An Interesting Cyclization of *N*-Methyl-3-phenyl-*N*-(2-(*Z*)-phenylethenyl)-*cis*-oxiranecarboxamide

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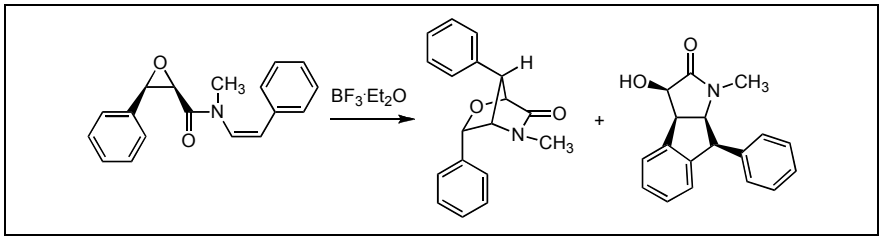

Under Lewis acid condition, *N*-methyl-3-phenyl-*N*-(2-(*Z*)-phenylethenyl)-*cis*-oxiranecarboxamide undergoes elegant double cyclizations to give interesting products.

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INTRODUCTION

Cyclic amides **1**-**5** were isolated from the aqueous extracts of *Clausena lansium* leave (Figure 1), which is used in Chinese folk medicine as an effective means for protecting the liver and been administered against acute and chronic viral hepatitis [1]. We have designed and synthesized *N*-methyl-3-phenyl-*N*-(2-(*Z*)-phenylethenyl)-*trans*-oxiranecarboxamide (**6**) to prepare Zetaclausenamide **1** [2], and *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-*trans*-oxiranecarboxamide (**7**) to prepare Homoclausenamide **2** [3] (Scheme 1). To further study how the stereochemistry of the starting material affect the cyclization paths, *N*-methyl-3-phenyl-*N*-(2-(*Z*)-phenylethenyl)-*cis*-oxiranecarboxamide (**11**), an isomer of **6** and **7**, was prepared and its cyclization was studied.

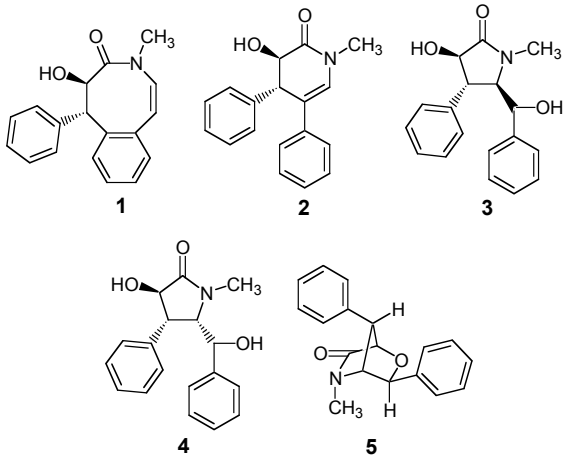
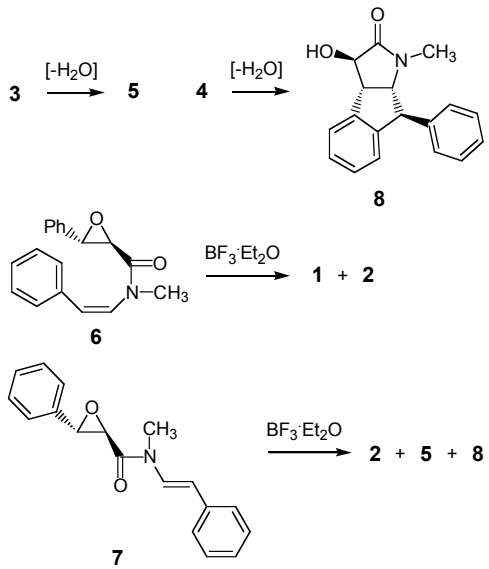


Figure 1

RESULTS AND DISCUSSION

Clausenamide chemistry is of particular interest. Compound **1**, **2** and **5** have the same molecular formula, but different skeletons. Dehydrating of amide **4** under acid condition afforded amide **8** [1a], and dehydrating of amide **3** gave **5** [4]. The cyclization of **6** under Lewis acid condition gave both **1** and **2** [2], and the cyclization of **7** afforded **2**, **5** and **8** [3] (Scheme 1).

