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Laboratory note

An elegant synthesis of Zetaclausenamide

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Abstract

Zetaclausenamide, which was isolated as a hepatoprotective agent from the leaves of medicinal plant *Clausena lansium*, was synthesized for the first time in six steps including Darzen's condensation, photoisomerization, and the final cyclization reactions.

Keywords: Zetaclausenamide; *Clausena lansium*; Darzen's condensation; Photoisomerization; Cyclization

1. Introduction

The medicinal plant *Clausena lansium* is locally produced in the south-west Yunnan province in China [1]. The aqueous extract of it's leaves has often been used in Chinese folk medicine as an effective means for protecting the liver and been administered against acute and chronic viral hepatitis [1,2]. These attracted chemical researchers to study it's chemical components in detail. As a result, Zetaclausenamide **1** and Clausenamide **2**, along with other five amides, were isolated [1–5]. The initial pharmacological study showed that both **1** and **2** have hepatoprotective activity against chemical toxins, such as carbon tetrachloride and thioacetamide, and have inducing effect on cytochrome P450, which is essential for the metabolisation of xenobiotics [2,4].

Further pharmacological studies required larger amounts of Zetaclausenamide **1** than can be obtained by the complicated extraction process. It is therefore necessary to provide a chemical process which facilitates the preparation of **1**. The total synthesis of Clausenamide **2** has attracted much attention, and several synthetic routes were reported [6–10]. We have not found any other literature regarding the synthesis of Zetaclausenamide **1**, except for our earlier report [11] as a summary. It is usually much more difficult to construct eight-membered ring than to construct five- or six-membered ring. The study of the synthesis of Zetaclausenamide **1** would be helpful in designing and synthesizing different eight-membered ring products.

2. Results and discussion

Zetaclausenamide **1** is a ζ-lactam. It has similar molecular formula as that of Clausenamide **2**, but different skeleton. From compound **6**, our lab has successfully fulfilled the total syntheses of **2** and dehydroclausamide, another product of the seven amides, by an elegant base induced cyclization (Fig. 1) [8,12]. Opening the α,β-epoxide of compound **6** to construct the α-hydroxy and β-phenyl of **2** indeed gave a useful clue in designing the synthesis of **1**. Based upon it and the retro-analysis of **1** (Fig. 1), compound **5** was designed as the key intermediate to prepare **1**. To convert the trans-double bond of **5** to cis is necessarily important. Photochemical condition needs to be carefully controlled in case of destroying the epoxide group.

As shown in Scheme 1, the key intermediate **5** can be obtained by straightforward reactions. 2-Phenylethanol **7** was oxidized with potassium dichromate using phase transfer reaction [13] to afford aldehyde **8** [14]. The reaction of phenylacetaldehyde **8** with methylamine proved troublesome.

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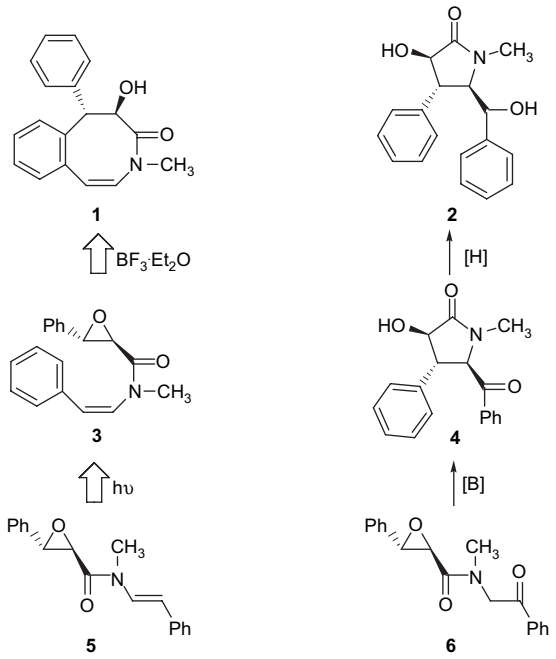
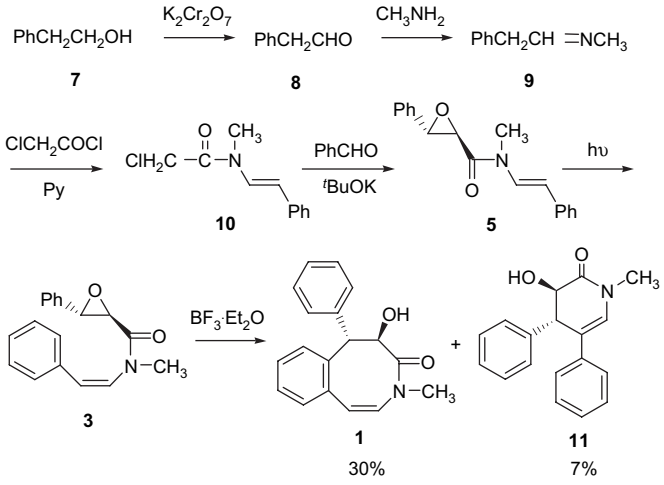


