110. Total Synthesis of (+)-(8*S*,13*R*)-Cyclocelabenzine

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Dedicated to Professor *Vladimir Prelog* on the occasion of his 90th birthday

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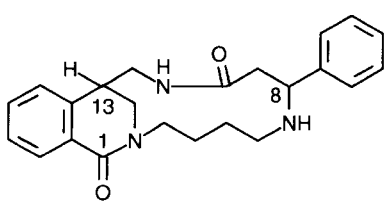
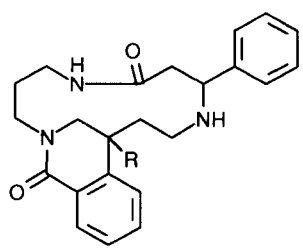
An asymmetric synthesis of the spermidine alkaloid (+)-cyclocelabenzine (**1a**) and its (–)-(13*S*)-epimer **1b** is described using optically active (+)-(3*S*)-3-amino-3-phenylpropionic acid as the chiral building block. The isoquinolin-1-one fragment **15** was synthesized by a modified *Bischler-Napieralski* reaction. The relative configuration of the (–)-isomer was determined by an X-ray crystal-structure analysis, which enabled us to determine the absolute configuration of natural (+)-**1a** as (8*S*,13*R*).

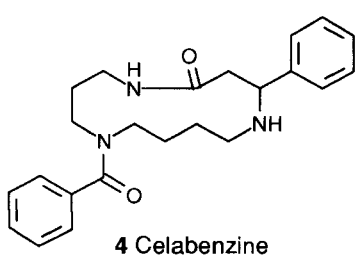
1. Introduction. – The optically active macrocyclic alkaloids (+)-cyclocelabenzine (**1**), (+)-isocyclocelabenzine (**2**), and (+)-hydroxyisocyclocelabenzine (**3**) were isolated from *Maytenus mossambicensis* (KLOTZSCH) BLAKELOCK *var. mossambicensis* by *Wagner* and coworkers [1] in 1978 (see *Fig. 1*).



1 Cyclocelabenzine



2 R = H Isocyclocelabenzine
3 R = OH Hydroxyisocyclocelabenzine



4 Celabenzine

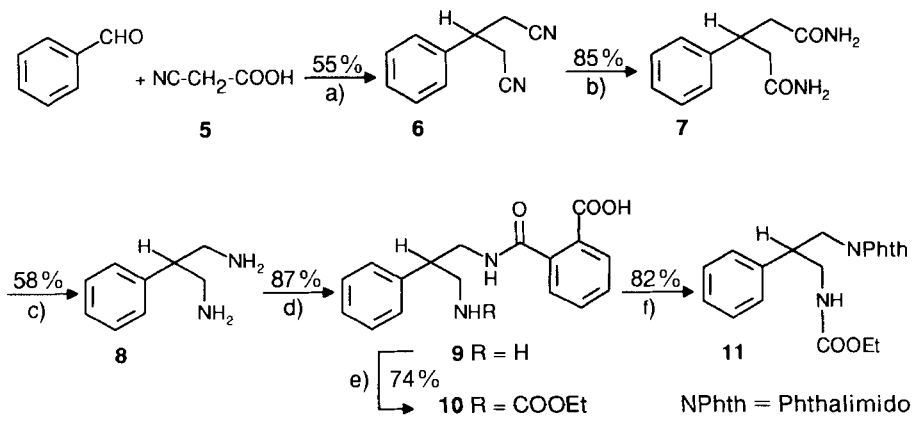
Fig. 1. *Spermidine alkaloids isolated from* Maytenus mossambicensis (KLOTZSCH) BLAKELOCK var. mossambicensis

[1]) Part of the planned Ph. D. Thesis of *K. S.*, Universität Zürich.

These three alkaloids have in common the celabenzine moiety **4**, a *N*-benzoyl-substituted 13-membered lactam ring, containing spermidine and (3-phenyl)propanoyl precursorial units. The benzoyl group in turn is linked to the spermidine unit of the macrocycle, forming an additional six-membered ring. The structures of these compounds were elucidated mainly by spectroscopic methods, particularly through ^{1}H- and ^{13}C-NMR studies, but no assignment of the configurations at the two chiral centers has been accomplished so far. In 1986, *Kikuchi* and coworkers [2] developed a total synthesis of (±)-isocyclocelabenzine (**2**) in order to verify the proposed structure, but no total synthesis of cyclocelabenzine (**1**) has previously been reported. Here, we present the total synthesis of (+)-cyclocelabenzine (**1a**) which allows the determination of its hitherto unknown absolute configuration by an X-ray crystal-structure analysis. The key step consists in the synthesis of a suitably substituted tetrahydroisoquinolin-1-one derivative **15** (*cf. Scheme 3*) which was prepared by a modified *Bischler-Napieralski* reaction. To introduce one of the two stereogenic centers directly, it was assumed that the chiral center at C(8) has the (*S*)-configuration, as found in all other structurally known macrocyclic spermidine alkaloids. Therefore, (+)-(3*S*)-3-amino-3-phenylpropanoic acid was used as the chiral building block.

