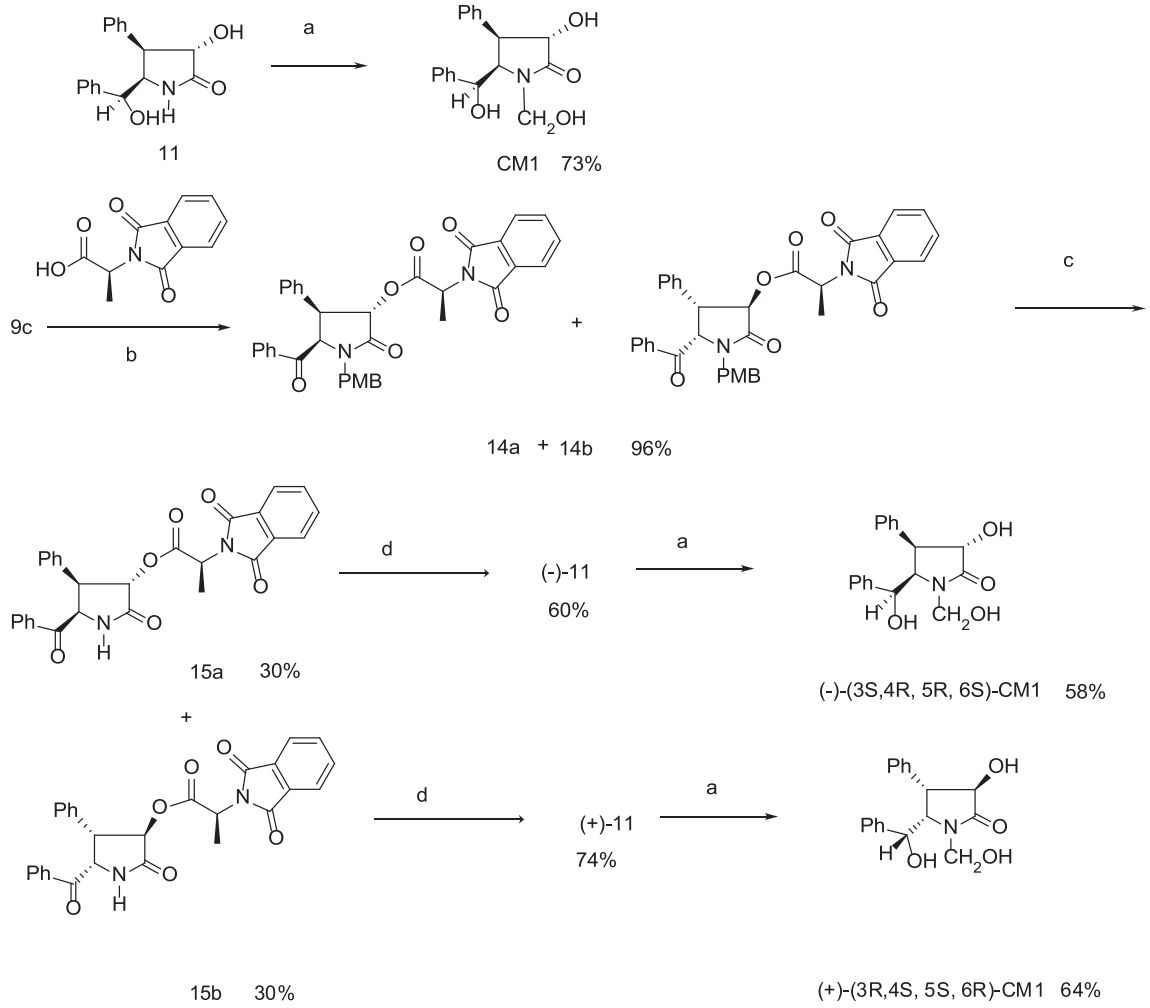
Long-term potentiation (LTP) is the long-lasting improvement in communication between two neurons that results from stimulating them simultaneously. Since neurons communicate via chemical synapses, and because memories are believed to be stored within these synapses, LTP is widely considered to be one of the major cellular mechanisms that underlie learning and memory.

Herein, the nootropic activity of (−) and (+) CM1, Piracetam analogue **1** and Nefiracetam analogue **2**, were evaluated herein in LTP assays compared with (−)-Clausenamide and (+)-Clausenamide [16,17]. As shown in Table 1, at an estimated final brain concentration of 1 μM, (−)-CM1 caused over 30% increase of PS amplitude relative to basal level, and 27%–41% increase relative to the vehicle control, while (+)-CM1 exhibited 18%–25% and 11%–20% of decrease in the PS amplitude when compared with basal and vehicle control, respectively. These results implied that the activity of (−)-Clausenamide could be partly contributed from its active metabolite (−)-CM1. The completely different behaviors of (−) and (+) CM1 further demonstrated that the stereochemistry around the pyrrolidin-2-one was a very important determinant for the activities of this type of cognition-enhancers.

Results in Table 1 also showed that 60 min after compounds administration, Nefiracetam analogue **2** increased PS amplitude by 37% and 22% relative to basal PS amplitude and vehicle control respectively. While no significant effect was observed for Piracetam analogue **1**. These results indicated that the structure of the side chain on the N atom of amide has a great impact on the nootropic activity of N-substituted Clausenamide analogues. But the relatively low activity of compounds **1** and **2** might be due to the antagonism



Scheme 2. Reagents and conditions: a: 3,4-2*H*-dihydropyran, PPTS/THF; b: (1) bromoacetate or 2-bromo-*N*-(2,6-dimethylphenyl) acetamide, NaH/benzene, reflux, (2) H^+/EtOH, reflux; c: NH_3/MeOH.



