lecular ion cluster the prominent peaks are displaced to $m/z$ 258 and 262, corresponding to 76 atom % $^{18}O$ enrichment of **2**. This result demonstrates unequivocally that the oxygen atom of **2** also originates from molecular oxygen; it confirms the conclusion of the earlier work[13] and places it on a much firmer experimental basis.

On the basis of the data presented above, mechanisms for C-ring closure as the one shown in Scheme II can be excluded. It seems therefore likely after all that the formation of ring C of the ergot alkaloids proceeds by a mechanism involving a potential carbocation at the benzylic carbon and a potential carbanion at C-$\alpha$, but modified to account for the fact that the process must take place after methylation of the amino group. Scheme I shows a plausible reaction sequence which is consistent with all the experimental data.

## Experimental Section

*Claviceps* sp. strain SD 58[14,15] was grown for 6 days in shake culture at 25 °C in 500-mL Erlenmeyer flasks containing 100 mL of medium NL 406.[15] The cultures were then filtered aseptically, and the mycelia were washed with sterile water and resuspended in 100 mL of 1/15 M phosphate buffer, pH 7.3. This process was repeated once, and the mycelia were then suspended in 100 mL of 1/15 M phosphate buffer, pH 7.3, containing 5 mg of L-tryptophan, 10 mg of D,L-mevalonic acid, and 5 mg of L-[$^{13}C^2H_3$]-methionine (synthesized from $^{13}C^2H_3I$, 99% $^{13}C$, 98% $^2H$, MSD Isotopes). The flasks were closed with a rubber septum, evacuated through a needle, filled with nitrogen, and evacuated again. They were than connected through a needle to a flask containing $^{18}O$-oxygen gas (1 L, 97.8 atom % $^{18}O$, MSD Isotopes). After pressure equilibration, the culture flasks were brought to atmospheric pressure with nitrogen and incubated for 2 days at 25 °C with shaking. Parallel cultures were treated in the same way with $^{16}O_2$ gas. Two flasks were used for each experiment.

The alkaloids were extracted with 1:2 2-propanol–chloroform from the culture filtrate made alkaline with ammonium hydroxide. The extract was evaporated to dryness in vacuo and partitioned between 2% aqueous succinic acid and $CH_2Cl_2$. The aqueous phase was washed twice with $CH_2Cl_2$, made alkaline with ammonium hydroxide, and extracted 3 times with $CH_2Cl_2$. The extract was dried over $Na_2SO_4$ and evaporated in vacuo, and the residue was subjected to preparative TLC (SIL G-25 $UV_{254}$, 0.25 mm, Macherey-Nagel, developed with 150:40:40:1 $CHCl_3$–MeOH–*t*-BuOH–$NH_4OH$). The bands of **2** ($R_f$ 0.23) and **3** ($R_f$ 0.69) were scraped off and eluted with 100:50:1 $CHCl_3$–MeOH–$NH_4OH$, and the alkaloids were analyzed by GC-MS (Hewlett-Packard 5970A GC-mass spectrometer, SPB-5 capillary column 0.25 mm × 15 m; flow rate 1.0 mL/min; temperature program: 60 °C for 4 min, then 10°/min to 295 °C, retention times, **2**, 22.3 min; **3**, 24 min).

**Acknowledgment.** This work was supported by National Institutes of Health Research Grant GM 32333.

**Registry No.** **2**, 2390-99-0; **3**, 548-43-6.

(14) Gröger, D. *Arch. Pharm. (Weinheim, Ger.)* **1959**, *292*, 389.
(15) Floss, H. G.; Gröger, D. *Z. Naturforsch. B Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **1963**, *18B*, 519.

# Diastereoselective and Enantioselective Total Synthesis of the Hepatoprotective Agent Clausenamide†

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The diastereoselective total synthesis of the naturally occurring hepatoprotective agent clausenamide (3-hydroxy-5-(α-hydroxybenzyl)-1-methyl-4-phenylpyrrolidin-2-one) is described, starting from ethyl cinnamate and diethyl acetamidomalonate. The enantioselective total synthesis of optically pure (+)-clausenamide is presented. The synthesis is based on a novel method for the preparation of optically pure (2*S*,3*S*)-3-phenylglutamic acid.

In Chinese folk-medicine the aqueous extract of the leaves of the plant *Clausena lansium* (lour) skeels is held to be an efficacious liver protecting agent and is used in cases of acute and chronic viral hepatitis. Scientists at the Institute of Materia Medica of the Chinese Academy of Medical Sciences in Peking[1] have studied this plant extract and have isolated as the main component of the extract γ-lactam 1[2] called clausenamide, occuring at about 4 × $10^{-2}$% on the basis of dry leaf weight (Figure 1).

Clausenamide showed a marked hepatoprotective effect against chemical toxins, such as carbon tetrachloride and thioacetamide, in initial tests. In addition, **1** was observed to have an inducing effect on cytochrome P450, which is of course essential for the metabolisation of xenobiotics.

Larger quantities of clausenamide were then required for more detailed pharmacological studies. As only 3.8 g of the natural product can be isolated from 10 kg of dried leaves, a total synthesis of clausenamide seemed to be a desirable alternative.

**Structure.** According to X-ray analysis (Figure 2), clausenamide has the 3*S**,4*R**,5*R**,7*S** relative configuration and, most surprisingly, is a racemate. This naturally reduces the synthetic problem quite drastically.

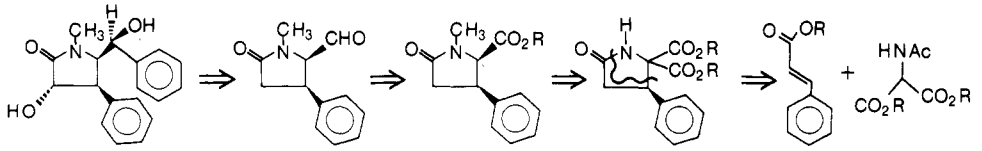
**Retrosynthetic Analysis.** According to the retrosynthetic approach (Scheme I) high stereoselectivity should be expected in the construction of the hydroxybenzyl unit in clausenamide from the aldehyde function, due to the inducing effect of the neighboring C(4)-phenyl ring. It should be possible to introduce the hydroxy group by base-induced oxidation. The C(4)-phenyl ring should also exert a benevolent influence here upon the stereoselectivity and direct the hydroxy group into the trans position. A

† Dedicated to Prof. U. Schoellkopf on the occasion of his 60th birthday.

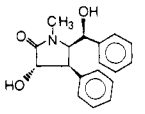
(1) Yan Rang Chen, Ming He Yang, Liang Huang, Tao Geng, Benz, U. Ger. Offen. DE 3 431 257 Appl. Aug 24, 1984; EP 172514; *Chem. Abstr.* **1986**, *105*, 72689r.
(2) For the sake of clarity, the descriptors for the other antipode are omitted.

