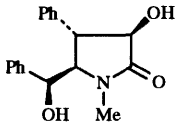
An asymmetric total synthesis of (+)-(3*R*,4*S*,5*R*,7*S*)-neoclausenamide

Jian-qiang Wang and Wei-sheng Tian *

Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, Shanghai 200032, China

A new hepatoprotective lactam (+)-(3*R*,4*S*,5*R*,7*S*)-neoclausenamide 1 isolated from the leaves of Chinese folk medicine *Clausena lansium* (Lour.) Skeel, has been readily synthesized from methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropanoate in 22.0% overall yield.

Neoclausenamide **1** is one of the novel lactams isolated from the dry leaves of the Chinese folk medicine *Clausena lansium* (Lour.) Skeels, which serves as an effective liver-protecting agent in cases of acute and chronic viral hepatitis. An aqueous extract of the compound showed a remarkable hepatoprotective effect against carbon tetrachloride in an initial test.[1] However, not only is the content of natural neoclausenamide in the plant low, but it also exists as a racemate. In order to investigate in detail the biological activity and toxicity of optically pure **1**, an enantioselective synthesis of it is much needed. Reported herein is such a synthesis of (+)-(3*R*,4*S*,5*R*,7*S*)-neoclausenamide employing Sharpless methods of asymmetric dihydroxylation[2] and stereospecific transformation of 1,2-diols into an epoxide.[3] The total synthetic route is depicted in Scheme 1.



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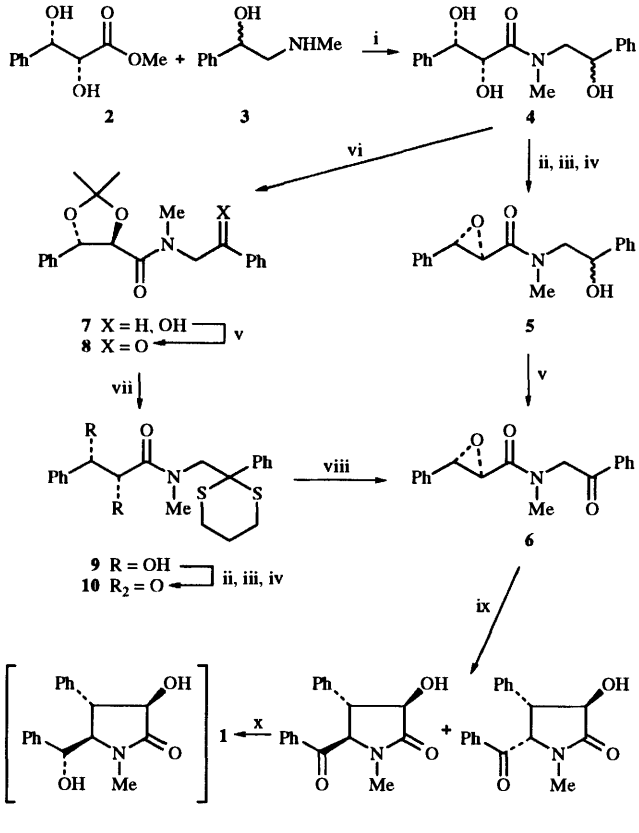
The starting material **2** was available in excellent chemical yield (80%) and high optical purity (ee > 95%, determined by chiral GC: β-cyclodextrin; column temperature: 150 °C) by asymmetric dihydroxylation of methyl cinnamate.[2] Treatment of **2** with 2-methylaminomethyl-1-phenylethanol[4] in the presence of a trace of MeONa at room temperature afforded **4** (80.0%) This compound could be converted into the key intermediate **6** by two related routes: **4**→**5**→**6** and **4**→**7**→**8**→**9**→**10**→**6**. The former route involving direct conversion of the vicinal diol **4** into its epoxide **5** and then oxidation of this to **6**, although shorter, provided an overall yield of only 21.0%; this was not considered satisfactory. The low product yield (30%) for the epoxidation of **4** to **5** was a result of the unfavourable influence of the hydroxy group nearest to the amino group.