Scheme 3. Reagents and conditions: a: formaldehyde, K_2CO_3/acetone, water; b: (1) $SOCl_2$/toluene, (2) pyridine/CH_2Cl_2; c: $(NH_4)_2Ce(NO_3)_6/CH_3CN$, H_2O; d: (1) $NaBH_4/CH_3OH$, (2) NaOH.

effect of their (+)-isomer. Additional N-substituted Clausenamide analogues and their enantiomers should be synthesized and evaluated to provide a better understanding of their SAR.

2. Conclusion

In summary, a practical synthesis of N-substituted Clausenamide analogues, including (−) and (+) CM1, Piracetam analogue **1** and Nefiracetam analogue **2**, have been developed. The nootropic activities of these targets compounds were evaluated by LTP assay. The result indicated that the stereochemistry around the pyrrolidin-2-one and the structure of the N-side chain have a great impact on the nootropic activities of N-substituted Clausenamide analogues. These hints will be helpful in the design of more efficient pyrrolidin-2-one type of cognition-enhancers.

3. Experiment

All the reagents for synthesis were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using an RY-1 apparatus and the thermometer is uncorrected. ^1H NMR spectra were recorded using a multinuclear FT NMR spectrometer YS-300 or

Table 1
Activity data in enhancing LTP of synthesized compounds at a concentration of 1 μM.

Compound	Animal number	Relative PS (PSA %)[a,b]			
		P.A.	15 min A A.	30 min A A.	60 min A A.
DMSO	6	100	110.0 ± 7.0	108.4 ± 6.4	112.5 ± 4.2
(−)-Clausenamide	6	100	131.8 ± 0.4	138.5 ± 8.9*	158.1 ± 4.2**
(+)-Clausenamidec	6	100	90.6 ± 0.3	110.2 ± 13.1	106.4 ± 4.1
(−)-CM1	5	100	134.5 ± 7.2*	133.5 ± 24.2*	133.0 ± 16.2*
(+)-CM1	5	100	81.7 ± 14.9*	74.5 ± 21.8*	76.6 ± 19.3*
(±)-1	3	100	85.2 ± 17.4	79.8 ± 22.3	117.4 ± 13.5
(±)-2	5	100	87.5 ± 19.6	97.4 ± 32.2	137.2 ± 37.2*

[a] Test $*p < 0.05$, $**p < 0.01$, vs Control.
[b] P.A.: Prior Administration, A.A., After Administration.

Bruker-500. Mass spectra were obtained from Micromass ZAD-2F and VG300 instruments.

3.1. Synthesis of racemic CM1

3.1.1. (±)-2-Amino-1-phenylethanol (**5a**)

To a cold solution of 25% aqueous ammonia (750 mL, 11.3 mol) in methanol (200 mL), styrene oxide **3**(12 mL, 0.11 mol) was added. The mixture was sealed and kept at 4 °C for 15 days. The solution was concentrated to give a yellow oily residue (24.5 g). It was acidified to pH ≈ 1 with aqueous hydrochloric acid (100 mL, 2 mol/L) and extracted with CH_2Cl_2. The water layer was alkalized with aqueous NaOH solution (50 mL, 4 mol/L) to pH ≈ 12 and extracted with CH_2Cl_2 (50 mL × 6). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate and concentrated to give pale yellow oil (12.2 g). The residue was purified with flash chromatography on silica gel eluted with EtOAc/methanol/aqueous ammonia (200/6/7.5) to afford the title compound as pale yellow solid (3.52 g), yield: 66.5%, mp: 60–63 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81, 2.97(2H, ddd (AB part of an ABX system), J = 12.9, 7.8, 4.2 Hz, C_2H), 4.64(1H, dd (X part of an ABX system), J = 7.8, 4.2 Hz, C_1H), 7.23–7.37(5H, m, Ph-H).

3.1.2. (±)-N-(2-Hydroxy-2-phenylethyl)-3-phenyl-glycidyl amide (**7a**)

To a cold solution of **5a** (5.0 g, 34.6 mol) in methanol (18 mL), methyl 3-phenyl-glycidate **6** (12 mL, 0.11 mol) was added. After the reactants were dissolved, a solution of sodium methoxide in methanol (3 mol/L, 3 mL) was introduced. The mixture was sealed and kept at −20 °C for 7 days. The precipitate was filtered off by suction, washed with cold methanol, and recrystallized from ethanol to yield the title compound (6.44 g) as a white solid, yield: 62%, mp: 143–146 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (1H, d + d, J = 1.8 Hz), 3.37–3.47(1H, m), 3.67–3.80 (1H, m), 3.78,3.81(1H, d + d, J = 1.8 Hz), 4.89(1H, dd, J = 3.0,5.1 Hz), 7.22–7.42(10H, m, Ph-H). ESI-MS (*m*/*e*, %): 306(MNa^+, 80), 284 (MH^+, 30), 266(100).

3.1.3. (±)-N-(2-Oxo-2-phenylethyl)-3-phenyl-glycidyl amide (**8a**)

To a solution of **7a** (1.4 g, 5.0 mmol) in methylene chloride (52 mL), potassium permanganate powder (200 mesh, 2.34 g, 14.8 mmol) and copper sulfate powder (200 mesh, 1.18 g, 7.4 mmol) were added. The mixture was stirred at room temperature for 24 h and then filtrated with the aid of Celite. The filtrate was concentrated to give a pale yellow oil (900 mg). The oil was recrystallized from ethanol to give the title compound as a white solid (464 mg), yield: 34%, mp:140–143 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60(1H, d, J = 2.1 Hz), 4.04 (1H, d, J = 2.1 Hz), 4.83, 4.81(2H, AB part of an ABX system, J = 19.8, 5.1, 4.5 Hz), 7.23–8.01(11H, m, Ph-H and N–H). ESI-MS (*m*/*e*,%): 304(MNa^+, 100), 282(45).