Fig. 1. Retro-analysis.

It's product **9** is unstable and is readily polymerized at room temperature [15]. So the reaction was conducted at low temperature (0–5 °C) and **9** was not isolated and treated directly with chloroacetyl chloride with pyridine as the base to afford desired 2-chloro-*N*-methyl-*N*-(2-(*E*)-phenylethenyl)-acetamide **10** in a poor 29% yield. After the reaction of aldehyde **8** with methylamine, it was dried with KOH at 0–5 °C. Possibly, the drying time is too long (~8 h), leaving more of **9** polymerized. The trans-ene conformation of **10** was determined by the $J_{H1,2} = 14.4$ Hz. The Darzen's condensation [16] of benzaldehyde with **10** occurred smoothly in toluene at 0–5 °C with potassium *tert*-butoxide as the base to afford trans-epoxide, *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-trans-oxiranecarboxamide **5** ($J_{H\alpha,\beta} = 2.2$ Hz) in 87% yield. Owing to the rotation hindrance of the molecules, the protons (NCH_3, CH-α) of **10** and (NCH_3) of **5** show two singlets, and



Scheme 1.

the protons (CH-2) of **10** and (CH-α, CH-β, CH-2) of **5** show two doublets in the ^{1}H NMR spectrum.

The photoisomerization [17] of compound **5** was conducted in degassed anhydrous benzene. The solution of **5** in benzene was irradiated with 450 W medium-pressure mercury lamp through a 0.1 M $SnCl_2$/concentrated hydrochloride filter ($\lambda > 300$ nm). There is equilibrium established in this reaction, and product **3** ($J_{H1,2} = 8.7$ Hz) was obtained in 50% yield based on 67% conversion. Conducting the reaction at $\lambda > 300$ nm is very important. Without the filter, the TLC of the reaction was complex, and no desired **3** was obtained.

The cyclization of **3** was conducted in anhydrous dichloromethane under the presence of boron trifluoride-diethyl etherate at room temperature to afford the desired Zetaclausenamide **1** in 30% yield. It's melting point (186–189 °C), IR, MS and ^{1}H NMR are identical with those of the naturally isolated Zetaclausenamide [4]. In addition, Homoclausenamide **11** was also isolated in 7% yield, which is another product of the seven natural amides. The cyclization condition was not optimized. Except for the above two products, several traces of different compounds were obtained, and their structures were not identified.

3. Conclusion

Zetaclausenamide was prepared in a very short way in 2.8% overall yield. The Darzen's condensation of *N*,*N*-disubstituted chloroacetamide with benzaldehyde and the olefin photoisomerization reactions play crucial roles during this process.

4. Experimental

4.1. General

Melting points were measured with a YANACO MP-500 apparatus and were not corrected. IR spectra were recorded on a Perkin–Elmer 399B spectrometer (KBr disk). Mass spectra (electron impact) were obtained on a ZAB-2F, MAT711 instrument. ^{1}H NMR spectra were recorded on a JEOL FX-90Q (90 MHz) spectrometer using TMS as internal standard. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. Column chromatography was performed using silica gel H. 450 W Hamonia medium-pressure mercury lamp was used for the photoisomerization. Anhydrous solvents (dichloromethane, benzene and toluene) were dried and distilled from P_2O_5; $BF_3 \cdot Et_2O$ was distilled from CaH_2 and related anhydrous reactions were conducted under dried $N_2/CaCl_2$.