The longer route for the conversion of **4** into **6** gave an overall product yield of 49.0%. In this, ketalization of **4** followed by oxidation with $KMnO_4$ at room temperature gave **8** in good yield; our attempt to convert **8** into **13**, however, failed (Scheme 2). Thus, treatment of **8** under a variety of deketalization conditions (*e.g.* PTSA–MeOH, propane-1,3-dithiol–Me_3SiCl, propane-1,3-dithiol–BF_3Et_2O, *etc*) gave only the intramolecular ketal **12** not compound **13**. This indicated that **12** was more stable than **13**. We found that **8** and **12** could be converted into the thioketal **9** with propane-1,3-dithiol in the presence of $TiCl_4$, the yield of **9** depending on the amount of $TiCl_4$ used in reaction (see Table 1). Compound **9** was easily converted into **6**[5] as depicted in Scheme 1.

A base-mediated cyclization of **6**[1e] furnished the lactams **11a** and **11b** (95% total yield) in the ratio of 3.1:1.[3] The C-5 configuration of **11a** and **11b** were assigned as *R* and *S*, respectively, according to their respective coupling constants (**11a** 5-H, *J* 6.0 Hz; **11b** 5-H, *J* 9.2 Hz). The assignment was further confirmed by the comparison of the ^1H NMR spectra to the known racemate (±)-(4,5)-*trans*-7-oxo-neoclausenamide, which was obtained by the oxidation of natural neoclausenamide.[1c]

Reduction of **11a** with K-selectride at −40 °C gave only the C-7 epimer of **1** in almost quantitative yield. Fortunately, reduction of **11a** with DIBAL-H at −78 °C yielded **1** as the main product. The reaction yield was 96.0% and the ratio of **1**



Scheme 1 *Reagents and conditions:* i, trace NaOMe–MeOH, RT, 80.0%; ii, $MeC(OMe)_3$, *p*-TsOH, CH_2Cl_2; iii, Me_3SiCl, CH_2Cl_2; iv, K_2CO_3, MeOH, −20 °C; **4**→**5**, 30.0%; **9**→**10**, 93.0%; v, $KMnO_4$–$CuSO_4$, CH_2Cl_2, RT; **5**→**6**, 68.5%; **7**→**8**, 88.0%; vi, acetone, *p*-TsOH, RT, 92.0%; vii, propane-1,3-dithiol, $TiCl_4$, RT, 76.8%; viii, NCS, $AgNO_3$, 2,4,6-trimethylpyridine, RT; 84.4%; ix, 1% aqueous Me_4NOH, RT; **11a**, 72.7%; **11b**, 22.0%; x, DIBAL-H, −78 °C, 82.0%

