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# ASYMMETRIC SYNTHESIS OF (-)-DEHYDROCLAUSENAMIDE**

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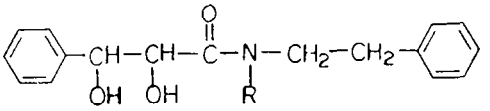
Abstract: Asymmetric synthesis of (-)-dehydroclausenamide **1** by scheme 2 was reported. Sharpless epoxidation was applied to cinnamyl alcohol for introduction of two desired chiral centers and the potential hydroxyl group. The key intermediate, γ-lactam (-)-**5**, was obtained by regio-selective intramolecular cyclization of (-)-**6**. Subsequent stereo-selective reduction was achieved by reducing $C_3$-tetrahydropyranyl ether of (-)-**5**. The title natural product was then obtained by successive tosylation, hydrolysis and cyclization.

(-)-Dehydroclausenamide (**1**) is one of the seven biologically active amides isolated from aqueous extract of dry leaves of Clausena lansium. Its potent hepatoprotective activity being showed in the preliminary animal test and its meager content in dry leaves (2.5ppm) prompted us to the study on the synthesis of **1**. Its structural elucidation and possible biogenetic enzymatic formation from neoclausenamide (**2**) which was found in racemic form in the extract were described in the previous paper[1]. Isolation of acyclic **3** and **4** along with five cyclic amides[2] led to the suggestion of the acyclic amides being the precursors of the lactams. On this rational basis, the biomimatic synthetic route (scheme 1) has been envisaged.

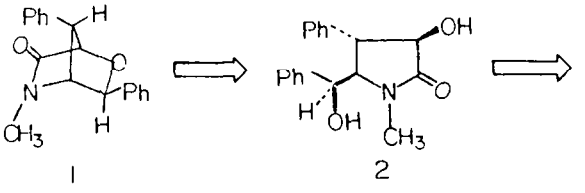
trans-Cinnamyl alcohol was selected as a starting material. Asymmetric introduction of epoxy group into the molecule can be carried out by Sharpless reaction[3]. The conversion of acyclic amide **6** to γ-lactam **5** through intramolecular stereo-selective trans opening of the epoxy group is the crucial step of this scheme. Cyclization to 5-membered

**Dedicated to Professor You Wang on the occasion of his 80th birthday.

ring from such structural type is against Baldwin's rule[4] which predicts the formation of 4-membered ring β-lactam instead of desired γ-lactam. However the above biogenetic evidence and the electronic effect induced by phenyl group at β-carbon of the epoxy group may be favorable factors for the nucleophilic attack at β-carbon to form γ-lactam. Besides, exceptions to Baldwin's rule have occasionally been reported[5-7]. Thus the proposed scheme 2 has a good chance of succeeding.



R = H 3
R = $CH_3$ 4



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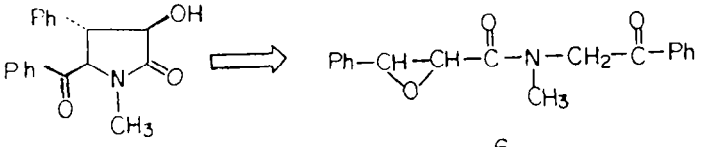

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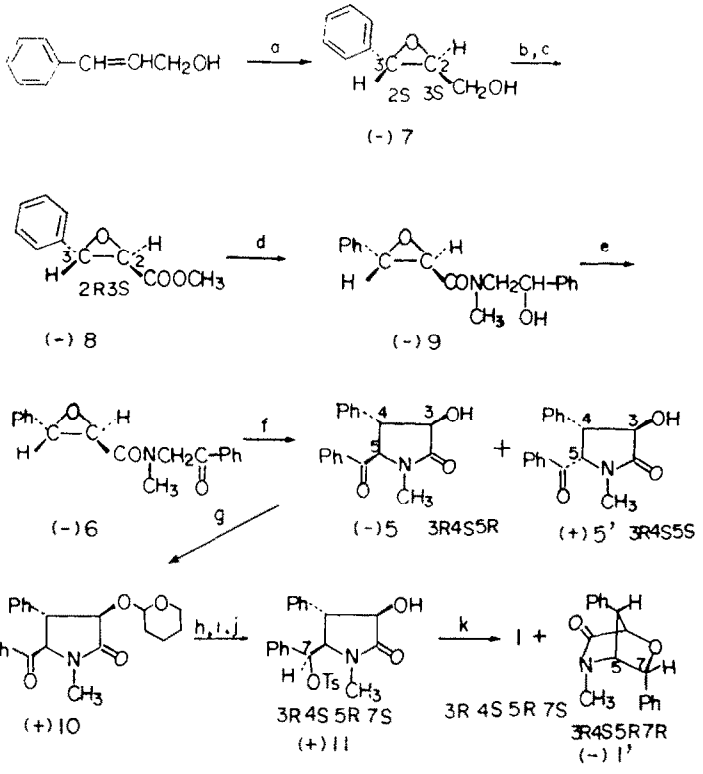
Scheme 1