3.1.4. Intramolecular cyclization of (±)-N-(2-oxo-2-phenylethyl)-3-phenyl-glycidyl amide (**8a**)

To a solution of **8a** (154 mg, 0.614 mmol) in methanol (4 mL) and water (2 mL), $LiOH\cdot H_2O$ (26 mg, 0.60 mmol) was added. The mixture was heated to 60 °C for 40 min. TLC analysis showed that the reactant had been consumed and complicated products formed. The mixture was cooled to room temperature, neutralized with diluted hydrochloric acid (2 mol/L), and concentrated under vacuum to remove methanol. The oily residue was dissolved in methylene dichloride (30 mL), washed with water and brine, dried over sodium sulfate, and concentrated to afford a pale yellow oil (142 mg). (±)-(3S*,4R*,5R*)-5-benzoyl-3-hydroxy-4-phenyl-pyrrolidin-2-one (demethyl-Clausenamidone, **9a**) (8 mg, yield: 5%) and (±)-(3S*,4R*,5S*)-5-benzoyl-3-hydroxy-4-phenylpyrrolidin-2-one (demethyl-Clausenamidone, **10a**) (56 mg, 36%) were finally separated by preparative thin-layer chromatography.

Compound **9a**: mp: 138–142 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (1H, dd, J = 9.3, 8.4 Hz), 4.74 (1H, d, J = 9.3 Hz), 5.76 (1H, d, J = 8.4 Hz), 6.96–7.66 (10H, m). FAB-MS (*m*/*e*,%): 282 (MH^+, 75), 176 (75), 148(40), 120 (85), 77(85), 91(55), 105(100); IR (KBr, cm^{-1}): 3372, 3213, 1701 1598, 1499,1452, 758, 698, 1231. ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 177.2, 135.6, 134.7, 133.4, 128.5, 128.4, 128.1, 128.0, 127.8, 72.7, 59.7, 52.8. HRMS (QFT-ESI): calculated for $C_{19}H_{16}N_1O_3$ (MH^+) 282.1125, found 282.1129.

Compound **10a**: mp: 211–215 °C, ^{1}H NMR (300 MHz, $CDCl_3$) 3.36 (1H, dd, J = 8.4, 8.1 Hz), 4.65 (1H,d, J = 8.4 Hz), 5.16 (1H, d, J = 8.1 Hz), 7.01–7.57(10H, m). ESI-MS (*m*/*e*,%): 563(2MH^+, 23), 282 (55), 158(100).

3.1.5. (±)-N-Benzyl-2-hydroxy-2-phenyl-ethylamine (**5b**)

The mixture of benzylamine **4b** (50 mL, 0.45 mol) and styrene oxide **3** (12 mL, 0.102 mol) was sealed and kept at room temperature for 7 days. The precipitated solid was collected by suction, washed with cold ether, and dried to afford title compound as a white solid (2.97 g), yield: 41%, mp 97–97 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70, 2.98 (2H, ddd (AB part of an ABX system), J = 12.6, 7.8, 4.2 Hz), 4.64 (1H, dd (X part of an ABX system), J = 7.8, 4.2 Hz), 7.24–7.37 (5H, m). ESI-MS (*m*/*e*, 100): 250(MNa^+, 17), 228(MH^+, 100), 210(82).

3.1.6. (±)-N-Benzyl-N-(2-hydroxy-2-phenylethyl)-3-phenyl-glycidyl amide (**7b**)

To a suspension of **5b** (7.45g, 32.8 mmol) and methyl 3-phenyl-glycidate **6** (6.42 g, 36.0 mol) in absolute methanol (18 mL), a solution of sodium methoxide in methanol (1.6 mol/L 12 mL) was added. The mixture was sealed and kept at −20 °C for 7 days. The precipitate was collected and washed with cold methanol to yield title compound as a white solid (31.21 g), yield: 66%. A sample was recrystallized from alcohol for analysis, mp: 158–159 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ 3.63, 3.95 (1H, d + d, J = 1.8 Hz), 4.07, 4.10 (1H, d + d, J = 1.8 Hz), 3.37–3.79 [2H, m (two AB part of ABX system)], 4.83–5.04 (1H, d + d (two X part of ABX system), J = 8.1, 3.0 Hz) 4.48–4.83 (2H, two AB system, J = 16.2 Hz, J = 14.1 Hz), 7.11–7.38 (15H, m). ESI-MS (*m*/*e*,%): 769 (2MNa^+, 45), 396 (MNa^+, 100), 374 (MH^+, 14).

3.1.7. (±)-N-Benzyl-N-(2-oxo-2-phenylethyl)-3-phenyl-glycidyl amide (**8b**)

To a solution of **7b** (18.2 g, 64.1 mmol) in methylene chloride (750 mL), potassium permanganate powder (30.3 g, 0.192 mol) and copper sulfate powder (15.4 g, 0.096 mol) were added. The mixture was stirred at room temperature for 12 h and then filtrated with the aid of Celite. The filtrate was concentrated to give a pale yellow oily residue (21.5 g), which was precipitated from ether, mp: 141–143 °C, yield: 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09, 4.14(1H, d + d, J = 1.2 Hz), 3.53, 3.79(1H, d + d, J = 1.2 Hz), 4.70, 4.77 and 4.78, 4.80 (2H, two AB system, J = 15.0, 18.6 Hz), 4.70, 4.97 and 4.70, 4.83 (2H, two AB system, J = 17.4 Hz, J = 17.1 Hz), 7.01(15H, m). ESI-MS (*m*/*e*,%): 394 (MNa^+, 46), 372(MH^+, 100).