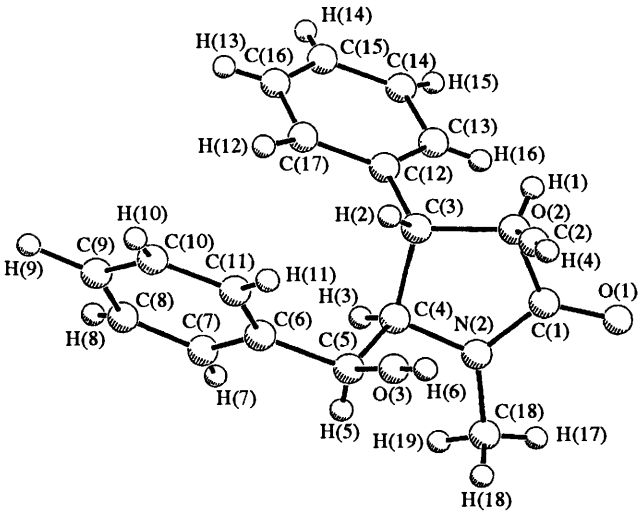


Fig. 1 X-Ray crystallographic numbering system for compound (+)-**1**

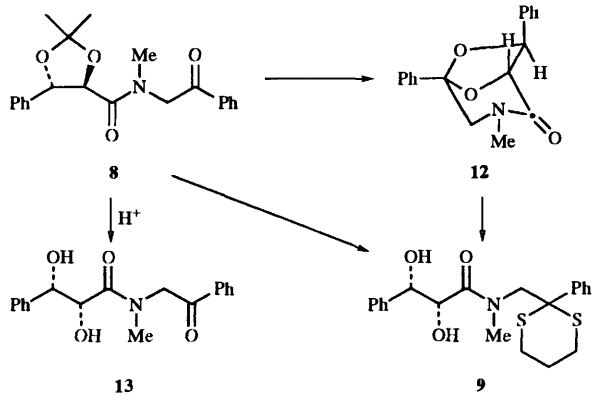
to its epimer was 5.8:1; **1**,† mp 179.6–181.4 °C, $[\alpha]_D^{25}$ +87.7 (*c*, 0.13 in MeOH). The IR, MS and ^{1}H NMR spectral data of synthetic **1** were identical with those of natural (±)-neoclausenamide.[1] An X-ray crystallographic analysis of (+)-**1** (recrystallized from MeOH) was carried out and the X-ray crystallographic numbering system is depicted in Fig. 1.

Experimental

Mps were measured on Büchi 535 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer and only the strongest/structurally most important peaks are listed. ^{1}H NMR spectra were obtained on Bruker AM300 (300 MHz), XL-200 or EM360 Spectrometer in $CDCl_3$, CD_3OCD_3 or $(CD_3)_2SO$ as stated using TMS as internal standard. For ^{19}F NMR spectra, CF_3CO_2H was used as an external standard (76.5 ppm upfield from $CFCl_3$) and peak positions are reported in ppm upfield from $CFCl_3$. Routine mass spectra were run on a Finnigan 4021 apparatus. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at the sodium D line and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was carried out using silica gel (10–40 μm, made in Qingdao, China).

(2*R*,3*S*)-2,3-Dihydroxy-*N*-[(2′*RS*)-2′-hydroxy-2′-phenylethyl]-*N*-methylpropanamide 4

Freshly prepared sodium methoxide (25% in methanol; 4 drops) was added to a solution of methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropanoate **2** (0.506 g, 2.50 mmol) and racemic 2-hydroxy-2-phenylethylamine (0.565 g, 3.75 mmol) in absolute methanol (4 cm^3). The mixture was stirred at 35 °C for 48 h, cooled to room temperature, adjusted to pH 7–8 with 10% hydrochloric acid and filtered through a short column of silica gel (200–300 mesh). The filtrate was evaporated and the residue was chromatographed on silica gel (eluent: dichloromethane–methanol, 40:1) to give white solid **4** (0.504 g, conversion 62%, yield 80%), mp 105.6–110.0 °C; ν(KCl)/cm^{-1} 3400 (OH) and 1640 (C=O); δ_H(200 MHz, $CDCl_3$) 7.45–7.20 (10 H, m, ArH), 4.95 (1 H, m, 2′-H), 4.72 (1 H, m, 3-H), 3.54 (2 H, m, 2-H), 2.84 (2 H, br, s, OH) and 2.38 (3 H, s, NCH_3); *m*/*z* (FAB) 316 (M + 1, 100), 298 (M + 1 − H_2O, 42) and 280 (M + 1 − $2H_2O$, 27) (Found: C, 68.4; H, 6.8; N, 4.3. $C_{18}H_{11}NO_4$ requires C, 68.57; H, 6.67; N, 4.44%).



Scheme 2

Table 1 Influence of the amount of $TiCl_4$ on the ratio of product **9** to **12** using **8** as the substrate*

Entry	Propanedithiol (equiv.)	$TiCl_4$ (equiv.)	BH_3·Et_2O (equiv.)	Yield (%) 12	9
1	3.0	0	4.0	78.0	Trace
2	3.0	2.5	0	46.3	46.4
3	3.0	3.0	0	6.2	66.8
4	3.0	4.0	0	2.5	76.8

* A typical procedure **8** (0.234 g, 0.66 mmol) and propane-1,3-dithiol (0.20 cm^3, 1.98 mmol) were dissolved in dichloromethane (3 cm^3) and the mixture was cooled to −10 to −15 °C. Immediately titanium tetrachloride was added to the mixture. After 10 min the mixture was slowly warmed to room temperature, stirred continuously for 5 h and then worked up.