Sharpless asymmetric epoxidation of cinnamyl alcohol using (+)-diethyl tartrate as the asymmetric adjuvant gave the (-)-epoxide **7** (2S,3S) in %ee>95 which was oxidized to (-)-epoxycinnamic acid (2R,3S) by ruthenium dioxide hydrate[8] and sodium periodate. The unstable acid was transformed to methyl ester (-) **8** followed by amine-ester interchange with N-methyl-2-phenylethanolamine in the presence of sodium methylate to gave (-)-**9** (2R,3S), mp 96-98 °C. Oxidation of (-)-**9** with potassium permanganate and copper sulfate furnished (-)-**6** in 81% yield. Without further purification, (-)-**6** was cyclized in a biphasic medium, methylene dichloride and 1% aqueous tetramethylammonium hydroxide. A mixture of cyclized products, (-)-**5** (3R,4S,5R) and (+)-**5'** (3R,4S,5S), in 75% yield with

5 to 5' ratio of 3:1 (the actual weight obtained). They were separated by chromatography to give (-)-5, mp 165-169°C, and (+)-5', mp 203-206 °C. No indication of presence of β-lactam was observed in the reaction product. (-)-5 with ee>95% (by $^1$HNMR using Eu(hfc)$_3$) was obtained.




a, (+)-diethyl tartrate, t-butyl hydroperoxide, Ti(OC$_3$H$_7^i$)$_4$
b, RuO$_2$.H$_2$O, NaIO$_4$ c, CH$_2$N$_2$ d, PhCH(OH)CH$_2$NHCH$_3$
e, KMnO$_4$, CuSO$_4$ f, CH$_2$Cl$_2$/1% aqueous (CH$_3$)$_4$NOH
g, dihydropyran h, L-Selectride i, tosyl chloride
j, p-toluenesulfonic acid k, 2,6-lutidine

Scheme 2

Reduction of the ketone group on the side chain in **5** with aluminium triisopropoxide, sodium borohydride or lithium tri-sec-butylborohydride (L-Selectride) gave a mixture of diastereomers, **2**(7S) and **2'**(7R), in ratios of 1:20, 1:1 and 3:1 respectively. When the 3-OH was transformed

to 3-tetrahydropyranyl ether (+)-**10**(mp 181-7°C), ratios of reduction products changed significantly to 1:1 for $Al(OC_3H_7^i)_3$, 10:1 for $NaBH_4$ and >10:1 for L-Selectride(by tlc and $^1$HNMR). The free hydroxyl group at $C_3$ and $C_5$ side chain which carries the ketone group to be reduced are cis to each other. They will readily coordinate with the cation of the reducing agent. The formation of tetrahydropyranyl ether not only increases the bulkiness of the substituent at $C_3$ but also decreases the coordinating incidence. Therefore it changes the course of stereoselectivity of the reduction. After reduction, the reaction mixture was treated with tosyl chloride directly followed by removal of the tetrahydropyranyl group by acid to yield 7-tosylate, (+)-**11** (3R,4S,5R,7S), mp 157-158°C, in 84% yield (based on the ether **10** used). The tosylate on treatment with 2,6-lutidine produced the final product in 66% yield, mp 199°C and $[\alpha]_D^{15}$-88.3°(c 0.14, MeOH), ee>95%(by NMR), which are higher than those reported for the natural product (mp 164-166°C, $[\alpha]_D^{25}$ -40° (c 0.225, MeOH)[1]. However they showed identical MS, IR, $^1$HNMR and crystalline X-ray diffraction data which gave relative configuration of 3R*,4S*, 5R*,7S* [1,9]. This indicates that the absolute configuration of (-)-**1** is 3R,4S,5R,7S and that the natural (-)-**1** is partially racemic, 45%ee according to its specific rotation.