0022-3263/87/1952-4352$01.50/0 

**Scheme I**

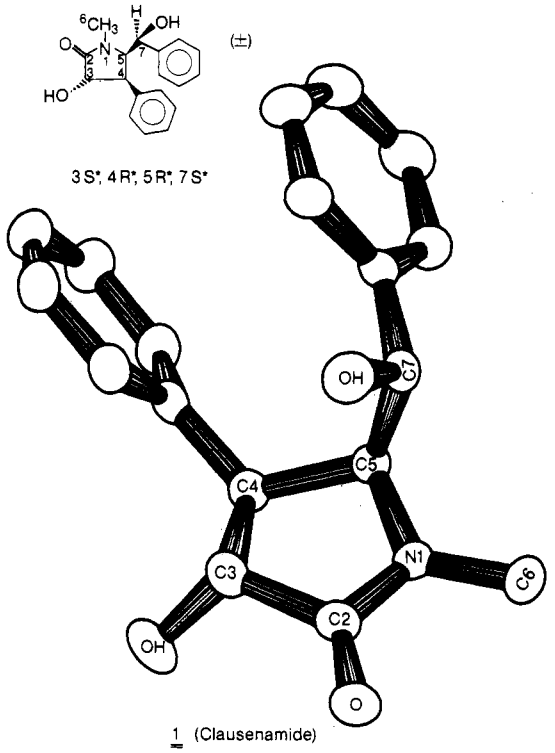


2



1 (Clausenamide)

**Figure 1.**



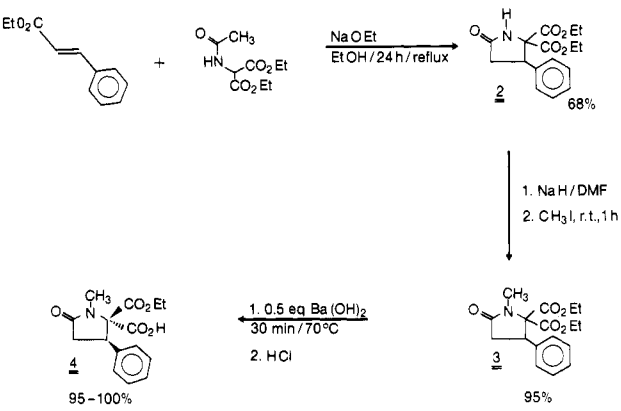

1 (Clausenamide)

**Figure 2.**

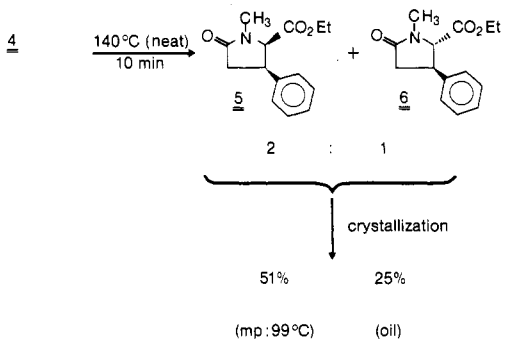
high degree of 4,5-cis stereoselectivity can be expected in the decarboxylation step. This is indicated by results on other cyclic systems with a similar substitution pattern. The 5,5-bis(ethoxycarbonyl)-4-phenylbutyrolactam (**2**) is literature-known[3] and can be prepared from ethyl cinnamate and diethyl acetamidomalonate.

**Synthesis.** After slight modifications to the literature procedure the pyrrolidinone **2** was obtained in 68% yield on a kilogram scale. Methylation of the amide nitrogen occurred smoothly upon deprotonation with sodium hydride and subsequent reaction with methyl iodide to give **3** in 95% yield. Treatment of **3** with barium hydroxide only hydrolyzed the ester group trans to the phenyl group to give the ester–acid **4** in nearly quantitative yield (Scheme II). For the selective decarboxylation of the ester–acid **4** leading to the 4,5-cis monocarboxylic acid ester **5**, there are good analogies in the literature. According to these literature sources,[4] heating a 1,2-disubstituted cyclic dicarboxylic acid monoester with collidine leads almost

**Scheme II**




**Scheme III**



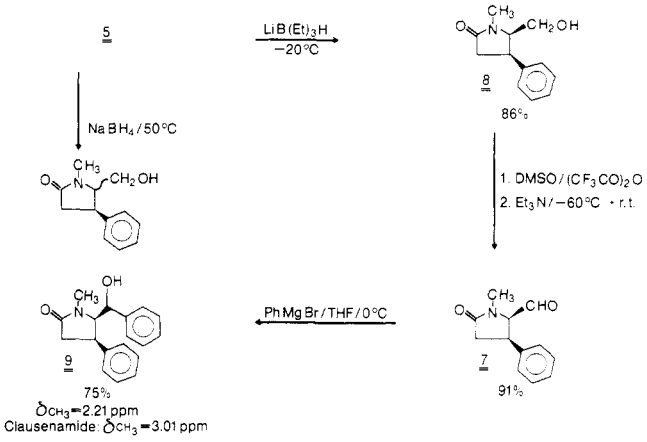

exclusively to the 1,2-cis-configurated monocarboxylic ester. Unfortunately, **4** gave under these conditions both isomers—cis and trans—in about equal proportions. On the other hand, simply heating of the ester–acid **4** without solvent provided the desired decarboxylated cis isomer **5** in the ratio 2:1 with its trans isomer **6**. By recrystallization **5** could be separated in a 51% yield of pure product (Scheme III). Alternatively, it is possible to separate the unwanted trans isomer **6** by selective hydrolysis with barium hydroxide and extraction into water (as barium carboxylate).

The direct conversion of the carboxylic ester **5** to the aldehyde **7** failed using reducing agents such as DIBAL-H. As a consequence reduction to the alcohol **8** and oxidation back to the aldehyde **7** was planned. Reduction with sodium borohydride led to cis/trans mixtures of **8**, but the sterically hindered Superhydride ($LiBEt_3H$) gave the pure cis alcohol **8** in 86% yield. Oxidation of **8** under Swern's conditions with DMSO/trifluoroacetic anhydride afforded the desired aldehyde **7** in high yield without epimerisation at the 5-position.

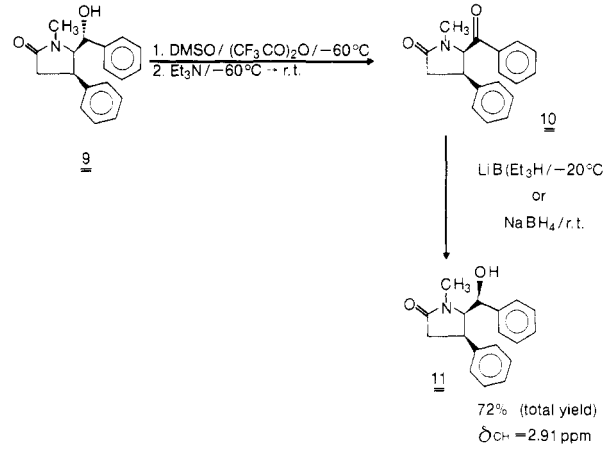
The coupling of the phenyl residue to the aldehyde group was predicted to proceed with high stereoselectivity due to the inducing effect of the C(4)-phenyl ring. In fact, the reaction of **7** with phenylmagnesium bromide gave only one diastereoisomer of the adduct **9** exclusively in 75% yield (Scheme IV). However, the configuration at C(7) of the adduct **9** could not by determined unambiguously from the NMR spectrum. Most remarkably, the N-methyl group gave an NMR signal at $\delta$ 2.21 in contrast to clau-

(3) Cocolas, G. H.; Hartung, W. H. *J. Am. Chem. Soc.* **1957**, *79*, 5203. Zymalkowski, F.; Pachaly, P. *Chem. Ber.* **1967**, *100*, 1137.
(4) E.g.: Abell, P. I.; Lennon, D. J. *J. Org. Chem.* **1965**, *30*, 1206. Musso, H. *Chem. Ber.* **1968**, *101*, 3710.