1,3-Epoxy-*N*-[(2′*RS*)-2′-hydroxy-2′-phenylethyl]-*N*-methylpropanamide 5

Trimethyl orthoacetate (0.15 cm^3, 1.176 mmol) was added to a stirred solution of the triol **4** (0.262 g, 0.832 mmol) and toluene-*p*-sulfonic acid monohydrate (4 mg) in dichloromethane (5 cm^3). After 15 min, the mixture was evaporated and residual methanol was removed at *ca.* 0.5 mmHg for 5 min. The residue was taken up in dichloromethane (2 cm^3) to which Me_3SiCl (0.17 cm^3, 1.18 mmol) was added. After 100 min, TLC showed almost complete absence of hydroacetates. The mixture was heated to reflux for 60 min and then allowed to cool, when it was evaporated under reduced pressure to give the crude acetoxy chloride as an oil. K_2CO_3 (0.148 g, 1.05 mmol) was added in 2 portions over 10 min to a vigorously stirred solution of the crude acetoxy chloride in methanol (5 cm^3) at −20 °C. After 2 h, the mixture was poured into saturated aqueous NH_4Cl (5 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (eluent: light petroleum–ethyl acetate, 2:1) afforded the epoxy amide **5** as a white solid (0.075 g, 30.4%), mp 100.0–111.0 °C; ν(KCl)/cm^{-1} 3400 (OH), 1640 (C=O) and 1060 (COC); δ_H(300 MHz, $CDCl_3$) 7.60–7.20 (10 H, m, ArH), 5.15–4.90 (1 H, m, 3-H), 4.20–4.05 (1 H, m, 2′-H), 3.80 (1 H, m, 2-H), 3.80–3.60 (3 H, m, 1′-H) and 3.07 and 2.98 (3 H, s, NCH_3); *m*/*z* (FAB) 298 (M + 1, 9), 280 (M + 1 − H_2O, 10), 178 (10), 149 (26), 107 (20) and 55 (100) (Found: C, 72.6; H, 6.8; N, 4.3. $C_{18}H_{19}NO_3$ requires C, 72.73; H, 6.40; N, 4.71%).

† Although the methyl (2*R*,3*S*)-dihydroxy-3-phenylpropanoate used as a starting material had a high ee value, we believed that the ee of the final product **1** would be even higher after multiple conversions and purifications. In the ^{19}F NMR spectra of the bis-MTPA esters of compound **1** (prepared by Mosher's procedure, J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543), only two signals appeared at −69.9 and −70.5 ppm (60 MHz, $CDCl_3$) which represent two CF_3 signals of bis-MTPA ester of product **1**. No signals for a second isomer were observed.

(2*R*,3*S*)-2,3-Epoxy-*N*-methyl-*N*-phenacyl-3-phenylpropionamide 6 (from 5)

Potassium permanganate (0.5 g) and powdered copper sulfate hydrate (0.25 g) were added to a solution of compound **5** (0.05 g, 0.168 mmol) in methylene dichloride (5 cm^3) and the mixture was stirred vigorously for 4 h at room temperature. It was then filtered through a short silica gel column (200–300 mesh) and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: light petroleum–ethyl acetate, 1.5:1) to give a light yellow oil **6** (0.0334 g, 68.5%), $[\alpha]_D^{25}$ −98.5 (*c* 1.5, $CHCl_3$);[1e] ν(KCl)/cm^{-1} 3050 (ArH), 2920 (CH), 1700 (C=O), 1650 (C=O) and 1120 (COC); δ_H(300 MHz, $CDCl_3$) 7.98–7.25 (10 H, m, ArH), 5.0 (0.8 H, d, *J* 17.4, 1′-H), 4.98 (0.2 H, d, *J* 17.3, 1′-H), 4.88 (0.2 H, d, *J* 17.4, 1′-H), 4.77 (0.8 H, d, *J* 17.4, 1′-H), 4.16 (0.8 H, d, *J* 1.2, 2-H), 4.01 (0.2 H, d, *J* 1.4, 2-H), 3.79 (0.8 H, d, *J* 1.2, 1-H), 3.48 (0.2 H, d, *J* 1.4, 1-H) and 3.21 and 3.07 (3 H, s, NCH_3); *m*/*z* (EI) 296 (M + 1, 36.10), 295 (M, 23.12), 189 (66.90), 224 (7.61), 176 (31.14), 150 (17.47), 119 (9.91), 105 (100), 91 (87.29) and 77 (33.37).