3.1.8. (±)-(3S*,4R*,5R*)-5-Benzoyl-3-hydroxy-1-benzyl-4-phenylpyrrolidin-2-one (N-benzyl-demethyl-Clausenamidone, **9b**) and (±)-(3S*,4R*,5S*)-5-benzoyl-3-hydroxy-1-benzyl-4-phenylpyrrolidin-2-one (N-benzyl-demethyl-neoclausenamide, **10b**)

To a suspension of **8b** (7.00 g, 18.8 mmol) in methanol (250 mL) and water (170 mL), $LiOH\cdot H_2O$ (160 mg, 3.8 mmol) was added. The mixture was stirred at room temperature for 48 h. It was neutralized with diluted hydrochloric acid (2 mol/L), and concentrated under vacuum to remove methanol. The solid was collected by filtration, washed with water, and dried to give a white solid (6.88 g), which was separated by chromatography on silica gel (ethyl acetate/petroleum ether/methylene dichloride, 2/2/1) to give

compounds **9b** (2.66 g, 38% yield) and **10b** (2.52 g, 36% yield). 1.4 g of unseparated **9b** and **10b** was recovered.

Compound **9b**: mp: 182–185 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (1H, dd, J = 9.9, 5.7 Hz), 3.78, 5.19 (AB system, J = 15.0 Hz),5.06 (1H, d, J = 9.9 Hz), 5.20 (1H, d, J = 5.7 Hz), 6.99–7.46 (10H, m). FAB-MS (*m*/*e*, %): 372 (MH^+, 100) 266 (5), 105 (40), 91(50), 77(5). HRMS (QFT-ESI): calculated for $C_{24}H_{22}N_1O_3$ (MH^+) 372.1594, found 372.1598.

Compound **10b**: mp: 154–156 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27(1H, dd, J = 6.6 Hz, 6.3 Hz), 3.94, 5.33 (2H, AB system, J = 14.4 Hz), 4.52 (1H, d, J = 6.6 Hz), 4.84 (1H, d, J = 6.3 Hz), 7.01–7.50 (10H, m). FAB-MS (*m*/*e*,%): 372(MH^+, 100) 266 (10), 105 (30), 91(60), 77(5).

3.1.9. (±)-N-(4-Methoxybenzyl)-2-hydroxy-2-phenyl-ethylamine (**5c**)

Compound **5c** was obtained by a similar procedure used for the preparation of **5b** except using **4c** instead of **4b** as reactant. Yield 66%, mp: 107–109 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.74, 2.91 (2H, AB part of ABX system, J = 12.0, 8.7 Hz), 4.72(1H, X part of ABX system, J = 8.7H), 3.80 (5H, m), 6.85–7.32 (9H, m). ESI-MS (*m*/*e*,100): 280 (MNa^+, 8), 258(MH^+,90), 121(100). HRMS (QFT-ESI): calculated for $C_{16}H_{20}N_1O_2$ (MH^+) 258.1488, found 258.1490.

3.1.10. (±)-N-(4-Methoxybenzyl)-N-(2-hydroxy-2-phenylethyl)-3-phenyl-glycidyl amide (**7c**)

Compound **7c** was obtained by a similar procedure used for the preparation of **7b** except using **5c** instead of **5b** as reactant. Yield: 86%. A sample was recrystallized from alcohol for analysis. mp: 142–146 °C ^{1}H NMR(300 MHz, $CDCl_3$), δ 3.41, 3.54 (1H, d + d, J = 1.8 Hz), 3.92, 4.07(1H, d + d, J = 1.8 Hz), 3.37–4.09(2H, two AB part of ABX system) 5.10, 4.81(1H, two X part of ABX system) 4.51, 4.67 (2H, two ABX system, J = 16.2 Hz, J = 14.1 Hz), 3.77, 3.80(3H, s + s). 6.80–7.36(15H, m), ESI-MS (*m*/*e*,100): 426(MNa^+,100), 404 (MH^+,50), 386(15). HRMS (QFT-ESI): calculated for $C_{25}H_{26}N_1O_4$ (MH^+) 404.1856, found 404.1859.

3.1.11. (±)-N-(4-Methoxybenzyl)-N-(2-oxo-2-phenylethyl)-3-phenyl-glycidyl amide (**8c**)

Compound **8c** was obtained by a similar procedure used for the preparation of **8b** except using **7c** instead of **7b** as reactant. Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50, 3.88 (1H, d + d, J = 1.8 Hz), 4.00, 4.08 (1H, d + d, J = 1.8 Hz), 4.77, 4.62 and 5.68, 4.64 (2H, two AB system, J = 16.5 Hz, J = 15.0 Hz), 4.95, 5.68 and 5.57, 5.64(2H, two AB system, J = 18.0 Hz, J = 22.5 Hz), 3.79 (3H, s), 6.80–7.31(14H, m). ESI-MS (*m*/*e*,100): 424(MNa^+,18), 402(MH^+,100). HRMS (QFT-ESI): calculated for $C_{25}H_{24}N_1O_4$ (MH^+) 402.1700, found 404.702.