**Scheme IV**




**Scheme V**



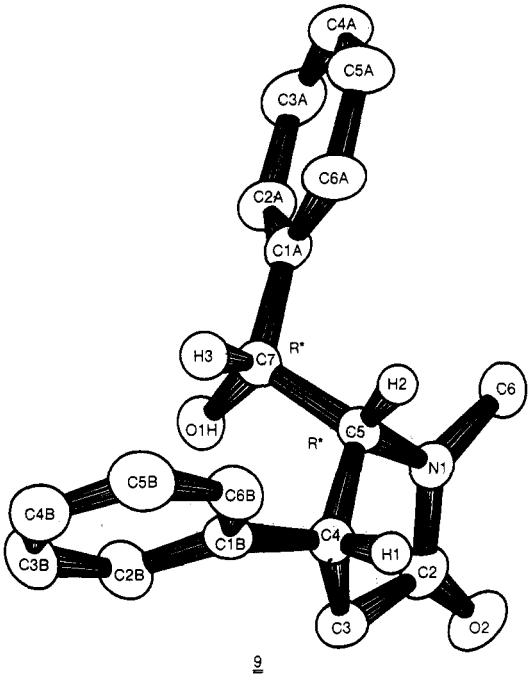
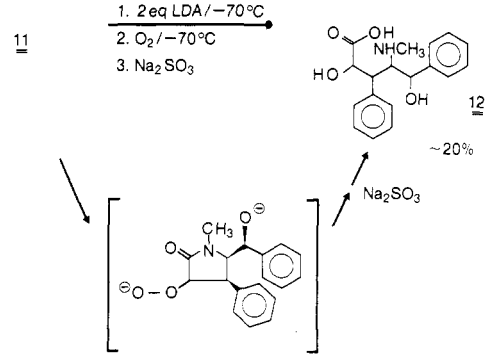
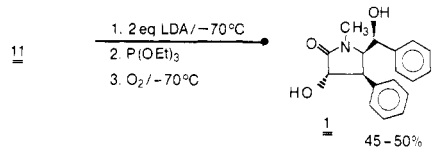




**Figure 3.**

**Scheme VI**




**Scheme VII**

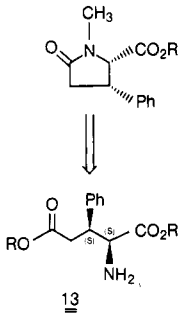



senamide where this signal appears $\delta$ 0.8 further downfield. An X-ray structural analysis showed that **9** had the wrong 5*R**,7*R** configuration (Figure 3). In contrast to clausenamide, the N-methyl group in **9** lies precisely in the anisotropic field of the newly introduced phenyl ring, thus explaining the unusual high-field shift of its NMR signal. In order to get to clausenamide, **9** had to be epimerized at C(7). An inversion of configuration by $SN_2$ exchange failed, possibly due to steric hindrance. Mechanistically, the stereochemical outcome (**8** → **9**) can be explained by an attack of the second phenyl residue from the side facing away from the C(4)-phenyl ring. If one were to formally reverse the sequence of entry of the substituents, first phenyl, then hydrogen, then the *S** configuration should be induced instead of *R**. In fact, oxidation of **9** to the benzoyl derivate **10** with DMSO/trifluoroacetic anhydride and subsequent reduction with $LiB(Et)_3H$ or $NaBH_4$ gave the desired 5*R**,7*S** epimer **11** exclusively in 72% overall yield (Scheme V). In the $^1H$ NMR spectrum of **11**, the signal for the N-methyl group appears at $\delta$ 2.91, indicating that the methyl group is no longer in the anisotropic field of the C(7)-phenyl ring. Now that three stereocentres had been established with the correct configuration, all that remained was the introduction of the hydroxy group at C(3).

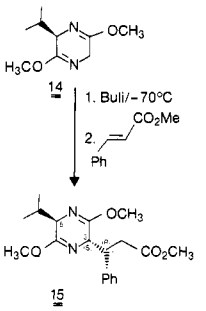
In the literature there are many reagents for introducing a hydroxy group. Among others we tried out Vedejs reagent,[5] 2-sulfonyloxaziridine,[6] and *m*-chloroperbenzoic acid,[7] none of which were successful in our case. Base-induced reaction with oxygen is an old literature method for hydroxylation.[8] Under these conditions, the deprotonation of **11** with 2 equiv of lithium diisopropylamide, reaction with oxygen and subsequent reduction of the intermediate peroxide with sodium sulfite, we obtained a new compound with a newly incorporated hydroxy group as desired, but this compound revealed itself to be the ring-opened amino acid **12** (Scheme VI). Mechanistically, this could be explained by the strongly nucleophilic peroxide anion attacking the amide carbonyl group intra- or intermolecularly. In situ reduction of the peroxide anion by triethyl phosphite added to the reaction mixture gave the desired hydroxylated product **1** in up to 50% yield. The 3,4-trans configurated product was formed exclusively and was identical with authentic clausenamide in all its physical data (Scheme VII).

(5) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(6) Davies, F. A.; Vishwarkarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3243.
(7) Rubottom, G. M.; Marrero, R. *Synth. Commun.* **1981**, *11*, 505.
(8) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731. Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578.

**Scheme VIII**



**Scheme IX**



**Enantioselective Synthesis of Optically Pure 1.** Natural clausenamide (1) is known to be a racemate. Because we have been interested in the activity and toxicity of the pure enantiomers, a synthesis of optically pure clausenamide was highly desirable. We considered the enantioselective synthesis of one of the intermediates in the total synthesis described in the foregoing to be an appropriate method. A key intermediate in the total synthesis described in the foregoing is the pyrrolidinone **5**, with the correct 4,5-cis configuration already established. In the synthetic strategy followed here, the stereocentre at C(4) (the phenyl substituent) will direct the correct relative configuration at C(3) and C(7). Retrosynthetically, for the enantioselective synthesis of optically pure **5** the ideal precursor should be the corresponding amino acid, in this case the *S,S*-configurated 3-phenylglutamic acid (**13**) (Scheme VIII).

Optically pure amino acids can be obtained according to the "bis lactim ether method".[9] Thus, metalation of the (2*R*)-(−)-dihydropyrazine (**14**)[10] with butyllithium and subsequent reaction with the *trans*-cinnamic methyl ester afforded in 77% yield optically pure adduct **15**, however, with the unwanted 3*S*,1′*R* configuration[11] (Scheme IX). This particular compound is of course useless for our purpose, leading to the wrong trans configurated pyrrolidinone.

Mechanistically, the stereochemical outcome can be explained with a chair-like transition state between carbon atoms 1′,2′,3′ of the cinnamic ester and nitrogen 1 and carbon atoms 2,3 of the dihydropyrazine, where the carbonyl group is oriented above the nitrogen forming a chelate with the lithium cation (Figure 4). If the assumption is true that the chair-like transition state is the deciding factor for the stereochemical outcome, then the 3*S*,1′*S* configuration should be expected by using the *cis*-cinnamic ester instead of the trans ester. Indeed, with the *cis*-cinnamic ester the desired adduct **16** with the correct 3*S*,1′*S* configuration was obtained in optically pure form in 73% of pure product after flash chromatography (Scheme X). The 3*S*,1′*R* epimer **15** could be isolated in 13.4% yield. Minor amounts of the 3*R*,1′*S* and 3*R*,1′*R* epimers were detected by GC/MS analysis. (Epimeric ratio = 3*S*,1′*S*:3*S*,1′*R*:3*R*,1′*S*:3*R*,1′*R* = 384:70:2.7:1).[12]