(4*R*,5*S*)-{*N*-[(2′*RS*)-2′-Hydroxy-2′-phenylethyl]-*N*-methylcarbamoyl}-2,2-dimethyl-5-phenyl-1,3-dioxolane 7

A mixture of compound **4** (0.150 g, 0.423 mmol) and dry acetone (5 cm^3) was stirred with anhydrous toluene-*p*-sulfonic acid (20 mg) for 5 h after which it was neutralised with 10% aqueous sodium hydrogen carbonate, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography on silica gel (eluent: light petroleum–ethyl acetate, 3:1) to give **7** as a clear oil (0.156 g, 92%), ν(KCl)/cm^{-1} 3400 (OH), 3020 (ArH), 2920 (CH) and 1650 (C=O); δ_H(200 MHz, $CDCl_3$) 7.54–7.24 (10 H, m, ArH), 5.68 and 5.52 (1 H, d, *J* 18.0, 5-H), 5.00 (1 H, m, β-H), 4.44 and 4.28 (1 H, d, *J* 8.0, 4-H), 3.66 (2 H, m, α-H), 3.06, 3.02, 2.85 and 2.78 (3 H, s, NCH_3) and 1.60 (6 H, m, 2-CH_3); *m*/*z* (EI) 356 (M + 1, 19.46), 338 (M + 1 − H_2O, 24.51), 298 (26.47), 249 (16.27), 191 (93.24), 178 (35.49), 105 (29.32), 77 (22.65) and 45 (100) (Found: C, 70.7; H, 7.1; N, 3.8. $C_{21}H_{25}NO_4$ requires C, 70.98; H, 7.04; N, 3.94%).

(4*R*,5*S*)-[*N*-Methyl-*N*-(2′-oxo-2′-phenylethyl)carbamoyl]-2,2-dimethyl-5-phenyl-1,3-dioxolane 8

When treated by the same procedure as described in the preparation of **6**, compound **7** (0.255 g, 0.718 mmol) gave (eluent: light petroleum ether–ethyl acetate, 6:1) a colourless oil **8** (0.223 g, 88%), $[\alpha]_D^{25}$ −25.1 (*c* 1.67, $CHCl_3$); ν(KCl)/cm^{-1} 3020 (ArH), 2950 and 2900 (CH), 1700 (C=O), 1660 (C=O) and 1220 (COC); δ_H(300 MHz, $CDCl_3$) 8.00–7.28 (10 H, m, ArH), 5.65 and 5.54 (1 H, d, *J* 7.56, 5-H), 5.02 and 4.95 (1 H, d, *J* 17.22, α-H), 4.59 and 4.26 (1 H, d, *J* 7.56, 4-H), 3.08 and 2.99 (3 H, s, NCH_3), 1.63, 1.57, 1.39 and 1.37 (6 H, s, 2-H); *m*/*z* (EI) 354 (M + 1, 4.40), 296 (8.98), 190 (43.43), 176 (32.42), 147 (26.39), 119 (52.47) and 105 (100) (Found: C, 71.4; H, 6.9; N, 3.85. $C_{21}H_{23}NO_4$ requires C, 71.38; H, 6.52; N, 3.96%).