3.1.12. (±)-(3S*,4R*,5R*)-5-Benzoyl-3-hydroxy-1-(4-methoxybenzyl)-4-phenylpyrrolidin-2-one (N-(4-methoxybenzyl)-demethyl-Clausenamidone, **9c**) and (±)-(3S*,4R*,5S*)-5-benzoyl-3-hydroxy-1-(4-methoxybenzyl)-4-phenylpyrrolidin-2-one (N-(4-methoxybenzyl)-demethyl-neoclausenamide, **10c**)

To a solution of **8c** (2.48 g, 6.17 mmol) in methanol (40 mL) and water (5 mL), $LiOH\cdot H_2O$ (52 mg, 1.24 mmol) was added. The mixture was stirred at room temperature for 25 min, and then neutralized with diluted hydrochloric acid (2 mol/L), concentrated under vacuum to remove methanol. The residue was dissolved in methylene dichloride (60 mL), washed with water, dried over sodium sulfate, and concentrated for chromatography on silica gel (ethyl acetate/petroleum ether/methylene dichloride, 2/2/1). Compounds **9c** (1.05 g, 42% yield) and **10c** (1.10 g, 45% yield) were obtained.

Compound **9c**: mp: 152–154 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (1H, dd, J = 10.8, 8.7 Hz) 3.76, 5.19 (2H, AB system, J = 14.4 Hz) 5.04 (1H, d, J = 10.8 Hz) 5.16 (1H, d, J = 8.7 Hz) 6.80–7.39 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ197.9, 174.9, 174.7, 159.4, 133.3, 130.2, 128.4, 128.3, 128.1, 127.9, 127.7, 114.2, 71.8, 61.2, 55.2, 51.2, 54.7. ESI-MS (*m*/*z*, 100) 475 (MNa^+, 30), 402 (MH^+, 100). HRMS (QFT-ESI): calculated for $C_{25}H_{23}Na_1N_1O_4$ (MNa^+) 424.1519, found 424.1525.

Compound **10c**: mp: 155–157 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25(1H, dd, J = 6.3, 6.3 Hz) 3.75 (3H, s) 3.81, 5.25 (2H, AB system, J = 14.4 Hz), 4.49 (1H, d, J = 6.3 Hz) 4.83 (1H, d, J = 6.3 Hz) 6.73–7.51 (10H, m, Ph-H). ESI-MS (*m*/*z*, 100) 475(MNa^+,22), 402(MH^+,100). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 175.4, 159.5, 136.5, 134.1, 133.5, 130.4, 128.5, 128.3, 128.0, 127.8, 126.9, 72.0, 61.4, 53.4, 55.4, 51.3, 45.8. ESI-MS (*m*/*z*,100) 475 (MNa^+, 24), 402(MH^+, 100). HRMS (QFT-ESI): Calculated for $C_{25}H_{23}Na_1N_1O_4$ (MNa^+) 424.1519, found 424.1524.

3.1.13. (±)-(3S*,4R*,5R*)-5-Benzoyl-3-hydroxy-4-phenylpyrrolidin-2-one (demethyl-Clausenamidone, **9a**)

To a solution of **9c** (515 mg, 1.33 mmol) in acetonitrile (18 mL) and water (6 mL), cerium ammonium nitrate (2.90 g, 5.29 mmol) was added. After stirring at room temperature for 25 min, the mixture was poured into water (150 mL) and extracted with ethyl acetate (40 mL × 4). The organic phase was washed with sat. aq. sodium bicarbonate (20 mL × 2), dried over sodium sulfate, and concentrated to give a filemot oil (422 mg). The crude oil was purified by chromatography on silica gel (methylene dichloride/methanol, 100/1) to afford a white solid (287 mg, 77%), mp: 149–152 °C. The ^{1}H NMR and MS data were identical with that of compound **9a** prepared from **8a**.

3.1.14. (±)-(3S*,4R*,5R*)-3-Hydroxy-5-((S*)-hydroxy(phenyl)methyl)-4-phenylpyrrolidin-2-one (demethyl-Clausenamide, **11**)

To a solution of **9a** (120 mg, 0.427 mmol) in methanol (10 mL), sodium borohydride (48 mg, 1.28 mol) was added. The reaction mixture was stirred at room temperature for 30 min, and then acidified with dilute hydrochloric acid to pH 3–4. The mixture was concentrated in vacuum to remove methanol. The residue was dissolved with methylene dichloride (40 mL), washed with water, dried over sodium sulfate, and concentrated for chromatography on silica gel (methylene dichloride/methanol, 100/2.5) to afford the title compound (117 mg), yield 96%, mp: 199–201 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (1H, dd, J = 9.9, 8.1 Hz), 3.78(1H, d, J = 9.9 Hz), 4.42(1H, dd, J = 8.1, 3.3 Hz), 4.62(1H, d, J = 3.3 Hz), 6.78–7.33(10H, m); CI-MS (*m*/*e*,%): 284 (MH^+, 68), 266(12), 177(15), 109(74). IR (KBr, cm^{-1}): 3393, 3052, 1703, 1602, 1495,1456, 1264, 1136, 1042, 754, 700. ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 140.8, 136.8, 128.5, 127.8, 127.6, 127.1, 127.0, 126.3, 72.4, 68.6, 59.0, 49.4. HRMS (QFT-ESI): calculated for $C_{17}H_{18}N_1O_3$ (MH^+) 284.1281.1700, found 284.1286.