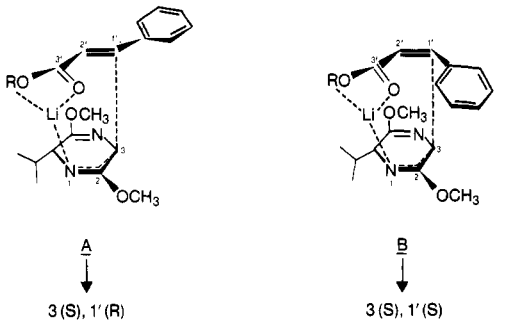
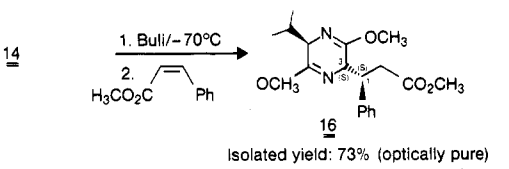
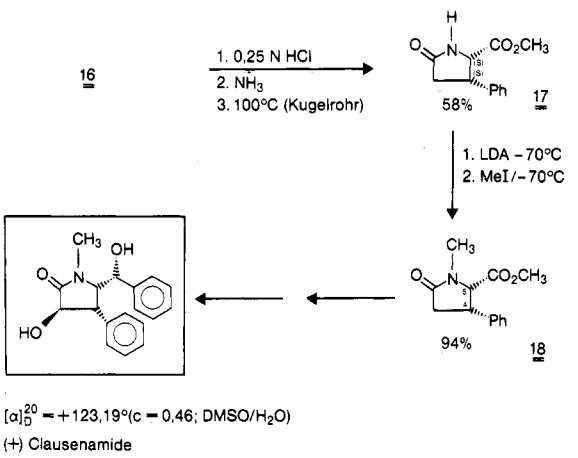


Figure 4.

**Scheme X**



**Scheme XI**



Hydrolysis of the intermediate **16** under mild conditions with dilute HCl, neutralization, and heating at 100 °C furnished directly the desired optically pure pyrrolidinone **17** while valine methyl ester was distilled off simultaneously. Methylation on the amide nitrogen proceeded smoothly upon metalation with LDA and reaction with methyl iodide to give the wanted optically pure key intermediate **18** (methyl ester of **5**). That could be transformed to optically pure (+)-clausenamide according to the procedure described in the foregoing with racemic material (Scheme XI).

**Conclusion.** With the synthetic strategy followed here, we are not only able to synthesize clausenamide but also

(9) (a) Hartwig, W.; Schoellkopf, U. Ger. Offen. DE 2 934 252, Appl. Aug 24, 1979; *Chem. Abstr.* **1981**, *95*, 62704c. Reviews: (b) Schoellkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65; (c) *Tetrahedron* **1983**, *39*, 2085; (d) *Pure Appl. Chem.* **1983**, *55*, 1799; (e) *Chem. Scr.* **1985**, *25*, 105. (f) Streith, J., Prinzbach, U., Schill, G., Eds. *Organic Synthesis: An Interdisciplinary Challenge*; Blackwell Scientific Publications: Oxford, London, Edinburgh, Boston, Palo Alto, Melbourne, 1985 p 101 ff.

(10) Commercially available from Merck-Schuchardt, Darmstadt (FRG).

(11) (3*S*,1′*S*)-**16** could be separated in 2.8% yield by flash chromatography. A comparable result was obtained by Schoellkopf, U. (see ref 9e).

(12) Hartwig, W. Ger. Offen. Appl. 3 616 989, May 20, 1986. After our work had been completed, Schoellkopf reported an epimeric ratio of 3*R*,1′*R*:3*R*,1′*S*:3*S*,1′*R*:3*S*,1′*S* = 148:46:<0.5:1 using (*S*)-**14** and methyl *cis*-cinnamate. See: Schoellkopf, U.; Pettig, D.; Busse, U.; Egert, E.; Dyrbusch, M. *Synthesis* **1986**, 737.

three further diastereomers when, in the course of the synthesis, the 4,5-trans configurated pyrrolidinone **6** or the 5*R**,7*R**-configurated compound **9** is elaborated in the final steps. (−)-Clausenamide is accessible when the *S* epimer of **14** is used. The pharmacological properties of optically pure (+)-clausenamide are currently under investigation.

## Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 281 infrared spectrophotometer. Optical rotations were determined on a Perkin-Elmer 241 MC polarimeter. The NMR spectra were recorded on Bruker WP 200, WM 250, and AM 300 spectrometers in either $CDCl_3$ or $(CD_3)_2SO$ solution. Chemical shifts are reported as $\delta$ values in ppm relative to tetramethylsilane ($\delta$ 0.0) as an internal standard. Data are reported as follows: chemical shift (multiplicity, coupling constants, integrated intensity, assignment). NMR multiplicities are recorded by using the following abbreviations: s, singlet; d, doublet; t, triplet, q, quartet; n, multiplet; br, broad; *J*, coupling constant (hertz). Mass spectra were obtained on a Kratos MS 80 mass spectrometer. Reactions were monitored by analytical thin-layer chromatography using 5 × 10 cm TLC plates: silica gel 60 F-254, layer thickness 0.25 mm, E. Merck. Silica gel columns for flash chromatography utilized E. Merck silica gel 60 (230–400 mesh ASTM) and a slightly positive pressure of air. Anhydrous solvents were distilled shortly before use from an appropriate drying agent. Lattice constants and intensity data were measured at 295 K on an Enraf-Nonius Cad-4 automated diffractometer using graphite-monochromatized Cu K$\alpha$ radiation.

**(±)-5,5-Bis(ethoxycarbonyl)-4-phenylpyrrolidin-2-one (2).** A solution of sodium (18 g, 0.8 mol) in absolute ethanol (40 mL) was added dropwise to a suspension of diethyl acetamidomalonate (432 g, 2 mol) in absolute ethanol (1.6 L) at room temperature under $N_2$ atmosphere. Ethyl cinnamate (564 g, 3.2 mol) was slowly added and the mixture was heated under reflux for 24 h. The reaction mixture was allowed to come to room temperature, chloroform (2.5 L) as added, and the mixture was neutralized with acetic acid. It was washed thoroughly with water (5 × 500 mL), dried over $MgSO_4$, and concentrated on a rotary evaporator. The oily residue was dissolved in a little acetone, hexane was added until crystallization occurred, and further hexane was then added until no further cloudiness was to be observed. Filtration with suction gave 398 g (54%) of the title compound **2**. The filtrate was concentrated and the residue was purified by chromatography ($SiO_2$; toluene/ethyl acetate = 1:1 as eluent) to give a further 85 g (14%) of the title compound: total yield, 413 g (68%); IR (KBr) 1770 (s, ester), 1700 (s, amide) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.84 and 1.28 (t each, $J$ = 7.5 Hz, 6 H, $CH_2CH_3$); ABX signal $\delta_A$ 2.63, $\delta_B$ 2.96 ($J_{AB}$ = 17.3 Hz, $J_{AX}$ = 6 Hz, $J_{BX}$ = 9 Hz, 2 H, C(3)-H); 3.66 and 3.71 (m each, 2 H, *cis*-$CH_2CH_3$); 4.28 (m, 2 H, *trans*-$CH_2CH_3$); 4.39 (dd, $J_{AX}$ = 6 Hz, $J_{BX}$ = 9 Hz, 1 H, C(4)-H); 6.95 (br, 1 H, NH); 7.39 (br, 5 H, $C_6H_5$). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.9; H, 6.3; N, 4.6. Found: C, 62.9; H, 6.1; N, 4.5.