(2*R*,3*S*)-2,3-Dihydroxy-*N*-methyl-*N*-(2′-phenyl-1′,3′-dithiolan-2′-ylmethyl)-3-phenylpropionamide 9

Compound **8** (0.234 g, 0.66 mmol) was dissolved in dichloromethane (3 cm^3) and the solution cooled to −10 to −15 °C, when it was immediately treated with titanium tetrachloride. After 10 min the mixture was slowly warmed to room temperature and continuously stirred for 5 h. After this the reaction mixture was poured into chloroform–water (1:1; 20 cm^3) and the organic phase separated. The aqueous layer was extracted with chloroform (3 × 20 cm^3) and the combined organic layer and extracts were washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (eluent: light petroleum–ethyl acetate, 3:1) to give a white solid **9** (0.205 g, 76.8%) and a colourless oil **12** (0.005 g, 2.5%). Compound **9**, mp 156.8–158.0 °C; $[\alpha]_D^{25}$ −2.75 (*c* 1.16, $CHCl_3$); ν(KCl)/cm^{-1} 3400 (OH), 3020 (ArH), 2950 (CH) and 1630 (C=O); δ_H(300 MHz, $CDCl_3$) 7.94–7.20 (10 H, m, ArH), 4.73 (0.6 H, d, *J* 3.30, 3-H), 4.38 (0.4 H, d, *J* 4.0, 3-H), 4.48 (0.6 H, d, *J* 3.3, 2-H), 4.12 (0.4 H, d, *J* 4.0, 2-H), 4.27 (0.6 H, d, *J* 14.0, 1′-H), 3.72 (0.6 H, d, *J* 4.0, 1′-H), 3.18 (0.4 H, d, *J* 15.5, 1′-H), 2.89 (0.4 H, d, *J* 15.5, 1′-H), 3.50 (br, s, OH), 2.72 and 2.47 (3 H, s, NCH_3), 2.87–2.55 (4 H, m, $SCH_2CH_2CH_2S$-), 1.80–2.10 (2 H, m, $SCH_2CH_2CH_2S$); *m*/*z* (EI) 368 (M–2H_2O, 9.08), 313 (7.19), 208 (5.39), 195 (25.21), 141 (76.60), 123 (24.34), 110 (35.43), 95 (41.79), 57 (71.26) and 43 (100) (Found: C, 62.45; H, 6.2; N, 3.7; S, 15.7. $C_{24}H_{21}NO_4S_2$ requires C, 62.54; H, 6.20; N, 3.47; S, 15.88%). Compound **12**, $[\alpha]_D^{20}$ 51.1 (*c* 0.48, $CHCl_3$); ν(KCl)/cm^{-1} 3060 and 3020 (ArH), 2920 and 2870 (CH), 1680 (C=O), 1290 and 1120 (COC); δ_H(300 MHz, $CDCl_3$) 7.70–7.18 (10 H, m, ArH), 5.45 (1 H, s, 7-H), 4.69 (1 H, s, 1-H), 3.59 (2 H, dd, *J* 12.20, 4-H) and 2.99 (3 H, s, NCH_3); *m*/*z* (EI) 296 (M + 1, 100), 295 (M, 26.21), 279 (74.20), 262 (23.17), 190 (4.11), 173 (19.66), 131 (3.32) and 105 (5.52) (Found: C, 73.05; H, 5.86; N, 4.40. $C_{18}H_{17}NO_3$ requires C, 73.22; H, 5.76; N, 4.74%).

(2*R*,3*S*)-2,3-Epoxy-*N*-methyl-*N*-(2′-phenyl-1′,3′-dithiolan-2′-ylmethyl)-3-phenylpropionamide 10