2. Results and Discussion. – The symmetrical 3-phenylglutarodinitrile (**6**) was prepared from benzaldehyde and 2-cyanoacetic acid (**5**) by the procedure of *Schiemenz* and *Engelhard* [3] (*Scheme 1*). The dinitrile **6** was converted into the corresponding diamide **7** by hydrolysis with aqueous Na_2CO_3 and H_2O_2 according to [4]. This method is generally preferable over hydrolysis with H_2SO_4 due to the improved ease of product isolation from the reaction mixture. Finally, the diamide was converted into 2-phenylpropane-1,3-diamine (**8**) by a double *Hofmann* rearrangement [5]. Treatment of **8** with phthalic anhydride led exclusively to the mono-protected product **9** in 87% yield. The surprisingly high yield is due to the insolubility of the compound **9** in the solvent system used. Thus, it was

Scheme 1



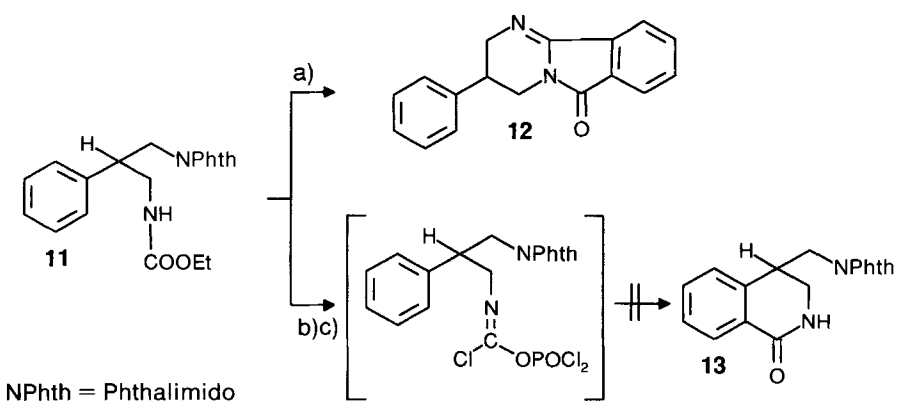
a) Piperidine, pyridine, reflux, 5 h. b) H_2O_2, Na_2CO_3, H_2O, 15 h. c) Br_2, NaOH, H_2O, 1 h, r.t. → 2 h, 70°. d) 1 equiv. of phthalic anhydride, THF/toluene, reflux. e) ClCOOEt, NEt_3, MeOH, r.t., 3 h. f) toluene, reflux, 15 h.

impossible to dehydrate **9** directly to the corresponding phthalimido derivative. This problem could be circumvented by a readily applicable two-step sequence that consisted in protecting the free amino group first, followed by ring closure to the carbamate **11**. Therefore, the second amino group of the propane-1,3-diamine unit was protected with ClCOOEt in MeOH to give crude **10**. Purification of the product was not possible because of its high polarity and reactivity, so the workup was followed immediately by refluxing **10** in toluene overnight in order to form the ethyl *N*-(2-phenyl-3-phthalimidopropyl)carbamate (**11**).

1,2,3,4-Tetrahydroisoquinolin-1-ones (dihydroisocarbostyrils) can be formed by cyclization of the β-arylethyl isocyanates of the β-arylethylurethans, respectively. So, to obtain the lactam fragment **13**, we attempted to cyclize compound **11** according to literature procedures with polyphosphoric acid [6], $POCl_3$, or $POCl_3$ in combination with $SnCl_4$ [7]. However, all attempts utterly failed. With polyphosphoric acid as the catalyst, 3,4-dihydro-3-phenyl-2*H*-pyrimido[2,1-*a*]isoindol-6-one (**12**) was formed in a yield of 39%. Compound **12** is an anhydro derivative of compound **9** (*Scheme 2*). Treatment of **11** with $POCl_3$ alone, as well as with subsequent addition of $SnCl_4$, gave either no conversion at all, even after prolonged reaction times, or, after elevating the temperature up to 175°, led to a mixture of undefinable products. The reason for the failure may be seen in the missing activation of the aromatic ring by an electron-donating substituent in the *meta*-position which was mentioned in the cited literature [7].