Small amount of **1'** (mp 170-171°C) was collected by chromatography of the mother liquid of above recrystallization. MS and elementary analysis gave the molecular formula of $C_{18}H_{17}NO_2$ identical with that of **1**. Its $^1$HNMR spectrum in comparing with that of **1** showed up field shift ($\Delta$=0.84ppm) of N-$CH_3$ peak and down shift of 0.46ppm for $C_7$H which was a broad peak against a singlet in **1**. Differences in the aromatic H between them were also observed. Thus it has been assigned to be an epimer of **1** different in $C_7$ with absolute configuration of 3R,4S,5R,7R.

Cyclization of (+)-**11**(3R,4S,5R,7S) would be expected to give 7R product with the inversion at $C_7$. However unexpectedly (-)-**1**(7S) was given as the major product and only 10% of **1'**(7R) was obtained. From the above synthetic route the over all yield of (-)-**1** from cinnamyl alcohol was 2.4% with ee>95%.

## Experimental

Apparatus used for determination: melting point, Boetius melting apparatus, uncorrected; IR spectrum, Perkin-Elmer-683, KBr disk; NMR spectrum, Jeol F90Q, $CDCl_3$ as solvent; MS, ZAB-2F; optical rotation, Perkin-Elmer 241.

(2S,3S)-3-Phenyl-2,3-epoxypropanol, (-)-**7**: To 100ml anhydrous methylene

dichloride, 0.5g 4Å molecular sieve (Aldrich, activated) was added and at -5 °C, 0.38g (1.85 mmol) of (+)-diethyl tartrate and titanium(IV) isopropoxide 0.35g (1.2mmol) were followed. After cooling to -20 °C, 9ml of 5M solution of tert-butyl hydroperoxide and a solution of 2.68g (20 mmol) of trans-cinnamyl alcohol in methylene chloride were added successively. The reaction mixture was stirred at -20 °C for 7h. Additional 0.56g of titanium(IV) isopropoxide, 0.60g of (+)-diethyl tartrate and 9Ml of 5M tert-butyl hydroperoxide were added. The reaction mixture was left at -18 °C for 2 days. Then 50ml of 2N sodium hydroxide solution saturated with sodium chloride was added and stirred for 3h at room temperature. The organic layer was separated, washed and dried as usual. The solvent was taken off and the oily residue left behind was chromatographed on silica gel to afford 1.7g of product in 57% yield, mp 50-51 °C, $[\alpha]_D^{15}$ -51.9°(c 1.5, abs EtOH) after recrystallization.(lit.$[\alpha]_D^{20}$+45.9° (c 1.5, abs EtOH) for (2R,3R) isomer[10]; mp 51.5-53 °C, $[\alpha]_D^{25}$-49.6°(c 2.4, $CHCl_3$), ee%>98 for (2S,3S) isomer[11]. m/e(%): 150($M^+$, 11), 107($C_6H_5CHOH^+$, 100). IR and $^1$HNMR were identical with those reported by Gao[11].

(2R,3S)-N-Methyl-N-(β-hydroxyphenylethyl)-3-phenyl-2,3-epoxypropionamide,(-)-**9**: To a mixed-solvent of acetonitrile(12ml), carbon tetrachloride(12ml) and water(18ml) were added 0.90g(6mmol) of (-)-**7**, 1.5ml of 2,6-lutidine and 3.85g(18mmol) sodium periodate then followed by 24mg of ruthenium(IV) oxide hydrate while stirring. After being stirred for 7h, the reaction mixture was cold and acidified with 10ml of 4N HCl and extracted with ether which was then washed and dried. To this solution, an ether solution of diazomethane was added. After standing, ether was taken off and the residue was chromatographed on silica gel to give an oil, (-)-**8** [$\eta_D^{15}$1.5282, $[\alpha]_D^{15}$ -171.2° (c 1.13, $CHCl_3$)] in 50% yield.

