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European Journal of Medicinal Chemistry 43 (2008) 1781–1784
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
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Laboratory note

Study of the intramolecular cyclization of *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-*trans*(*cis*)-oxiranecarboxamide – Syntheses of Homoclausenamide and Dehydroclausenamide

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Received 27 September 2007; received in revised form 22 November 2007; accepted 27 November 2007
Available online 11 January 2008

Abstract

Homoclausenamide was synthesized for the first time, and the intramolecular cyclization study of *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-*trans*(*cis*)-oxiranecarboxamide well demonstrated how the stereochemistry affects the cyclization paths.

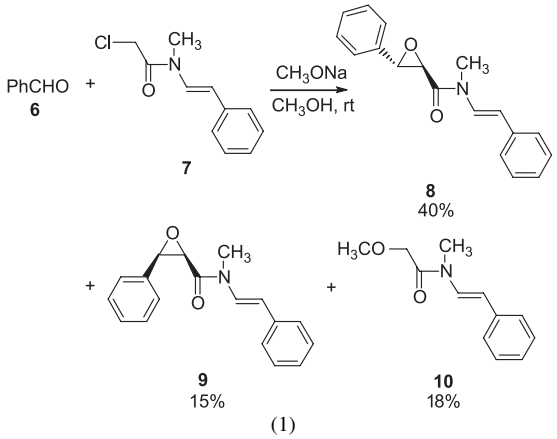
Keywords: Homoclausenamide; Dehydroclausenamide; Amides; Bicyclic compound; Biomimetic syntheses

1. Introduction

Clausena lansium has attracted increasing attention for its leaves can be used as Chinese Traditional Medicine for hepatoprotection [1,2]. The components of the leaves were studied and five cyclic amides, among which **1**–**4** are racemic mixtures and **5** is optically active, were isolated (Fig. 1) [1,3–5]. The initial pharmacological study showed that all of the cyclic amides **1**–**5** have hepatoprotective activity against chemical toxins, such as carbon tetrachloride and thioacetamide, and have inducing effect on cytochrome P450 [1,3–5]. The total syntheses of Clausenamide **3**, Neoclausenamide **4**, and Dehydroclausenamide **5** have been fulfilled via different routes [6–11]. However, no other work has been reported on the synthesis of Homoclausenamide **1**, except for our earlier report as a summary [12]. Its poor content (16.2 ppm) [4] in the leaves stimulated us to study its synthesis by the cyclization of *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-*trans*-oxiranecarboxamide **8** under Lewis acid condition.

2. Results and discussion

The Darzen's condensation [13] of benzaldehyde with 2-chloro-*N*-methyl-*N*-(2-(*E*)-phenylethenyl)-acetamide **7** was conducted in anhydrous MeOH with NaOMe as the base to give *trans* and *cis* epoxides: *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-*trans*-oxiranecarboxamide **8** ($J_{H\alpha,\beta} = 2.2$ Hz) and *N*-methyl-3-phenyl-*N*-(2-(*E*)-phenylethenyl)-*cis*-oxiranecarboxamide **9** ($J_{H\alpha,\beta} = 4$ Hz), along with a base replaced by-product **10**. The reaction was slow and more (15%) of kinetically controlled **9** was produced (Eq. (1)).



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doi:10.1016/j.ejmech.2007.11.022

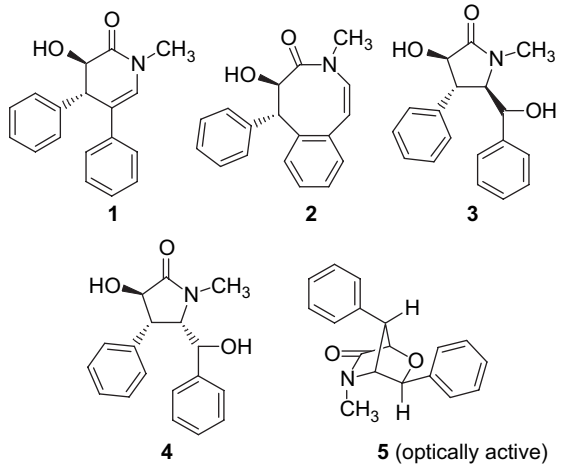
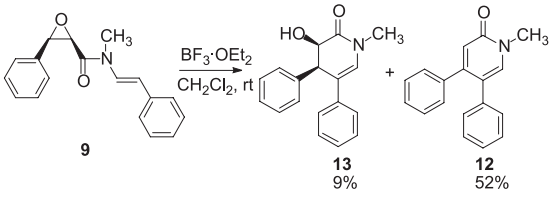


Fig. 1.