**(±)-5,5-Bis(ethoxycarbonyl)-1-methyl-4-phenylpyrrolidin-2-one (3).** A solution of **2** (100 g, 0.33 mol) in absolute dimethylformamide (500 mL) was added dropwise to a suspension of sodium hydride (9.64 g, 0.36 mol) in absolute dimethylformamide (200 mL) at room temperature under $N_2$ atmosphere. The mixture was stirred at room temperature until the evolution of gas had ended, a solution of methyl iodide (93.7 g, 0.66 mol) in absolute dimethylformamide (50 mL) was added, and the mixture was stirred at room temperature until the starting material had been consumed (ca. 1 h, checked by TLC). The reaction mixture was poured into 2 L of phosphate buffer (pH 7) and extracted five times with 600 mL of diethyl ether. Drying of the organic extracts ($MgSO_4$) and evaporation of the solvent in vacuo gave 105 g (99.6%) of the title compound **3** (95% pure according to $^1H$ NMR) which was further reacted directly. Bulb-to-bulb distillation at 240 °C (0.5 mm) provided the analytical sample: $R_f$ 0.36 (toluene/ethyl acetate, 2:1); IR (neat) 1735 (s, ester), 1700 (s, amide); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.9 and 1.33 (t each, $J$ 7.5 Hz, 6 H, $CH_2CH_3$); ABX signal $\delta_A$ 2.66, $\delta_B$ 3.0 ($J_{AB}$ = 18 Hz, $J_{AX}$ = 6 Hz, $J_{BX}$ = 8.3 Hz, 2 H, C(3)-H); 3.06 (s, 3 H, NCH); 3.62 and 3.79 (m each, 2 H, *cis*-$CH_2CH_3$); 4.31 (m, 3 H, *trans*-$CH_2CH_3$ and C(4)-H); 7.26 (m, 5 H, $C_6H_5$). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 64.0; H, 6.6; N, 4.6.

**(±)-(4*R**,5*R**)- and (±)-(4*R**,5*S**)-5-(Ethoxycarbonyl)-1-4-phenylpyrrolidin-2-one (5 and 6).** Barium hydroxide octahydrate (49.5 g, 0.156 mol) was heated in distilled water (483 mL) at 70 °C until an almost clear solution was formed. A solution of **3** (100 g, 0.313 mol) in ethanol (724 mL) was added and the mixture was stirred at 70 °C for 20 min until the starting material had been consumed (ca. 20 min, checked by TLC). The mixture was cooled and acidified to pH 1–2 with concentrated HCl while cooling with ice, and the ethanol was evaporated (bath temperature 30–40 °C). The solid was filtered off with suction and the aqueous phase was extracted, with addition of sodium chloride, 3 times with 200 mL of ethyl acetate. Drying and evaporation of the solvent in vacuo gave a residue which was combined with the solid obtained above, and the mixture was dried in a desiccator over $P_4O_{10}$ for 24 h. The solid was then heated to 170 °C, while stirring thoroughly, until the evolution of gas had ended (5–10 min). Recrystallization of the crude product from 1:1 cyclohexane/ethyl acetate afforded pure **5** (41%). Alternatively, the crude product, containing **5** and **6**, was dissolved in ethanol (600 mL) and added to a solution of barium hydroxide octahydrate (50 g, 0.156 mol) in water (250 mL) at 70 °C. Stirring was continued at this temperature until **6** had been consumed (ca. 20 min, checked by TLC, 1:1 cyclohexane/ethyl acetate; **5** $R_f$ 0.10; **6** $R_f$ 0.20). Ethanol was evaporated in vacuo, and the precipitate was filtered with suction, washed with water, and dried over $P_4O_{10}$ in vacuo to give 29.2 g (37.6%) of **5** (mp 111 °C). Extraction of the filtrate with ethyl acetate, drying, and evaporation of the solvent in vacuo gave a further 10.3 g (13.1%) of **5**. Total yield: 39.3 g (50.7%). Acid **6** could be isolated from the aqueous filtrate by acidification and extraction with ethyl acetate.

**5**: IR (KBr) 1736, 1690 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 0.83 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$); ABX signal $\delta_A$ 2.67, $\delta_B$ 2.95 ($J_{AB}$ = 17.5 Hz, $J_{AX}$ = 9 Hz, $J_{BX}$ = 10 Hz, 2 H, C(3)-H); 2.87 (s, 3 H, $NCH_3$); 3.75 (m, 2 H, $CH_2CH_3$); 3.91 (q, $J$ = 9–10 Hz, 1 H, C(4)-H); 4.36 (d, $J$ = 9 Hz, 1 H, C(5)-H); 7.28 (m, 5 H, $C_6H_5$). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.1; H, 7.0; N, 5.7. **6**: $^1H$ NMR $\delta$ 1.30 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$); ABX signal $\delta_A$ 2.54, $\delta_B$ 2.82 ($J_{AB}$ = 18.5 Hz, $J_{AX}$ = 5 Hz, $J_{BX}$ = 9 Hz, 2 H, C(3)-H); 3.80 (s, 3 H, $NCH_3$); 3.53 (ddd, $J$ = 9 Hz, $J$ = 5 Hz, $J$ = 4 Hz, 1 H, C(4)-H); 4.07 (t, $J$ = 4 Hz, 1 H, C(5)-H); 4.27 (m, 2 H, $CH_2$-$CH_3$); 7.3 (m, 5 H, $C_6H_5$).

**(±)-(4*R**,5*R**)-5-(Hydroxymethyl)-1-methyl-4-phenylpyrrolidin-2-one (8).** A 1 M solution of $LiB(Et)_3H$ in tetrahydrofuran (0.317 mol, 316.9 mL) was added dropwise to a solution of **5** (39.2 g, 0.159 mol) in absolute tetrahydrofuran (390 mL) at −15 to −20 °C under $N_2$ atmosphere. The reaction mixture was stirred at 0 °C for 1 h, poured into ice-cold 2 N hydrochloric acid (200 mL), and extracted twice with 200 mL of ethyl acetate. The aqueous phase was saturated with sodium chloride and extracted twice with 200 mL of ethyl acetate. The collected organic extracts were washed with a little water, dried over $MgSO_4$, and concentrated on a rotary evaporator. The residue was triturated with ether until crystallization occurred; then pentane was slowly added until no further cloudiness was to be observed. Filtration with suction and drying afforded 29.1 g (89.2%) of the title compound (mp 93–95 °C): IR (KBr) 3324, 1687 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) AB part of ABM system: $\delta_A$ 2.59, $\delta_B$ 2.97 (dd each, $J_{AB}$ = 15 Hz, $J_{AM}$ = 7.5 Hz, $J_{BM}$ = 9 Hz, 2 H, C(3)-H); 2.97 (s, 3 H, $NCH_3$); AB part of ABM system $\delta_A$ 3.36, $\delta_B$ 3.62 (dd each, $J_{AB}$ = 11.2 Hz, $J_{AM}$ = $J_{BM}$ = 3 Hz, 2 H, C(7)-H); 3.72–3.85 (m, 2 H, C(4)-H, C(5)-H); 7.32 (m, 5 H, $C_6H_5$). Anal. Calcd for $C_{12}H_{15}NO_2$ (35 mol % $H_2O$): C, 68.1; H, 7.4; N, 6.6. Found: C, 68.2; H, 7.3; N, 6.6.

**(±)-(4*R**,5*R**)-5-Formyl-1-methyl-4-phenylpyrrolidin-2-one (7).** A solution of trifluoroacetic anhydride (29.7 mL) in absolute methylene chloride (56 mL) was added dropwise at −60 °C to a solution of absolute DMSO (19.9 mL, 0.28 mol) in absolute methylene chloride (140 mL) under $N_2$ atmosphere during 10 min. The mixture was stirred at this temperature for 15 min and a solution of **8** (28.8 g, 0.14 mol) in anhydrous methylene chloride (250 mL) was added dropwise such that the temperature did not exceed −60 °C. The mixture was stirred at −60 °C for 90 min, warmed briefly to −30 °C (5–10 min), and cooled to −60 °C.