To a cold solution of 0.46g(2.56mmol) of above ester in 1ml of anhydrous methanol at -20 °C, 0.46g Of N-methyl-β-hydroxy-phenylethylamine in 1ml of cold anhydrous methanol and 2 drops of 25% sodium methoxide in methanol were added and agitated. After standing at -18 °C for 48h, two drops of 10% HCl and 10ml of water were added. White solid (111mg) was separated out, mp 96-98 °C, $[\alpha]_D^{15}$-62.7°(c 0.53, MeOH). m/e(%): 298($M^+$+1, 0.1), 297($M^+$, 0.2), 191(18), 120(70), 104(80), 91(100). IR: 3390, 1640cm$^{-1}$. $^1$HNMR δ : 2.04-3.09(1H, br, $D_2O$ exchangeable, OH), 2.96+3.05(3H, 2s, $NCH_3$), 3.20-4.08(4H, m, $CH_2$ & $\overset{O}{\overset{\frown}{CH-CH}}$), 4.80-5.09(1H, m, CHOH), 7.10-7.45(10H, m, ArH). Another crop (0.32g) of the product was collected from mother liquid. It was recrystallized from aqueous ethanol to yield additional 240mg of solid, mp 96-98 °C. This gave a total yield of 46%.

(2R,3S)-N-Methyl-N-(phenacyl)-3-phenyl-2,3-epoxy-propionamide,(-)-**6**: To a solution of 99mg of (-)-**9** in 5ml of methylene dichloride, 0.5g of potassium permanganate and 0.25g of powder copper sulfate hydrate were added. The mixture was stirred for 3h at room temperature and then decolorized with active carbon. The filtrate was concentrated to give 80mg of oily residue in 81% yield, $[\alpha]_D^{15}$-132.3°(c 0.2, MeOH). m/e,(%): 295($M^+$, 6), 190(29), 189(35), 105(95), 91(93). IR: 1690, 1668, 1650$cm^{-1}$. $^1$HNMR$\delta$: 3.12+3.26(3H, 3s, $NCH_3$), 3.85+3.52(1H, 2d, J=2Hz, $\overset{O}{\frown}$CH), 4.07+4.19(1H, 2d, J=2Hz, $\overset{O}{\frown}$CH), 4.88, 5.10(2H, q, J=18Hz, $CH_ACH_B$), 7.32-8.18(10H, m, ArH).

(-)-Neoclausenamidone,(-)-**5**: In a mixture of methylene dichloride and 1% tetramethylammonium hydroxide, 80mg of (-)-**6** was dissolved. After stirring vigorously for 5h, the organic layer was separated, washed and dried. The solvent was taking off and 60mg of white solid was left behind. It was chromatographed on silica gel to afford 36mg of (-)-**5** in 45% yield. After being recrystallized from ether it gave a solid with mp 165-169°C, $[\alpha]_D^{15}$-14.55°(c 0.50, $CHCl_3$). Found: C, 72.90; H, 5.93; N, 4.70; calc. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%. m/e(%): 295($M^+$, 0.6), 190(M-PhCO, 100), 162(22), 133(19), 119(10), 105(15). IR: 3270, 1685$cm^{-1}$. $^1$HNMR$\delta$: 2.70(1H, br. $D_2O$ exchangeable, OH), 2.92(3H, s, $NCH_3$), 3.26(1H, t, J=6Hz, $C_4H$), 4.46(1H, d, J=6Hz, $C_3H$), 5.07(1H, d, J=6Hz, $C_5H$), 7.07-7.68(10H, m, ArH). From the above chromatography, (+)-**5'** also was obtained, mp 203-206°C, $[\alpha]_D^{15}$+333°(c 0.01, MeOH). $^1$HNMR spectrum was identical with that of racemic isomer[2b].

Tetrahydropyranyl ether of neoclausenamidone,(+)-**10**: Compound (-)-**5**, 443mg(1.5mmol), 380mg of 3,4-dihydropyran(4.5mmol) and 38mg of pyridinium tosylate were dissolved in 15ml of methylene dichloride and stirred at room temperature over night. The solution was washed and dried. After taking off the solvent, the residue was triturated with cold ethyl ether to give 0.51g(+)-**10** in 90% yield, mp 181-187°C, $[\alpha]_D^{15}$+13.5°(c 0.42, $CHCl_3$), Rf 0.57(ethyl acetate:hexane 2:1). Found: C, 72.49; H, 6.58; N, 3.54; calc. for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69%. m/e(%): 380($M^+$+1, 1), 296(23), 274(19), 190(37), 172(100), 105(25), 85(71). $^1$HNMR : 1.2-2.0(6H, m, $(CH_2)_3$), 2.93(3H, s, $NCH_3$), 3.35+3.38(1H, 2t, J=5.7HZ, $C_4H$), 3.1-3.5+3.98-4.34(2H, m, $-CH_2O-$), 4.47+4.64(1H, 2d, J=5.7Hz, $C_3H$), 4.97+4.96(1H, 2d, J=5.7Hz, $C_5H$), 4.52+5.19(1H, 2t, OCHO), 7.05-7.72(10H, m, ArH).