3.2. Synthesis of Piracetam analogue 1, Nefiracetam analogue 2

3.2.1. (±)-(3S*,4R*,5R*)-4-Phenyl-5-((1S*)-phenyl(tetrahydro-2H-pyran-2-yloxy)methyl)-3-(tetrahydro-2H-pyran-2-yloxy) pyrrolidin-2-one (3,6-di-O-tetrahydropyranyl-demethyl-Clausenamide, **12**)

A mixture of demethyl-Clausenamide **11** (443 mg, 1.5 mmol), 3,4-dihydropyran (280 mg, 4.5 mmol) and pyridinium p-toluenesulonate (38 mg, 0.15 mmol) in methylene dichloride (10 mL) was stirred at room temperature overnight. The mixture was then diluted with methylene dichloride (10 mL), washed with aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated to give the title compound as a mixture of diastereomers (0.51 g,), yield: 90%, mp: 181–187 °C. ESI-MS (*m*/*e*,%): 474 (MNa^+, 100), 452 (MH^+, 33).

3.2.2. (±)-Ethyl 2-((3S*,4R*,5R*)-3-hydroxy-5-((S*)-hydroxy(phenyl)methyl)-2-oxo-4-phenyl pyrrolidin-1-yl)acetate (N-ethoxycarbonyl-methyl-demethyl-Clausenamide, **13**)

To a solution of **12** (120 mg, 0.266 mol) in anhydrous benzene (5 mL), sodium hydride (21 mg) was added. The mixture was

refluxed for half an hour. After cooling to room temperature, a solution of ethyl bromoacetate (66 mg) in dried benzene (5 mL) was added. The mixture was heated at 60 °C for 20 min and then cooled to room temperature, followed by the addition of water (3 mL) and neutralization with hydrochloric acid (2 N). The resulted mixture was extracted with methylene chloride. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated to an oily product.

To the alcoholic solution (5 mL) of the oily product, *p*-toluenesulfonic acid (10 mg) was added. The mixture was heated at 60 °C overnight. It was then concentrated for column chromatography (methylene dichloride/methanol, 100/1) to obtain the oily title compound (79 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) 1.27(3H, t, J = 7.2 Hz), 3.85 (1H, dd, J = 11.1, 8.4 Hz), 4.03, 4.39 (2H, AB system, J = 18.0 Hz), 4.24 (1H, d, J = 11.1 Hz), 4.22 (2H, q, J = 7.2 Hz), 4.43(1H, dd, J = 8.4, 3.6 Hz), 4.78 (1H, d, J = 3.6 Hz), 6.76–7.31 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 175.6, 169.26, 138.6, 134.5, 128.5, 128.4, 128.1, 128.0, 127.3, 126.9, 73.5, 69.2, 64.5, 61.7, 50.0, 44.8, 14.1. FAB-MS (*m*/*e*, %) 370(MH^+, 52), 352(83), 334(12), 324(17), 278 (35), 105 (64), 91(100), 77(25). HRMS (QFT-ESI): calculated for $C_{21}H_{24}N_1O_5$ (MH^+) 370.1649, found 370.1650.

3.2.3. (±)-N-(2,6-Dimethylphenyl)-2-((3S*,4R*,5R*)-3-hydroxy-5-((S*)-hydroxy(phenyl)methyl)-2-oxo-4-phenylpyrrolidin-1-yl) acetamide {N-[N-(2,6-dimethylphenyl)-aminocarbonyl-methyl]-demethyl-Clausenamide, 2}

Compound **2** was prepared as described for compound **13**, with 2-bromo-N-(2,6-dimethylphenyl)acetamide instead of ethyl bromoacetate as the alkylating agent. mp: 242–245 °C, yield:51%, ^{1}H NMR(500 MHz, DMSO-d_6): 3.64 (1H, dd, J = 11.5, 8.5 Hz), 3.92 (1H, d, J = 11.5 Hz), 4.47 (1H, dd, J = 8.4, 2.5 Hz) 4.69(1H, d, J = 2.5 Hz), 4.32, 4.62(2H, AB system, J = 16.5 Hz) 6.67–7.25(13H, m) 9.44(1H, s, exchangeable), 2.20 (6H, s). ^{13}C NMR (100 MHz, CD_3COOD) δ 177.3, 169.0, 140.5, 136.4, 136.1, 134.6, 129.3, 128.7, 128.6, 128.3, 128.1, 128.0, 127.5, 73.9, 70.1, 65.4, 50.5, 46.5. FAB-MS (*m*/*e*,%) 445 (MH^+, 93), 427 (26), 91(100). HRMS (QFT-ESI): calculated for $C_{27}H_{29}N_2O_4$ (MH^+) 445.2122, found 445.2125.

3.2.4. (±)-2-((3S*,4R*,5R*)-3-Hydroxy-5-((S*)-hydroxy(phenyl) methyl)-2-oxo-4-phenyl pyrrolidin-1-yl) acetamide [N-(aminocarbonyl-methyl)-demethyl-Clausenamide, 1]

Compound **13** (100 mg, 0.252 mmol) was treated with NH_3/CH_3OH (10 mL) overnight, then the mixture was concentrated for column chromatography (methylene dichloride/methanol, 100/2) to obtain the title compound as a white solid (40 mg). mp: 146–148 °C, yield 72%. ^{1}H NMR (300 MHz, DMSO-d_6) 4.07, 4.32 (2H, AB system, J = 5 Hz), 3.61 (1H, dd, J = 11.0, 8.5 Hz), 3.89 (1H, dd, J = 11.0, 6.5 Hz), 4.01 (1H, dd, J = 8.5, 2.0 Hz), 4.63 (1H, s) 5.45 (1H, d, J = 6.5 Hz, exchangeable), 5.60 (1H, d, J = 4.0 Hz, exchangeable), 6.62–7.24 (10H, m), 7.47, 7.49(2H, 2× d, J = 2.0 Hz, exchangeable). FAB-MS (*m*/*e*, %) 341 (MH^+, 8), 284(20). ^{13}C NMR (100 MHz, CD_3COOD) δ 177.3, 172.6, 140.4, 136.1, 129.3, 128.7, 128.2, 128.1,127.9,127.4, 73.8, 70.0, 65.2, 50.5, 46.0. HRMS (QFT-ESI): calculated for $C_{19}H_{21}N_2O_4$ (MH^+) 341.1496, found 341.1500.