Triethylamine (56 mL) was slowly added at this temperature and the mixture was stirred at −60 °C for 30 min and warmed to room temperature. Water (600 mL) was added, the phases were separated, and the aqueous phase was extracted three times with methylene chloride (250 mL). The collected organic extracts were washed twice with water (300 mL) and dried over magnesium sulfate. The solvent was evaporated to give 28.3 g (100%) of the title compound with $R_f$ 0.25 (ethyl acetate) (91% pure according to $^1$H NMR). The crude product thus obtained was further reacted directly, after drying (24 h over $P_4O_{10}$ in vacuo): IR ($CHCl_3$) 1734, 1689 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.79 (dd, $J$ = 5.3 Hz, $J$ = 9.7 Hz, 2 H, C(3)-H), 2.91 (s, 3 H, $NCH_3$), 4.02 (q, $J$ = 9.7 Hz, 1 H, C(4)-H), 4.30 (dd, $J$ = 1 Hz, $J$ = 9.7 Hz, 1 H, C(5)-H), 7.3 (m, 5 H, $C_6H_5$), 9.17 (d, $J$ = 1 Hz, 1 H, CHO).

**(±)-(4*R**,5*R**,7*R**)-5-(α-Hydroxybenzyl)-1-methyl-4-phenylpyrrolidin-2-one (9).** A solution of bromobenzene (24.8 g, 0.156 mol) in anhydrous tetrahydrofuran (44 mL) was added dropwise to Mg filings (3.89 g) under $N_2$ such that the tetrahydrofuran simmered. Anhydrous tetrahydrofuran (100 mL) was then added and the mixture was heated under reflux until all the magnesium had dissolved (1–2 h). The mixture was cooled to 0 °C and a solution of **7** (24.7 g 0.12 mol) in anhydrous tetrahydrofuran (250 mL) was added dropwise, with vigorous stirring, such that the temperature did not exceed 5 °C. In some runs, tetrahydrofuran had to be added for better stirrability. The reaction mixture was then stirred at 0–5 °C for 1 h, poured onto 0.5 N HCl–ice (350 mL), and extracted four times with ethyl acetate (300 mL) and twice with methylene chloride (300 mL). The collected ethyl acetate and methylene chloride extracts were washed (separately) twice with water (200 mL), combined, and dried over magnesium sulfate. The solvent was evaporated and the residue was triturated ether (100 mL) until crystallization occurred. Pentane (500 mL) was slowly added and the mixture was left to stand overnight in a refrigerator. Filtration of the solid gave 25 g (74.3%) of the title compound (mp 210–212 °C). Recrystallization from acetone gave the analytical sample: mp 214–215 °C; IR (KBr) 3362 (br), 1654 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.21 (s, 3 H, $NCH_3$); 2.24 (dd, A-part of ABM system, $J_{AB}$ = 15.7 Hz, $J_{AM}$ = 9.4 Hz, 1 H, *cis*-C(3)-H); 3.05 (dd, B-part of ABM system, $J_{BM}$ = 12.7 Hz, 1 H, *trans*-C(3)-H); 3.80 (dt, M-part of ABM system, $J_{AM}$ = 8.5 Hz, $J_{AB}$ = 12.7 Hz, $J_{4,5}$ = 8.5 Hz, 1 H, C(4)-H); 4.15 (dd, $J$ = 8.5 Hz, $J$ = 1 Hz, 1 H, C(5)-H); 4.26 (dd, $J$ = 6 Hz, $J$ = 1 Hz, 1 H, C(7)-H); 5.35 (d, $J$ = 6 Hz, 1 H, OH); 7.15–7.5 (m, 10 H, $C_6H_5$). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0. Found: C, 76.6; H, 6.9; N, 5.0.

**(±)-(4*R**,5*R**)-5-Benzoyl-1-methyl-4-phenylpyrrolidin-2-one (10).** A solution of trifluoroacetic anhydride (18 mL) in absolute methylene chloride (34 mL) was added dropwise to a solution of absolute dimethyl sulfoxide (12.24 mL, 0.171 mol) in anhydrous methylene chloride (87 mL) at −60 °C under an $N_2$ atmosphere during 10 min. The mixture was stirred at this temperature for 15 min and a solution of **9** (24 g, 0,085 mol) in absolute methylene chloride (700 mL) was added dropwise such that the temperature did not exceed −60 °C. The mixture was subsequently stirred at −60 °C for 90 min, warmed briefly to −30 °C (9–10 min), and cooled again to −60 °C. Triethylamine (34.2 mL) was slowly added at this temperature and the mixture was stirred at −60 °C for 23 min and warmed to room temperature. Water (370 mL) was added, the phases were separated, and the aqueous phase was extracted three times with methylene chloride (250 mL). The combined organic extracts were washed twice with water (300 mL), dried over magnesium sulfate, and concentrated on a rotary evaporator. The residue was evaporated in a rotary evaporator twice with ether (200 mL) to give 23.5 g (100%) of the title compound **10** as a solid (mp 115–116 °C). The crude product (pure according to $^1$H NMR) was further reacted directly. Chromatography on silica gel with ethyl acetate as eluant afforded the analytical sample: $R_f$ 0.25; mp 121–122 °C; IR (KBr) 1695, 1682 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.78 and 2.91 (AB-part of ABM spectrum, $J_{AB}$ = 16.5 Hz, $J_{AM}$ = $J_{BM}$ = 8.3 Hz, 2 H, C(3)-H); 2.88 (s, 3 H, $NCH_3$); 4.02 (q, $J$ = 8.3 Hz, 1 H, C(4)-H); 5.42 (d, $J$ = 8.3 Hz, 1 H, C(5)-H); 7.0, 7.21, 7.59, and 7.50 (m each, 10 H, $C_6H_5$). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.1; N, 5.0. Found: C, 77.3; H, 6.2; N, 4.9.

**(±)-(4*R**,5*R**,7*S**)-5-(α-Hydroxybenzyl)-1-methyl-4-phenylpyrrolidin-2-one (11).** $LiB(Et)_3H$ (83 mL of a 1 M solution in tetrahydrofuran) was added dropwise to a solution of **10** (23 g, 82.3 m mol) in absolute tetrahydrofuran (250 mL) at −15 °C to −20 °C under $N_2$ atmosphere. The reaction mixture was stirred at 0 °C for 1 h, poured into ice-cold 1 N HCl (100 mL), and extracted twice with ethyl acetate (200 mL). The aqueous phase was saturated with sodium chloride and extracted twice with ethyl acetate (200 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator. The residue was dissolved in methylene chloride and washed twice with water (100 mL). The organic phase was dried ($MgSO_4$) and concentrated on a rotary evaporator. The residue was triturated with ether (100 mL) until crystallization occurred. Pentane was slowly added, with stirring, until no further cloudiness was to be observed. Filtration of the precipitate gave 16.6 g (72%) of the title compound **11** (mp 189–195 °C). The product is 95% pure according to $^1$H NMR and was further reacted directly. Recrystallization from acetone gave the analytical sample (mp 197–198 °C): IR (KBr) 3251, 1692 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO) $\delta$ 1.97 and 2.05 (ABM signal, $J_{AB}$ = 13.5 Hz, $J_{AM}$ = 8.2 Hz, $J_{BM}$ = 13 Hz, 2 H, C(3)-H); 2.91 (s, 3 H, N-$CH_3$); 3.82 (dt, $J_{AM}$ = $J_{4,5}$ = 8.2 Hz, $J_{BM}$ = 13 Hz, 1 H, C(4)-H); 4.27 (dd, $J$ = 8.2 Hz, $J$ = 1.5 Hz, 1 H, C(5)-H); 4.65 (dd, $J$ = 1.5 Hz, $J$ = 3.5 Hz, 1 H, C(7)-H); 5.34 (d, $J$ = 3.5 Hz, 1 H, OH); 6.70, 7.11 and 7.25 (m each, 10 H, $C_6H_5$). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0. Found: C, 77.0; H, 6.9; N, 5.0.