When treated by the same procedure as described in the preparation of **5**, the diol **9** (0.194 g, 0.481 mmol) gave (eluent: light petroleum–ethyl acetate, 3:1) the epoxy amide **10** (0.173 g, 93%) as a light yellow oil, $[\alpha]_D^{25}$ −57.6 (*c* 1.34, $CHCl_3$); ν(KCl)/cm^{-1} 3020 (ArH), 2900 (CH), 2880 (CH), 1660 (C=O) and 1265 (COC); δ_H(300 MHz, $CDCl_3$) 8.00–7.16 (10 H, m, ArH), 4.14 (0.4 H, d, *J* 14.1, 1′-H), 4.06 (0.6 H, d, *J* 15.2, 1′-H), 4.03 (0.4 H, d, *J* 14.1, 1′-H), 3.79 (0.4 H, d, *J* 15.2, 1′-H), 3.90 (0.4 H, d, *J* 1.9, 3-H), 3.84 (0.4 H, d, *J* 1.9, 2-H), 3.51 (0.6 H, d, *J* 1.9, 3-H), 3.01 (0.6 H, d, *J* 1.9, 2-H), 2.93 and 2.77 (3 H, s, NCH_3), 2.90–2.60 (4 H, m, $SCH_2CH_2CH_2S$), 2.10–1.80 (2 H, m, $SCH_2CH_2CH_2S$); *m*/*z* (EI) 385 (M, 2.18), 278 (0.57), 195 (100), 121 (21.2) and 91 (22.4).

(2*R*,3*S*)-2,3-Epoxy-*N*-methyl-*N*-phenacyl-3-phenylpropionamide 6 (from 10)

A solution of **10** (0.133 g, 0.34 mmol) in acetonitrile (2 cm^3) was added quickly to a well-stirred solution of *N*-chlorosuccinimide (0.182 g, 1.36 mmol), silver nitrate (0.261 g, 1.53 mmol) in aqueous 80% acetonitrile (25 cm^3) and 2,6-dimethylpyridine (0.77 cm^3, 0.408 mmol) at 25 °C. Silver chloride separated immediately as a voluminous white precipitate and the liquid phase became yellow. The mixture was stirred for 10 min and then treated successively at 1 min intervals with saturated aqueous sodium sulfite, saturated aqueous sodium carbonate and brine (1 cm^3 each); The mixture was extracted with ethyl acetate (3 × 30 cm^3) and the combined organic layers were washed subsequently with saturated aqueous cupric sulfate, water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel to give **6** as a light yellow oil (0.086 g, 84.4%).

Neoclausenamidone 11a and 11b

1% Aqueous Me_4NOH was added to a solution of compound **6** (0.284 g, 0.963 mmol) in CH_2Cl_2 (20 cm^3) and the mixture was stirred vigorously for 6 h. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel (eluent: light petroleum–ethyl acetate, 1:1) to give a white solid comprising **11a** (0.256 g, 72.7%) and **11b** (0.862 g, 22.0%). Compound **11a**, mp 169–172 °C (lit.,[1e] mp 165–169 °C); $[\alpha]_D^{25}$ −11.8 (*c* 0.85, $CHCl_3$) {lit.,[1e] $[\alpha]_D^{15}$ −14.55 (*c* 0.50, $CHCl_3$)} ν(KCl)/cm^{-1} 3260 (OH) and 1685 (C=O); δ_H(300 MHz, $CDCl_3$) 7.68–7.07 (10 H, m, ArH), 5.08 (1 H, d, *J* 6.0, 5-H), 4.48 (1 H, d, *J* 6.0, 3-H), 3.29 (1 H, dd, *J* 6.0, 4-H), 2.95 (3 H, s, NCH_3) and 2.70 (br, s, OH); *m*/*z* (EI) 296 (M + 1, 2.49), 295 (M, 0.77), 190 (100), 162 (36.59), 134 (47.99), 119 (15.85), 105 (24.18), 91 (13.61) and 77 (35.55). Compound **11b**, mp 214–217.2 °C (lit.,[1e] mp 207–210 °C); $[\alpha]_D^{25}$ 316.3° (*c* 0.87, MeOH) (lit.,[1e] 333 (*c* 0.01,

MeOH); ν(KCl)/cm^{-1} 3375 (OH) and 1695 (C=O); δ_H(300 MHz, $CDCl_3$) 7.54–7.00 (10 H, m, ArH), 5.39 (1 H, d, *J* 9.18, 5-H), 4.92 (1 H, d, *J* 9.18, 3-H), 3.86 (1 H, dd, *J* 9.18, 4-H), 2.89 (3 H, s, NCH_3), 2.80 (br, s, OH); *m/z* (EI) 296 (M + 1, 0.87), 295 (M, 0.94), 190 (100), 162 (27.21), 134 (31.57), 119 (9.74), 105 (10.91), 91 (7.56) and 77 (14.68).