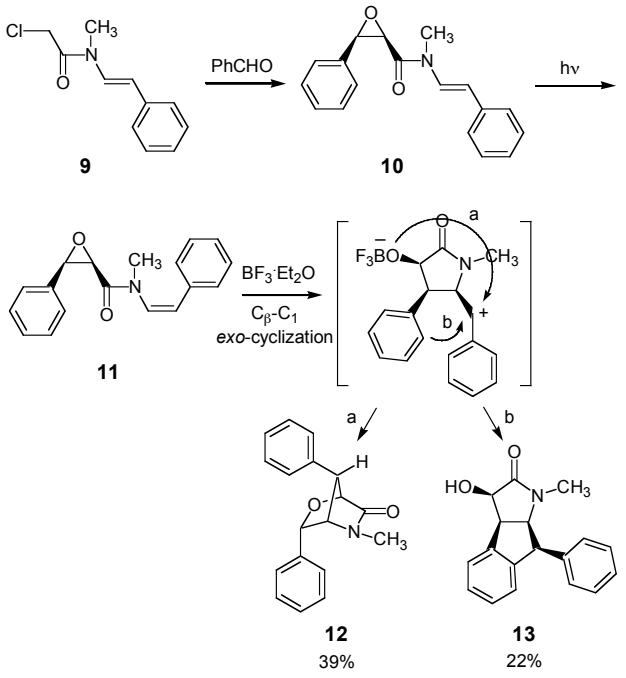
Scheme 1



Compound **10** was prepared by the Darzen's condensation [5] of benzaldhyde with compound **9** using CH_3ONa as the base in yield of 15% (*trans* isomer in

yield of 40%) [3]. Under stronger base condition, *e.g.*, ^{t}BuOK, the reaction progressed quickly, and thematically controlled *trans* isomer was predominantly obtained (87%), leaving **10** in only 2% yield [3]. The photo-isomerization of **10** was conducted in benzene with a 450W medium-pressure mercury lamp as irradiation source. The epoxide group was not stable under irradiation [6]. Carefully controlling the reaction at $\lambda >$ 300 nm using a solution of $SnCl_2$ in concentrated hydrochloride (0.1 *M*) as the filter, compound **11** can be obtained successfully in 73% yield based on 62% conversion (Scheme 2).

Scheme 2



The cyclization of **11** was conducted in anhydrous CH_2Cl_2 under the presence of $BF_3{\cdot}Et_2O$. For compound **11**, three kinds of cyclizations could take place to give 5-membered ring, 6-membered ring, and 8-membered ring products, respectively. Opening the epoxide and the cyclization was taking place at the same time, so each product should have one configuration. From our experiment, mainly two products, **12** and **13**, isomers of **5** and **8**, respectively, were isolated, which means the 5-membered ring closure is predominantly favored. The detailed ^{1}H nmr analyses of **12** and **13** were not done. Both complicated supposed structures were confirmed by X-ray analyses [7,8].

In conclusion, by comparing with its isomers, the cyclization study of *N*-methyl-3-phenyl-*N*-(2-(*Z*)-phenyl-ethenyl)-*cis*-oxiranecarboxamide (**11**) showed clearly that varying the conformation of the epoxide and the double bond not only affects the stereo-conformation of the products, but also changes the cyclization paths to give different skeleton products.

EXPERIMENTAL

Melting points were measured with a YANACO MP-500 apparatus and were not corrected. 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. Tlc plate were prepared by coating silica gel G_{254} (Qingdao Haiyang Chemical Factory, China) on sheets of glass. 450W Hamonia medium-pressure mercury lamp was used for the photoisomerization. Anhydrous solvents (dichloromethane, benzene) 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 N_2.