**(±)-(3*S**,4*R**,5*R**,7*S**)-3-Hydroxy-5-(α-hydroxybenzyl)-1-methyl-4-phenylpyrrolidin-2-one (Clausenamide) (1).** A solution of lithium diisopropylamide (0.152 mol) in anhydrous tetrahydrofuran/hexane (180 mL) [prepared from diisopropylamine (22.1 mL) in tetrahydrofuran (80 mL) by addition of a 1.5 N solution of *n*-butyllithium (103 mL) in hexane at −20 °C to 0 °C] was added dropwise at −70 °C under $N_2$ atmosphere to a solution of **11** (17.7 g, 62.8 mmol) in anhydrous tetrahydrofuran (490 mL) and absolute hexamethylphosphoric acid triamide (130 mL). The mixture was stirred at −70 °C to −60 °C for 1 h. Freshly distilled trimethyl phosphite (5.3 mL) (dissolved in a little anhydrous tetrahydrofuran) was added and absolute oxygen (dried over $H_2SO_4$ and $P_4O_{10}$) was passed in (50–100 mL/min). As soon as the product/starting material ratio no longer changed (2–3 h, checked by TLC, $SiO_2$; 2:1 ethyl acetate/MeOH; 1 $R_f$ 0.3, **11** $R_f$ 0.37, molybdatophosphoric acid spray reagent for visualization), the mixture was poured onto 600 mL of 0.5 N HCl, while cooling with ice, and acidified to pH 3 to 4. The phases were separated and the aqueous phase was extracted four times with ethyl acetate (300 mL). The combined organic extracts were washed three times with water (300 mL), dried over $MgSO_4$, and concentrated on a rotary evaporator. The residue was taken up in 50–100 mL of ether, the mixture was stirred until crystallization started, and pentane was slowly added, with stirring, until no further cloudiness was to be observed. The mixture was left to stand overnight in a refrigerator and filtered with suction. The crude product (17 g, containing 35–40% **11**) was recrystallized twice from 2-propanol to give 7.65 g (41%) of **1** (about 95% pure, by $^1$H NMR). Alternatively, the crude product can be chromatographed on aluminum oxide (neutral): the crude product is absorbed onto silica gel (dissolving in warm MeOH, addition of 5 parts by weight of silica gel, concentration on a rotary evaporator, and evaporation several times with ethyl acetate until a MeOH-free product results). The adsorbate is introduced onto a column containing $Al_2O_3$ (neutral, 50 parts by weight). **11** (5 g) is eluted first with ethyl acetate (flash chromatography, checked by HPLC). The title compound **1** is eluted with ethyl acetate/methanol mixtures (40/1, 20/1, and then 10/1) to give 8.6 g (46.1%) of **1** (mp 236–237.5, °C, 98% pure according to $^1$H NMR; authentic clausenamide mp 236–237 °C): IR (KBr) 3402, 3321, 1689 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO) $\delta$ 3.01 (s, 3 H, $NCH_3$); 3.50 (dd, $J$ = 8 Hz, $J$ = 10.5 Hz, 1 H, C(4)H); 3.82 (dd, $J$ = 10 Hz, $J$ = 7 Hz, 1 H, C(3)-H); 4.30 (dd, $J$ = 8 Hz, $J$ = 2 Hz, 1 H, C(5)-H); 4.65 (dd, $J$ = 2 Hz, $J$ = 3 Hz, 1 H, C(7)-H), 5.39 (d, $J$ = 7 Hz, 1 H, C(3)-OH); 5.45 (d, $J$ = 3 Hz, 1 H, C(7)-OH); 6.61–6.64 (m, 2 H, aromatic H); 7.03–7.28 (m, 8 H, aromatic H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.5; N, 4.7. Found: C, 72.6; H, 6.6; N, 4.6.

**(3*S*,6*R*,1′*S*)-2,5-Dimethoxy-6-isopropyl-3-[2′-(methoxycarbonyl)-1′-phenylethyl]-3,6-dihydro-1,4-pyrazine (16).** A 1.6 N solution of *n*-butyllithium in hexane (70 mL, 108.4 mmol) was added under an $N_2$ atmosphere to a precooled (−70 °C)

solution of (3*R*)-(−)-2,5-dimethoxy-3-isopropyl-3,6-dihydro-1,4-pyrazine (**14**) (20 g, 108, 4 mmol) in anhydrous tetrahydrofuran (120 mL). Stirring was continued at −70 °C during 10 min, methyl *cis*-cinnamate (19.36 g, 119.2 mmol) dissolved in tetrahydrofuran (60 mL) was added, and stirring was continued during 12 h at this temperature and 1 h at −20 °C. A solution of acetic acid (6.83 mL, 108.4 mmol) was added, and the reaction mixture was warmed to room temperature and poured onto ice water (300 mL). The mixture was extracted three times with 150 mL of ethyl acetate, the combined extracts were dried over $MgSO_4$, and the solvent was evaporated in vacuo, to give 33.1 g (88%) of crude **16**. Flash chromatography on silica gel (Amicon, mesh 20–45) with 20:1 toluene/ethyl acetate gave 27.4 g (73%) of the pure title compound **16** as a light yellow oil with $R_f$ 0.46 (toluene/ethyl acetate, 9:1) and 4.9 g (13%) of the diastereoisomer **15** with $R_f$ 0.36 (toluene/ethyl acetate, 9:1).

**15**: $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 0.57 and 0.89 (d each, $J$ = 6.9 Hz, $(CH_3)_2C$, 2 H); 2.1 (m, $(CH_3)_2CH$, 1 H); ABM-signal ($\delta_A$ = 2.91, $\delta_B$ = 3.18, $J_{AB}$ = 15.6 Hz, $J_{AM} = J_{BM}$ = 6.8 Hz, 2 H, 2′-H); 3.08 (t, $J$ = 3.1 Hz, 1 H, C(3)-H); 3.61, 3.65 and 3.72 (s each, 3 H each, $OCH_3$); 3.9 (dt, $J$ = 6.8 Hz, $J$ = 3.1 Hz, 1 H, C(1′)-H); 4.34 (t, $J$ = 3.1 Hz, 1 H, C(6)-H); 7.0–7.25 (m, 5 H, aromatic H); MS, $M^+$ 347. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.9; H, 7.6; N, 8.1. Found: C, 66.5; H, 7.7; N, 8.0.

**(4*S*,5*S*)-(+)-5-(Methoxycarbonyl)-4-phenylpyrrolidin-2-one (17).** A suspension of **16** (13.7 g, 39.5 mmol) in 0.25 N HCl (317 mL) was stirred thoroughly for 3 days at room temperature. The reaction mixture was extracted three times with diethyl ether (100 mL, recovering of starting material). The aqueous solution was lyophilizated and the residue was suspended in water (5 mL). Concentrated ammonia was added to pH 9–10, followed by sodium chloride until saturation, and the suspension was extracted five times with 100 mL of ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude product was heated at 100 °C/0.1 mm in a bulb-to-bulb distillation apparatus, while methyl D-valinate was distilled off. The residue was triturated with ethyl ether/pentane to give 5 g (58%) of the title compound **17** with $R_f$ 0.2 (ethyl acetate): mp 113–114 °C; $[\alpha]^{20}_D$ +209.05° (*c* 0.54 MeOH); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.78 (dd, $J$ = 7.5 Hz, $J$ = 2 Hz, 2 H, C(3)-H); 3.30 (s, 3 H, $OCH_3$); 3.99 (q, $J$ = 7.5 Hz, 1 H, C(4)); 4.58 (d, $J$ = 7.5 Hz, 1 H, C(5)-H); 6.85 (br, 1 H, NH); 7.19–735 (m, 5 H, $C_6H_5$). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.7; H, 6.0; N, 6.4. Found: C, 65.5; H, 6.1; N, 6.4.