The cyclization of compound **8** was conducted in anhydrous CH_2Cl_2 under the presence of $BF_3 \cdot OEt_2$. The reaction was progressed slowly, and it took 12 h to complete even at room temperature under the presence of excess (4 eq) $BF_3 \cdot OEt_2$. Four compounds were isolated in which the desired compound **1** with m.p. 199–201 °C and identical spectra with those of the authentic sample (m.p. 201.5–202.5 °C) [4] were obtained but only in yield of 13%. Compound **5** with m.p. 164–166 °C gave identical ^{1}H NMR and MS with those of the natural Dehydroclausenamide **5** (m.p. 164–166 °C) [1], except it is a racemic compound while the natural product is optically active with optical purity of 50% ee [5]. The structure of compound **11** with m.p. 188–191 °C was identified as a bicyclic compound which (m.p. 188–190 °C) has been obtained previously while treating Neoclausenamide **4** with acid on heating [1]. In addition, a dehydrated product **12** was also obtained. Apparently C_1–C_β (exo) and C_2–C_β (endo) cyclizations of compound **8** have taken place giving the corresponding five and six member rings (Scheme 1).

The cyclization of compound **9** was also conducted under the presence of $BF_3 \cdot OEt_2$. But the reaction was progressed very quickly (30 min), and the result was very different, giving mainly six-membered ring products. Opening the epoxide and the cyclization was taking place at the same time, so the cyclizations of **8** and **9** afforded only compounds **1** and **13**, respectively. For the cyclization of **9**, *anti*-elimination is greatly favored to give predominantly dehydrated product **12** (Eq. (2)).



(2).

3. Conclusion

The cyclization study of compounds **8** and **9** well demonstrated how the stereochemistry of the starting materials affects the cyclization to give absolutely different products. In addition, the cyclization of **8** not only gave the desired Homoclausenamide **1**, but also afforded Dehydroclausenamide **5** and the dehydro-derivative **11** of Neoclausenamide **4**, which would provide important information for the biomimetic syntheses of the cyclic amides.

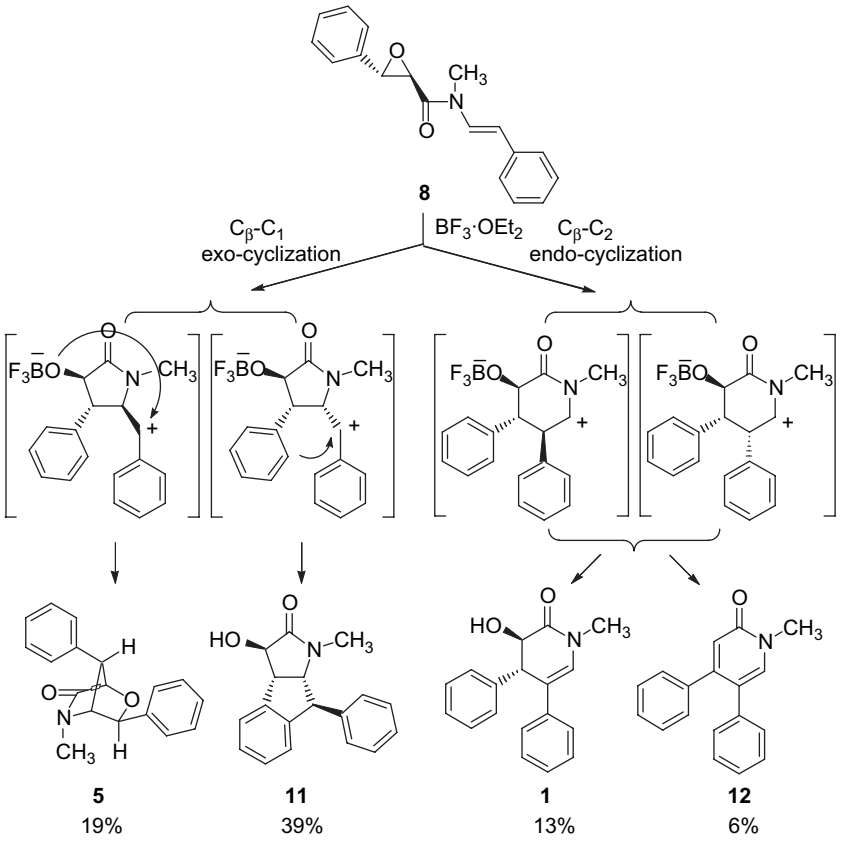
4. Experimental

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. UV spectra were recorded on a Shimadzu UV240 spectrometer. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. Column chromatography was performed using silica gel H (10–40 μm, Qingdao Haiyang Chemical Factory, China). TLC plate was prepared by coating silica gel G_{254} (Qingdao Haiyang Chemical Factory, China) on a sheet of glass, and the sample to be analyzed ran two times on the plate unless otherwise mentioned. Anhydrous CH_2Cl_2 was dried and distilled from P_2O_5; MeOH was treated with Mg, and related anhydrous reactions were conducted under N_2.