4.1.1. Synthesis of compound *10*

Into a separatory funnel (3000 ml) containing a solution of potassium dichromate (36.2 g, 0.123 mol) in 9 M sulfuric acid (750 ml) was added the solution of **7** (36.7 ml, 0.30 mol) and tetra-*n*-butylammonium bisulfate (9.0 g, 0.27 mol) in dichloromethane (750 ml). It was shaken vigorously until no more heat was exited. The organic phase was separated and the aqueous layer was extracted with diethyl ether. The combined organic phase was washed with brine, dried (Na_2SO_4) and

concentrated to the volume of ~60 ml. Gaseous-mass spectrometer analysis shows 73% of **8** formed.

To the solution of methanamine in dichloromethane (175 ml, 7.1% g/ml, 0.40 mol) was added dropwise the above aldehyde solution at 0–5 °C. After the addition, it was stirred for 20 min, followed by addition of potassium hydroxide (12.0 g, 0.21 mol) and saturated aqueous sodium chloride (50 ml). After being vigorously stirred at 0–5 °C for 20 min, the organic layer was separated, dried with potassium hydroxide at 0 °C (8 h) and decanted for the following reaction.

The above solution was diluted with anhydrous dichloromethane (100 ml) and pyridine (42.2 ml, 0.30 mol) was added. It was cooled to 0–5 °C, and a solution of 2-chloroacetyl chloride (36.6 ml, 0.45 mol) in anhydrous dichloromethane (50 ml) was added dropwise under stirring. After the addition, it was allowed to warm to room temperature and stirred for 10 h. It was washed with water and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated for chromatography using petroleum ether (bp: 30–60 °C) and diethyl ether (2:1) as the eluent to afford **10** (17.1 g, 29% from **8**); m.p.: 77–79 °C. ^{1}H NMR (90 MHz, $CDCl_3$): δ ppm: 3.26 and 3.30 (s, 3H, NCH_3), 4.20 and 4.26 (s, 2H, CH_2CO), 6.04 and 6.08 (d, $J = 14.4$ Hz, 1H, =CH–Ph), 7.10–7.60 (m, 6H, H-Ar and N–CH=). MS *m/z* (%): 211 (33) and 209 (M^+, 100), 174 (24), 133 (83), 132 (46), 117 (61), 91 (72), 90 (80), 77 (17), 42 (33). Anal. $C_{11}H_{12}ClNO$ (C, H, N).

4.1.2. Synthesis of compound 5

To the solution of benzaldehyde (1.07 g, 99%, 10.0 mmol) and compound **10** (2.10 g, 10.0 mmol) in anhydrous toluene (150 ml) was added dropwise the solution of potassium *tert*-butoxide (prepared from potassium and *tert*-butyl alcohol) in *tert*-butyl alcohol (11.20 g, 3.8% g/g, 11.0 mmol) at 5–10 °C. After the addition, it was stirred for 1 h at the same temperature, then it was diluted with diethyl ether (200 ml) and washed with water. The aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated for recrystallization (dichloromethane/diethyl ether) to afford **5** (2.26 g). The mother solution was concentrated for column chromatography using petroleum ether (bp: 30–60 °C) and EtOAc (5:1) as the eluent to afford more of **5** (160 mg, overall yield 87%); m.p.: 103–105 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 3.29 and 3.32 (s, 3H, NCH_3), 3.75 and 3.77 (d, $J = 2.2$ Hz, 1H, Ph–CH), 4.09 and 4.13 (d, $J = 2.2$ Hz, 1H, CH–CO), 6.02 and 6.08 (d, $J = 14.4$ Hz, 1H, =CH–Ph), 7.00–7.60 (m, 11H, H-Ar and N–CH=). MS *m/z* (%): 280 ($M^+ + 1$, 6), 279 (M^+, 30), 193 (18), 173 (20), 144 (65), 133 (52), 132 (28), 117 (30), 91 (100). Anal. $C_{18}H_{17}NO_2$ (C, H, N).