3.3. Synthesis of racemic and optical active CM1

3.3.1. (±)-(3S*,4R*,5R*)-3-Hydroxy-5-((S*)-hydroxy(phenyl) methyl)-1-(hydroxymethyl)-4-phenyl-pyrrolidin-2-one (CM1)

To a solution of demethyl-Clausenamide **11** (67 mg, 0.24 mmol) in acetone (2.5 mL) and a drop of water, formaldehyde (11 mg, 0.37 mmol) and K_2CO_3 (3 mg, 0.09 mmol) were added. The mixture was heated at 60 °C for 25 min and then quickly cooled to room temperature with ice and water. Then the mixture was concentrated for column chromatography (CH_2Cl_2/CH_3OH 100/2) to obtain the title compound as a white solid (54 mg). Yield 73%, mp: 199–201 °C, ^{1}H NMR (300 MHz, CD_3COCD_3) δ 3.58(1H dd J = 11.7, 8.4 Hz), 3.82(1H, d, J = 11.7), 4.58 (1H, dd, J = 8.4, 2.7 Hz), 4.69 (1H, d, J = 2.7 Hz), 5.10, 5.15(2H, AB system), 6.67–7.25(10H, m). ^{13}C NMR (100 MHz, Acetone-d_6) δ 176.8, 141.7, 137.9, 129.5, 128.9, 128.6, 128.4, 128.2, 127.5, 73.9, 70.5, 60.5, 51.0. FAB-MS (*m*/*e*,%): 314 (MH^+, 98), 296(100), 284(20), 266(20). IR (KBr, cm^{-1}): 3456, 3348, 3028, 1703, 1475, 1447, 1265, 1151, 1061, 1016, 756, 747, 693. Element Analysis: $C_{18}H_{19}N_1O_4$ Found C: 68.81, 68.75, H: 5.81, 6.01 N: 4.66, 4.52 for C: 68.88, H: 6.11, N: 4.47. HRMS (QFT-ESI): calculated for $C_{18}H_{20}N_1O_4$ (MH^+) 314.1399, found 314.1387.

3.3.2. (−)-(3S,4R,5R)-5-Benzoyl-3-(phthalyl-L-alanyloxy)-1-(4-methoxybenzyl)-4-phenylpyrrolidin-2-one (**14a**) and (+)-(3R,4S,5S)-5-benzoyl-3-(phthalyl-L-alanyloxy)-1-(4-methoxybenzyl)-4-phenylpyrrolidin-2-one (**14b**)

(1) To a stirred solution of the phthalyl-L-alanine (1.71 g, 7.78 mmol) in toluene (20 mL) was added thionyl chloride (3.71g, 31.2 mmol) at room temperature. The mixture was heated to reflux for 2 h and then cooled to room temperature. It was concentrated *in vacuo* to afford the phthalyl-L-alanyl chloride as pale-yellow oil.

(2) To a stirred solution of **9c** (2.60 g, 6.49 mmol) in methylene chloride (20 mL) was added a solution of phthalyl-L-alanyl chloride in methylene chloride (20 mL) in one portion. The mixture was cooled to 0 °C, a solution of dried pyridine (0.77 g, 9.47 mmol) in methylene chloride (20 mL) was added dropwise. The resultant mixture was allowed to warm to room temperature and stirred for 3 h. Water (40 mL) was added to quench the reaction. The aqueous layer was separated and extracted with dichloromethane (10 mL). The combined organic extracts were washed with dilute hydrochloric acid (2 mol/L), sat. aq. sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford the title compounds mixture as a pale yellow oily residue (4.35 g), crude yield 96%. It was recrystallized from ethyl acetate twice to provide 789 mg (18%) of (3S,4R,5R)-**14a**, mp: 173–175 °C,$[\alpha]_D^{25}$ = −175 (*c*, 0.460,$CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65(3H, d, J = 7.2 Hz), 3.73 (3H, s), 3.81(1H, dd, J = 8.7, 8.7 Hz), 3.84, 5.09 (2H, AB system, J = 16.2 Hz), 5.07 (1H, d, J = 8.7 Hz), 5.01–5.12(1H, m), 6.06 (1H, d, J = 8.7 Hz), 6.67–7.76 (18H, m). ^{13}C NMR(100 MHz, $CDCl_3$) δ 197.0, 169.9, 168.7, 166.9, 159.2, 136.0, 134.0, 133.4, 132.8, 131.7, 130.2, 128.3, 128.2, 127.8, 126.6, 123.4, 114.0, 74.4, 61.3, 55.1, 48.3, 47.3, 45.7, 15.5. ESI-MS (*m*/*e*, %): 603(MH^+, 100). HRMS (QFT-ESI): calculated for $C_{36}H_{31}N_2O_7$ (MH^+) 603.2126, found 603.2129.