4.1.1. Synthesis of compounds 8 and 9

To the solution of benzaldehyde (1.70 g, 99%, 16.0 mmol) and compound **7** [14] (2.10 g, 10.0 mmol) in anhydrous MeOH (100 ml) was added dropwise a solution of sodium methoxide (prepared from Na and MeOH) in MeOH (15.46 g, 5.59% g/g, 16.0 mmol) at 15–20 °C. After the addition, it was stirred at the same temperature till the starting material **7** was disappeared (4 days, settled during night). It was cooled to 0–5 °C, and AcOH (0.36 g, 6.0 mmol) was added to neutralise the base. It was concentrated, and the residue was dissolved in CH_2Cl_2 (100 ml). It was washed with water, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated for column chromatography using petroleum ether (30–60 °C) and EtOAc (2:1) as the eluent to afford **8** [14] (1.11 g, 40%) and **9** (0.42 g, 15%); m.p.: 152–154 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 3.00 and 3.16 (s, 3H, NCH_3), 4.01 and 4.05 (d, $J = 4$ Hz, 1H, Ph–CH), 4.32 and 4.37 (d, $J = 4$ Hz, 1H, CH–CO), 5.82 and 5.90 (d, $J = 14.4$ Hz, 1H, =CH–Ph), 7.00–7.60 (m, 11H, H–Ar and N–CH=). MS *m/z* (%): 280 ($M^+ + 1$, 9), 279 (M^+, 40), 193 (24), 173 (22), 144 (90), 133 (41), 132 (19), 117 (23), 91 (100). Anal. $C_{18}H_{17}NO_2$ (C, H, N). In addition, by-product **10** (370 mg, 18%) was obtained; m.p.: 37–39 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 3.21 (s, 3H, NCH_3), 3.44 (s, 3H, OCH_3), 4.26 (s, 2H, CH–CO), 5.98 (d, $J = 14.4$ Hz, 1H, =CH–Ph), 7.00–7.50 (m, 6H, H–Ar and N–CH=). Anal. $C_{12}H_{15}NO_2$ (C, H, N).



Scheme 1.

*4.1.2. The intramolecular cyclization of compound **8***

To the solution of **8** (419 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (40 ml) was added dropwise a solution of $BF_3 \cdot OEt_2$ (859 mg, 6 mmol) in anhydrous CH_2Cl_2 (4 ml) at 20–25 °C. After being stirred for 12 h, it was diluted with Et_2O (80 ml) and washed with water. The aqueous phase was extracted with Et_2O. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated for column chromatography using petroleum ether (30–60 °C) and EtOAc (2:1) as the eluent to afford following products.

Dehydroclausenamide **5** [1] (81 mg, 19%); m.p.: 164–166 °C; R_f: 0.64 (petroleum ether–EtOAc, 2:1). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 2.94 (s, 3H, NCH_3), 3.59 (br s, 1H, CH–CO), 4.07 (br s, 1H, CH–N), 4.81 (br s, 1H, Ph–CH), 4.99 (br s, 1H, Ph–CH–O), 7.11–7.51 (m, 10H, H–Ar). MS *m/z* (%): 280 ($M^+ + 1$, 1), 279 (M^+, 2), 173 (100), 144 (61), 91 (19), 77 (13), 65 (4), 42 (22).

Homoclausenamide **1** [4] (54 mg, 13%); m.p.: 199–201 °C; R_f: 0.47 (petroleum ether–EtOAc, 2:1). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 2.96–3.16 (br s, 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, CH–CO), 6.38 (s, 1H, N–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), 42 (26). IR (KBr, cm^{-1}): 3263, 1663, 1648, 1394, 1219, 1058.