***N*-Methyl-3-phenyl-*N*-(2-(*Z*)-phenylethenyl)-*cis*-oxirane-carboxamide (11).** Into a cylindrical and jacketed quart reaction vessel (500 mL) with a solution of $SnCl_2$ in concentrated hydrochloride (0.1 *M*) in its jacket, was added the solution of compound **10** [3] (400 mg, 1.432 mmoles) in anhydrous benzene (100 mL). It was irradiated with 450 W Hamonia medium-pressure mercury lamp from outside the vessel under a nitrogen atmosphere while stirring. The reaction vessel was cooled with air gun and the irradiation was stopped after 30 minutes to let the reaction solution cool. It was then irradiated for another 30 minutes. This process was repeated and the reaction was monitored by tlc till no more starting material was obviously reacted (4 hours). It was cooled and concentrated for chromatography using petroleum ether (bp 30-60 °C) and EtOAc (2:1, v/v) as the eluent to afford unreacted **10** (151 mg, 38% recovered) and **11** (181 mg, 73% based on 62% conversion) as white crystals (methanol), mp 116-118 °C; R_f (petroleum ether (bp 30-60 °C)/EtOAc, 2:1, v/v) 0.41; ^{1}H nmr [9] (deuteriochloroform): δ 2.74 and 2.76 (s, 3H, NCH_3), 3.85 and 3.97 (d, J = 4.3 Hz, 1H, Ph-CH), 4.20 and 4.28 (d, J = 4.3 Hz, 1H, CH-CO), 6.07 (d, J = 8.6 Hz, 1H, =CH-Ph), 6.23 (d, J = 8.6 Hz, 1H, N-CH=), 6.80-7.50 (m, 10H, phenyl protons); ms: m/z (%) 280 (M^++1, 5), 279 (M^+, 26), 193 (54), 173 (31), 144 (80), 133 (49), 132 (25), 117 (26), 103 (18), 91 (100); *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.62; H, 5.78; N, 5.20.

The cyclization of compound 11. To the solution of compound **11** (200 mg, 0.72 mmole) in anhydrous dichloro-methane (20 mL) was added dropwise the solution of boron trifluoride-diethyl etherate (106 μL, 0.86 mmole) in anhydrous dichloromethane (2 mL) at room temperature while stirring. After the addition, the reaction was continued for 30 minutes. Tlc showed the reaction was finished. It was diluted with diethyl ether (100 mL), washed with water, and the aqueous phase was extracted with diethyl ether (50 mL × 2). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated for chromatography using dichloromethane: methanol (100:1.25, v/v) as the eluent to afford compound **12** (77 mg, 39%) and **13** (44 mg, 22%). Data of **12** [7]: white crystals (methanol), mp 203-205 °C; R_f (dichloromethane: methanol, 100:1.25, v/v, ran 3 times) 0.33; ^{1}H-nmr (deuteriochloroform): δ 2.29 (s, 3H, NCH_3), 3.45 (d, J = 2.2 Hz, 1H), 4.07 (m, 1H), 4.94 (m, 2H), 7.10-7.50 (m, 10H, phenyl protons); ms: m/z (%) 280 (M^++1, 2), 173 (100), 144 (85), 105 (17), 91 (19), 77 (30), 42 (32). Data of **13** [8]: colorless crystals (methanol), mp 231-233 °C; R_f

(dichloromethane:methanol, 100:1.25, v/v, ran 3 times) 0.29; ^{1}H-nmr (deuteriochloroform): δ 2.06 (s, 3H, NCH_3), 2.36 (brs, 1H, exchangeable with D_2O, OH), 4.18 (m, 1H), 4.40-4.68 (m, 3H), 7.10-7.40 (m, 9H, phenyl protons); ms: m/z (%) 280 (M^++1, 18), 279 (M^+, 92), 262 (18), 204 (30), 192 (72), 178 (35), 165 (44), 144 (23), 115 (44), 103 (18), 91 (23), 77 (23), 42 (100).

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[7] For the X-ray analysis of compound **12** see: Zhao, B.; Zhou, J.; Meng, G.; Wang, Z.; Lu, Y.; Zhou, T. *Yaoxue Xuebao* **2001**, *36(5)*, 373-376; *Chem. Abstr*. **2002**, *136*, 325710b.

[8] For the X-ray analysis of compound **13** see: Zhou, J.; Lu, Y.; Zheng, Q. *Zhongguo Yaowu Huaxue Zazhi* **1998**, *8(1)*, 38-40; *Chem. Abstr*. **1998**, *129*, 324042d.

[9] Owing to the rotation hindrance of the molecule, related H shows two singlets or two doublets, respectively, on the spectrum.