Neoclausenamide 1

Under N_2, diisobutylaluminium hydride (1 mol dm^{-3} in toluene; 0.542 cm^3, 0.544 mmol) was dropped into a solution of **11a** (0.040 g, 0.136 mmol) in THF (2 cm^3) at −78 °C over 10 min. The mixture was vigorously stirred for 16 h, after which it was cautiously treated with water (1 cm^3) to quench the reaction and then extracted with ethyl acetate (3 × 5 cm^3). The combined extracts were dried, filtered and evaporated and the residue was chromatographed on silica gel column (eluent: light petroleum–ethyl acetate, 1 : 1) to give a colourless solid **1**[6] (0.023 g, 82%) which was recrystallized from methanol for X-ray structural analysis. Compound **1**, mp 179.6–181.4 °C (lit.,[1] mp 205–206 °C); $[\alpha]_D^{25}$ +87.7 (*c* 0.13, MeOH); ν(KCl)/cm^{-1} 3340 (OH) and 1660 (C=O); δ_H(300 MHz, [$^2H_6$]-DMSO) 7.26–6.85 (10 H, m, ArH), 5.00 (1 H, d, *J* 2.62, 7-H), 3.88 (2 H, m, 3-H and 5-H), 3.06 (1 H, dd, *J* 7.13, 4-H) and 2.91 (3 H, s, NCH_3); *m/z* (EI) 298 (M + 1, 1.13), 280 (M + 1 − H_2O, 0.50), 190 (100), 174 (16.74), 162 (51.16), 134 (75.22), 119 (26.16), 105 (22.61), 91 (26.30) and 77 (37.46).

X-Ray crystallographic analysis of compound 1

Crystal data, data collection and processing. A colourless prismatic crystal of $C_{18}H_{19}NO_2$ having approximate dimensions of 0.10 × 0.20 × 0.40 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12 KW rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the range 16.41 < 2θ < 19.53° corresponded to a primitive orthorhombic cell with dimensions: *a* 7.438(5), *b* 33.511(7), *c* 6.109(6) Å, *V* = 1522(1) Å^3. For *Z* = 4 and *M* = 297.35, the calculated density is 1.30 g cm^{-3}. The systematic absences of: *h*00: *h* ≠ 2*n*, 0*k*0: *k* ≠ 2*n*, 00*l* ≠ 2*n* uniquely determine the space group to be: $P2_12_12_1$ (#19). The data were collected at a temperature of 20 ± 1 °C using the ω–2θ scan technique to a maximum 2θ valve of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.39° with a take-off 6.0°. Scans of (1.27 + 0.30 tan θ)° were made at a speed of 16.0° min^{-1} (in omega). The weak reflections [$I < 15.0\sigma(I)$] were re-scanned (maximum of 5 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 m, the crystal to detector distance was 235 mm, and the computer-controlled detector aperture was set to 9.0 × 13.0 mm (horizontal vertical). A total of 1629 reflections were collected. The intensities of three representative reflections were measured after every 200 reflections. Over the course of data collection, the standard changed by −0.5%. A linear correction factor was applied to the account for this phenomenon. The linear absorption coefficient, μ, for Mo-Kα radiation is 0.9 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.95 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure analysis and refinement

The structure was solved by direct methods and refined using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included, but their positions were not refined; isotropic *B* values were refined. The final cycle of full-matrix least-squares refinement was based on 1036 observed reflections [$I > 3.00\sigma(I)$] and 219 variable parameters and converged (largest parameter was 1.32 times its e.s.d.) with unweighted and weighted agreement factors of: R = 0.078, R_w = 0.089. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.29 and −0.27 e Å^{-3}, respectively.

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