**(4*S*,5*S*)-(+)-*N*-Methyl-5-(methoxycarbonyl)-4-phenylpyrrolidin-2-one (18).** To a solution of **17** (5 g, 22.8 mmol) in anhydrous tetrahydrofuran (50 mL) and hexamethylphosphoric acid triamide (15 mL) was added under $N_2$ atmosphere at −70 °C a solution of lithium diisopropylamide (25 mmol) in tetrahydrofuran/hexane (prepared from 15.7 mL of 1.55 N *n*-butyllithium and 3.5 mL of diisopropylamine in 15 mL of tetrahydrofuran). Stirring was continued for 20 min at −70 °C, methyl iodide (4.2 mL, 0.114 mol), dissolved in tetrahydrofuran (5 mL), was added dropwise, and stirring was continued for 1 h at −70 °C. The temperature was allowed to rise to room temperature during 30 min and as soon as the starting material had been consumed (checked by TLC), the reaction mixture was poured onto phosphate buffer solution (pH 7, 200 mL). The mixture was extracted four times with 100 mL of ethyl acetate by addition of NaCl until saturation of the aqueous phase. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated to give crude **18**, which was filtrated through silica gel with ethyl acetate as eluant. Pure **18** (5.05 g, 94.6%) was obtained with $R_f$ 0.3 (ethyl acetate): mp 100 °C; $[\alpha]^{20}_D$ +205.95° (*c* 0.38, MeOH); IR (KBr) 1736, 1690 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$) ABX-signal ($\delta_A$ = 2.70 $\delta_B$ = 2.95, $J_{AB}$ = 17.5 Hz, $J_{AX}$ = 10 Hz, $J_{BX}$ = 11 Hz, 2 H, C(3)-H); 2.89 (s, 3 H, $NCH_3$); 3.30 (s, 3 H, $OCH_3$); 3.91 (q, $J$ = 10 Hz, 1 H, C(4)-H); 4.39 (d, $J$ = 9–10 Hz, 1 H, C(5)-H); 7.18–7.38 (m, 5 H, $C_6H_5$). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 67.1; H, 6.5; N, 6.0.

**(+)-(3*R*,4*S*,5*S*,7*R*)-3-Hydroxy-5-(α-hydroxybenzyl)-1-methyl-4-phenylpyrrolidin-2-one ((+)-1) [(+)-Clausenamide].** Optically pure (+)-(4*S*,5*S*,7*R*)-**11** was hydroxylated according to the procedure described for racemic **11**: 0.88 g (3.14 mmol) of (+)-**11** gave 0.44 g (46.1%) of (+)-**1** [(+)-clausenamide]. To remove traces of methanol (200 ppm), the product was stirred thoroughly with water, filtrated with suction, and dried over $P_4O_{10}$ in vacuo to give (+)-clausenamide as hydrate (contains $^1/_4$ mol of $H_2O$) with mp: 152–153 °C and $[\alpha]^{20}_D$ +123.19° (*c* 0.46 DMSO/$H_2O$ = 9:1 vol %). The $^1$H NMR spectrum of (+)-**1** was identical with that of an authentic sample of (racemic) clausenamide.

**Single-Crystal X-ray Structure Determination of 9.** Crystals suitable for X-ray diffraction analysis were grown from acetone. A colorless, transparent, parallelepiped-shaped crystal measuring 0.5 × 0.225 × 0.2 mm was used for data collection. Unit cell dimensions were obtained by least-squares methods from the adjusted angular settings of 25 large-angle reflections. The crystal data are as follows: $C_{18}H_{19}NO_2$, triclinic space group $P\bar{1}$; $a$ = 6.0867 (7) Å, $b$ 10.183 (2) Å, $c$ = 12.349 (2) Å, $\alpha$ = 102.80 (1)°, $\beta$ = 91.42 (2)°, $\gamma$ = 95.57 (1)°, $V$ = 742.0 Å$^3$, $Z$ = 2, $d_c$ = 1.259 g/cm$^3$, $\mu$(Cu K$\alpha$) = 6.1 cm$^{-1}$. Data collection was attempted to $\theta \leq 65°$ in the $\omega$–$2\theta$ scanning mode. A total of 2657 reflections were collected ($\pm h,\pm k,l$) yielding 2329 unique reflections with $I > 3.0\sigma(I)$. This set of reflections was used in the structure solution. Data reduction included corrections for background, Lorentz, and polarization effects, extinction, and absorption by a semiempirical method.[13]

The non-hydrogen atoms were located by direct methods (MULTAN).[14] The positions of the hydrogen atoms were calculated geometrically or in the case of the methyl and hydroxyl H atoms located from Fourier difference maps. Full-matrix least-squares refinement was carried out with anisotropic temperature factors for non-H atoms and isotropic factors for H atoms, using all reflections with $I > 3.0\sigma(I)$ and sin $\theta/\lambda < 0.5$ Å$^{-1}$. The final $R_1$ (1507 reflections, 267 variables) was 0.032. The following programs were used: Enraf-Nonius SDP[15] and ORTEP.[16]

**Single-Crystal X-ray Structure Determination of 1 (Clausenamide).** Crystals suitable for X-ray diffraction analysis were grown from methanol. For data collection was used a colorless, transparent, parallelepiped-shaped crystal measuring 0.35 × 0.175 × 0.075 mm. Unit cell dimensions were obtained by least-squares methods from the adjusted angular settings of 24 large-angle reflections. The crystal data are as follows: $C_{18}H_{19}NO_3$, monoclinic space group $P2_1/c$; $a$ = 16.128 (3) Å, $b$ = 6.502 (1) Å, $c$ = 14.333 (3) Å, $\beta$ = 87.27 (1)°, $V$ = 1501.2 Å$^3$, $Z$ = 4, $d_c$ = 1.316 g/cm$^3$, $\mu$(Cu K$\alpha$) = 6.9 cm$^{-1}$. Data collection was attempted to $\theta \leq 60°$ in the $\sigma$–$2\theta$ scanning mode. A total of 2343 reflections were collected ($\pm h,k,l$) yielding 1901 unique reflections with $I > 3.0\sigma(I)$. This set of reflections was used in the structure solution. Data reduction included corrections for background, Lorentz, and polarization effects, extinction, and absorption by a semiempirical method.[13]

By direct methods (MULTAN)[14] the non-hydrogen atoms were located. The positions of the hydrogen atoms were calculated geometrically or in the case of the methyl and hydroxyl H atoms located from Fourier difference maps. Full-matrix least-squares refinement was carried out with anisotropic temperature factors for non-H atoms and isotropic factors for H atoms, using all reflections with $I > 3.0\sigma(I)$ and sin $\theta/\lambda < 0.5$ Å$^{-1}$. The final $R_1$ (1454 reflections, 276 variables) was 0.027. The following programs were used: Enraf-Nonius SDP[15] and ORTEP.[16]

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**Supplementary Material Available:** X-ray data for compounds **1** and **9**, table of bond distances, table of bond angles, table of positional parameters and their estimated standard deviations, and table of general temperature factor expressions (8 pages). Ordering information is given on any current masthead page.

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