4.1.3. Synthesis of compound 3

Into a cylindrical and jacketed quart reaction vessel (500 ml) with a solution of $SnCl_2$ in concentrated hydrochloride (0.1 M) in it's jacket was added the solution of compound **5** (1.05 g, 3.76 mmol) in anhydrous benzene (250 ml). It was degassed and irradiated with 450 W Hamonia medium-pressure mercury lamp from outside under nitrogen while stirring. The reaction vessel was cooled with strong air gun and the irradiation was stopped after 30 min to let the reaction solution to cool. It was then irradiated for another 30 min. This process was repeated and the reaction was monitored by TLC till no more starting material was obviously reacted (4 h). It was cooled and concentrated for column chromatography using petroleum ether (bp: 30–60 °C) and EtOAc (3:1) as the eluent to afford unreacted **5** (350 mg, 33% recovered) and **3** (350 mg, 50% based on 67% conversion); m.p.: 115–118 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 3.12 (s, 3H, NCH_3), 3.75 (d, $J = 1.4$ Hz, 1H, Ph–CH), 3.81 (d, $J = 1.4$ Hz, 1H, CH–CO), 6.19 (d, $J = 8.6$ Hz, 1H, =CH–Ph), 6.35 (d, $J = 8.6$ Hz, 1H, N–CH=), 6.90–7.40 (m, 10H, H-Ar). MS *m/z* (%): 280 ($M^+ + 1$, 25), 279 (M^+, 8), 193 (14), 173 (22), 144 (41), 133 (38), 132 (21), 117 (23), 103 (24), 91 (100). Anal. $C_{18}H_{17}NO_2$ (C, H, N).

4.1.4. Synthesis of Zetaclausenamide 1

To the solution of compound **3** (250 mg, 0.9 mmol) in anhydrous dichloromethane (25 ml) was added dropwise the solution of boron trifluoride-diethyl etherate (136 μl, 1.1 mmol) in anhydrous dichloromethane (2 ml) at room temperature while stirring. After the addition, the reaction was continued for 30 min. Then it was diluted with diethyl ether (100 ml), washed with water, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated for chromatography using petroleum ether (bp: 30–60 °C) and EtOAc (1:1) as the eluent, the so obtained main products were concentrated for chromatography again using dichloromethane and methanol (100:1.25) as the eluent to afford Zetaclausenamide **1** (74 mg, 30%); m.p.: 187–189 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 2.92 (s, 3H, NCH_3), 2.96–3.16 (brs, 1H, exchangeable with D_2O, OH), 4.10 (d, $J = 9$ Hz, 1H, Ph–CH), 5.06 (d, $J = 9$ Hz, 1H, HO–CH), 6.14 (d, $J = 8$ Hz, 1H, Ph–CH=), 6.80 (d, $J = 8$ Hz, 1H, N–CH=), 6.98–7.38 (m, 9H, H-Ar). MS *m/z* (%): 280 ($M^+ + 1$, 3.4), 279 (M^+, 11), 262 (0.2), 250 (100), 222 (43), 192 (77), 178 (37), 144 (73), 91 (31), 77 (28), 42 (60). IR (KBr, cm^{-1}): 3337, 1641, 1394, 1259, 1071. In addition, compound **11** was also obtained (17 mg, 7%); m.p.: 196–200 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 2.96–3.16 (brs, 1H, exchangeable with D_2O, OH), 3.22 (s, 3H, NCH_3), 4.17 (d, $J = 10$ Hz, 1H, Ph–CH), 4.37 (d, $J = 10$ Hz, 1H, HO–CH), 6.38 (s, 1H, CH=), 6.90–7.30 (m, 10H, H-Ar). MS *m/z* (%): 280 ($M^+ + 1$, 18), 279 (M^+, 84), 262 (2), 251 (18), 250 (100), 222 (15), 91 (18), 77 (10). IR (KBr, cm^{-1}): 3263, 1663, 1648, 1394, 1219, 1058. It's melting point, IR, MS and ^{1}H NMR are identical with those of the naturally isolated Homoclausenamide [4].

Acknowledgments

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