Product **12** (25 mg, 6%); m.p.: 177–179 °C; R_f: 0.42 (petroleum ether–EtOA, 2: 1). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 3.68 (s, 3 H, NCH_3), 7.20–7.80 (m, 12 H, H–Ar and CH–CO, N–CH=). MS *m/z* (%): 262 ($M^+ + 1$, 18), 261 (M^+, 100), 233 (16), 192 (2), 191 (7), 91 (20), 41 (27). ^{13}C NMR (125 Hz, $CDCl_3$) δ ppm: 38.5, 120.0, 125.8, 127.3, 127.8, 128.1, 128.7, 129.1, 131.4, 134.7, 136.6, 136.7, 137.5, 161.2. IR (KBr, cm^{-1}): 3445, 3063, 1648, 1595, 1555, 1500, 755, 697. UV/vis ($CHCl_3$) λ_{max} (log ε) (nm): 255 (4.34), 340 (3.98). Anal. (recrystallized from MeOH) $C_{18}H_{15}NO_2 \cdot 1/5CH_3OH$ (C, H, N).

Product **11** [1] (165 mg, 39%); m.p.: 188–191 °C; R_f: 0.20 (petroleum ether–EtOAc, 2:1). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 2.71 (br s, 1H, exchangeable with D_2O, OH), 2.92 (s, 3H), 3.96 (m, 1H), 4.32 (m, 3H), 6.80–7.48 (m, 9H). MS *m/z* (%): 280 ($M^+ + 1$, 25), 279 (M^+, 100), 262 (17), 204 (33), 192 (72), 178 (25), 165 (30), 144 (17), 115 (30), 91 (19), 77 (12), 42 (56).

*4.1.3. The intramolecular cyclization of compound **9***

To the solution of **9** (279 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (20 ml) was added dropwise the solution of $BF_3 \cdot OEt_2$ (170 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (2 ml) at 10–15 °C. After being stirred for 30 min (TLC showed that reaction was finished), it was diluted with Et_2O (50 ml) and washed with water. The aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated for column chromatography using petroleum ether (30–60 °C) and EtOAc (2:1) as the eluent to afford **13** (25 mg, 9%); m.p.: 153–155 °C; R_f: 0.71

(petroleum ether–EtOAc, 3:1, ran three times). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm: 3.24 (s, 3H, NCH_3), 3.22–3.32 (br s, 1H, exchangeable with D_2O, OH), 4.18 (d, $J = 7.6$ Hz, 1H, Ph–CH), 4.74 (d, $J = 7.6$ Hz, 1H, CH–CO), 6.61 (s, 1H, N–CH=), 7.04–7.60 (m, 10H, H–Ar). MS *m/z* (%): 280 ($M^+ + 1$, 15), 279 (M^+, 82), 262 (2), 251 (16), 250 (100), 222 (15), 91 (14). Anal. $C_{18}H_{17}NO_2$ (C, H, N). In addition, compound **12** (136 mg, 52%) was isolated.

Acknowledgment

We are grateful to National Science Foundation of China for financial support.

References

[1] M.H. Yang, Y.H. Cao, Y.Q. Yang, Y.Y. Chen, L. Huang, Yaoxue Xuebao 22 (1) (1987) 33–40.
[2] V. Lakshmi, R. Kumar, S.K. Agarwal, Nat. Prod. Res. 19 (4) (2005) 355–357 and references cited therein.
[3] M.H. Yang, Y.Y. Chen, L. Huang, Phytochemistry 27 (2) (1988) 445–450.
[4] M.H. Yang, Y.Y. Chen, L. Huang, Chin. Chem. Lett. 2 (4) (1991) 291–292.
[5] M.H. Yang, L. Huang, Chin. Chem. Lett. 2 (6) (1991) 775–776.
[6] W. Hartwig, L. Born, J. Org. Chem. 52 (19) (1987) 4352–4358.
[7] G.Z. Yang, L.H. Wang, L. Huang, Chin. Chem. Lett. 4 (12) (1993) 1035–1036.
[8] E.C. Rao, H. Hong, G.Z. Yang, H. Lin, L. Huang, Chin. Chem. Lett. 5 (4) (1994) 267–268.
[9] M.W. Cappi, R.W. Flood, S.M. Roberts, J. Skidmore, N.M. Williamson, W.P. Chen, Y.W. Liao, J.A. Smith, Chem. Commun 10 (1998) 1159–1160.
[10] T. Yakura, Y. Matsumura, M. Ikeda, Synlett 1991 (5) (1991) 343–344.
[11] D.F. Huang, L. Huang, Tetrahedron 46 (9) (1990) 3135–3142.
[12] N.C. Ma, K.M. Wu, L. Huang, Chin. Chem. Lett. 7 (8) (1996) 706–708.
[13] C.C. Tung, A.J. Speziale, H.W. Franzier, J. Org. Chem. 28 (6) (1963) 1514–1521.
[14] For the preparation of compounds 7 and 8 see: N. Ma, K. Wu, L. Huang Eur. J. Med. Chem. (2007) Available online 3 June.