7-O-Tosylneoclausenamide,(+)-**11**: A solution of 379mg of (-)-**10**

(1.0mmol) in 10 ml of anhydrous tetrahydrofuran was added slowly under nitrogen to 3ml of 1M solution of lithium tri-sec-butylborohydride at -(25-35)°C. The reaction mixture was stirred for an hour and 353mg of tosyl chloride in 2ml of anhydrous tetrahydrofuran was added at -15°C. After being stirred over night at room temperature, it was then poured into 20g of ice water containing 1 ml of 4N HCl and extracted with methylene dichloride. The organic extract was washed and dried. The residue obtained after taking off the solvent was dissolved in absolute ethanol at once. About 20mg of p-toluenesulfonic acid was added, and it was heated in a 60°C water bath for 15min. (+)-**11**(381mg, 84% yield, single spot on tlc) separated out after cooling was collected. The solid showed mp 157-158°C, $[\alpha]_D^{15}$+52.3° (c 0.44, $CHCl_3$). Found: C, 66.43; H, 5.61; N, 2.99%; calc. for $C_{25}H_{25}NO_5S$: C, 66.50; H, 5.58; N, 3.10%. m/e(%): 452($M^+$+1, 2), 280(50), 279(52), 190(100), 173(50), 91(48). IR: 3240, 1631, 1340, 1172$cm^{-1}$. $^1$HNMR δ: 2.20(1H, br. $D_2O$ exchangeable, OH), 2.36(3H, s, $ArCH_3$), 2.84(3H, s, $NCH_3$), 3.15(1H, t, J=5.5Hz, $C_4H$), 3.90(1H, dd, J=4.0, 5.5Hz, $C_5H$), 4.14(1H, d, J=5.5Hz, $C_3H$), 5.69(1H, d, J=4.0Hz, $C_7H$), 6.80-7.56(14H, m, ArH).

(-)-Dehydroclausenamide, (-)-1: A solution of 1.18g(2.6mmol) of (+)-**11** in 100ml of 2,6-lutidine was refluxed for 5h. The solvent was removed and the residue was dissolved in 100ml of methylene dichloride. It was washed and dried. After removal of the solvent, the residue was recrystallized from methanol to afford 352 mg of (-)-**1**, mp 199-199.5 °C, $[\alpha]_D^{15}$-88.3°(c 0.14, MeOH). The ee was determined by $^1$HNMR using $Eu(hfc)_3$ as shifting agent and no peaks related to (+)-1 was observed, ee>95%. (lit[1] mp 164-166°C, $[\alpha]_D^{25}$-40°(c 0.225, MeOH). Found: c, 77.63; H, 6.14; N, 4.93%; calc for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.02%. m/e(%): 280($M^+$+1, 0.75), 173(100), 144(70), 91(13), 77(14). IR: 1690$cm^1$. $^1$HNMR* δ : 2.966(3H, s, $NCH_3$), 3.615(1H, br. $C_4H$), 4.101(1H, t, J=1Hz, $C_5H$) 4.835(1H, dd, J=1.2, 2.7Hz, $C_3H$), 5.014(1H, s, $C_7H$), 7.00-7.50(10H, m, ArH).

The mother liquid of the above recrystallization was chromatographed on silica gel and eluted with ethyl acetate and hexane (1:1) to give 70mg of (-)-**1'**, mp 170-171°C, $[\alpha]_D^{15}$-178°(c 0.31, MeOH). m/e(%): 280($M^+$+1, 0.3), 173(100), 144(100), 91(19), 77(17). IR: 1690 $cm^{-1}$. $^1$HNMR δ: 2.13(3H, s, $NCH_3$), 3.84(1H, br. $C_4H$), 4.16(1H, br, $C_5H$), 4.81(1H, br. $C_3H$), 5.47(1H, br. $C_7H$), 7.13-7.35(10H, m, ArH). And another crop of (-)-**1** (135mg) was obtained from the latter part of the eluate. This raised the yield of (-)-**1** up to 66.4%.

*Varian XL-300 NMR

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