3.3.3. (−)-(3S,4R,5R)-5-Benzoyl-3-(phthalyl-L-alanyloxy)-4-phenylpyrrolidin-2-one (**15a**) and (+)-(3R,4S,5S)-5-benzoyl-3-(phthalyl-L-alanyloxy)-4-phenylpyrrolidin-2-one (**15b**)

The crude mixture of **15a** and **15b** was obtained by a similar procedure used for the preparation of **9a** except using the mixture of **14a** and **14b** instead of **9c** as reactant. Crude yield: 86%, the crude products were purified by chromatography on silica gel (methylene dichloride/ethyl acetate, 4/1). Compounds **15a** (30% yield) and **15b** (30% yield) were obtained, respectively. 20% was recovered as a mixture of **15a** and **15b**.

Compound **15a**: mp: 186–188 °C, ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.69 (3H, d, J = 7.2 Hz), 4.15(1H, dd, J = 6.6, 2.1 Hz), 5.08(1H, q, J = 7.2 Hz), 5.27(1H, d, J = 2.1 Hz), 5.41(1H, d, J = 6.6 Hz), 6.39(1H, s), 6.88–7.88(14H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 171.9, 168.9, 167.0, 135.3, 134.3, 134.1, 133.4, 131.7, 128.3, 128.3, 127.9, 127.8, 127.7, 123.5, 76.5, 60.6, 49.8, 47.4, 15.2. ESI-MS (*m*/*e*,%): 505 (MNa^+, 60),

483 (MH^+, 100). HRMS (QFT-ESI): calculated for $C_{28}H_{22}N_2Na_1O_6$ (MNa^+) 505.1370, found 505.1376.

Compound **15b**: mp: 213–216 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (3H, dd, J = 7.2 Hz), 3.57(1H, dd, J = 6.6, 6.3 Hz), 5.00(1H, q, J = 7.2 Hz), 5.15(1H, d, J = 6.3 Hz), 5.51(1H, d, J = 6.6 Hz), 6.89–7.82 (14H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ195.3, 171.0, 169.2, 167.2, 134.9, 134.5, 133.8, 131.8, 128.7, 128.6, 127.9, 127.8, 123.6, 78.3, 62.1, 50.4, 47.4, 15.8. ESI-MS (*m/e*,%): 505(MNa^+, 63), 483 (MH^+, 100). HRMS (QFT-ESI): calculated for $C_{28}H_{22}N_2Na_1O_6$ (MNa^+) 505.1370, found 505.1376.

3.3.4. (+)-(3S,4R,5R)-3-Hydroxy-5-((S)-hydroxy(phenyl)methyl)-4-phenylpyrrolidin-2-one (demethyl-Clausenamide, (+)-**11**)

To a solution of **15b** (565 mg, 1.17 mmol) in methanol (6 mL) and methylene chloride (4 mL), sodium borohydride (67 mg, 1.757 mol) was added. The reaction mixture was stirred at room temperature for 30 min. Sodium hydroxide (187 mg, 4.684 mmol) was added. The mixture was stirred overnight, neutralized with diluted hydrochloric acid (2 mol/L), concentrated in vacuum to remove methanol and methylene chloride. The residue was dissolved with methylene dichloride (60 mL), washed with water and brine, dried over sodium sulfate, and concentrated for chromatography on silica gel (methylene dichloride/methanol, 100/2.5) to afford the title compound (247 mg), which showed the same Rf value and ^{1}H NMR as racemic **11**, yield 74%, mp: 204–207 °C, $[\alpha]_D^{15} = +140°$ (c = 0.419, methanol).

3.3.5. (−)-(3R,4S,5S)-3-Hydroxy-5-((R)-hydroxy(phenyl)methyl)-4-phenylpyrrolidin-2-one (demethyl-Clausenamide, (−)-11)

Compound (−)-**11** was obtained by a similar procedure used for the preparation of (+)-**11**. Treatment of compound **15a** (250 mg, 0.52 mmol) with sodium borohydride (30 mg, 0.78 mmol), and sodium borohydride (83 mg, 2.08 mol) gave compound (−)-**11** (87 mg, 60% yield) as a white solid, which showed the same Rf value and ^{1}H NMR as racemic **11**. mp: 203–205 °C, $[\alpha]_D^{15} = -144°$ (c = 0.497, methanol).

3.3.6. (−)-(3S,4R,5R)-3-Hydroxy-5-((S)-hydroxy(phenyl)methyl)-1-(hydroxymethyl)-4-phenylpyrrolidin-2-one [(−)-CM1]

Compound (−)-CM1 was obtained with the same procedure as described for racemic CM1. Treatment of (−)-**11** (78 mg, 0.28 mmol) with formaldehyde (13 mg, 0.43 mmol) and K_2CO_3 (4 mg, 0.12 mmol) gave compound (−)-CM1 (54 mg, 64% yield) as a white solid, which showed the same Rf value and ^{1}H NMR as racemic CM1. mp: 191–193 °C, $[\alpha]_D^{18} = -119°$ (c = 0.261,CH_3OH).

3.3.7. (+)-(3R,4S,5S)-3-hydroxy-5-((R)-hydroxy(phenyl)methyl)-1-(hydroxymethyl)-4-phenylpyrrolidin-2-one ((+)-CM1)

Compound (+)-CM1 was obtained by a similar procedure to that used for racemic CM1. Treatment of (+)-**11** (78 mg, 0.50 mmol) with formaldehyde (23 mg, 0.77 mmol) and K_2CO_3 (7 mg, 0.21 mmol) gave compound (+)-CM1 (90 mg, 58% yield) as a white solid, which showed the same Rf value and ^{1}H NMR as racemic CM1. mp: 189–191 °C, $[\alpha]_D^{18} = +117°$ (c = 0.394, CH_3OH).

Acknowledgments

We are grateful to the National Natural Science Foundation of China for financial supports and to professor Jun-Tian Zhang and the group of the neouropharmacological laboratory for affording LTP assay data.

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