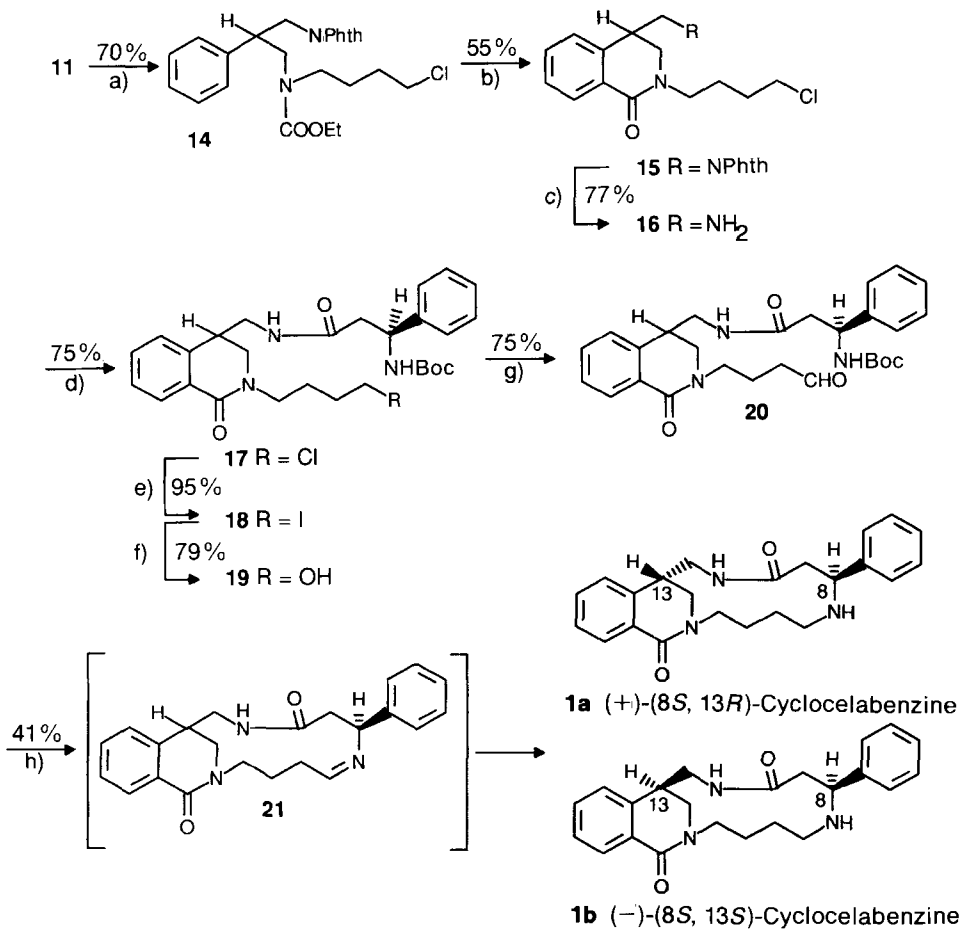
N-Alkylation of the carbamate **11** prior to the cyclization step should solve the problem of forming the tetrahydroisoquinolin-1-one system, since the reactive intermediate (*Scheme 2*), formed by treatment of **11** with $POCl_3$ under the *Bischler-Napieralski* conditions, carries an additional positive charge. Therefore, the generated activated species would represent a much stronger electrophile, which should render the cyclization possible, even without activation of the aromatic ring. Thus, *N*-alkylation with 1-bromo-4-chlorobutane was carried out in the presence of NaH in DMF, yielding ethyl *N*-(4-chlorobutyl)-*N*-(2-phenyl-3-phthalimidopropyl)carbamate (**14**; *Scheme 3*). Starting material (10%) could be recovered. Indeed, the cyclization was successfully achieved by heating compound **14** with $POCl_3$ at 155° overnight. Finally, $POCl_3$ was partly removed, and the violet residue was heated for another 8 h at 175°. After workup of the resulting violet gum and purification by column chromatography, 2-(4-chlorobutyl)-4-[(phthal-

Scheme 2



a) Polyphosphoric acid, 120°. b) $POCl_3$, 100–170°. c) $POCl_3$, 100–170°, then $SnCl_4$, r.t.

Scheme 3



a) 1. NaH, DMF, 0°, 30 min → r.t., 3 h; 2. 1-bromo-4-chlorobutane, 5 d. b) $POCl_3$, 155°, 15 h → 175°, 8 h. c) $N_2H_4 \cdot H_2O$, EtOH, 30 min, 60°. d) 3-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoic acid, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, r.t., 2.5 h. e) NaI, acetone, reflux, 15 h. f) HMPA, H_2O, 100°. g) PCC, CH_2Cl_2, 3-Å molecular sieves, r.t., 2.5 h. h) 1. CF_3COOH, 30 min; 2. MeOH, Et_3N, pH 8; 3. $NaBH_3CN$, r.t., 3 d.

imido)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**15**) was obtained as colorless crystals. 2-Phenyl-*N*,*N*′-diphthalimidopropane-1,3-diamine was isolated as by-product in a yield of 8%. Aromatization of the 1,2,3,4-tetrahydroisoquinolin-1-one ring only occurred to a negligible extent of 3%. Afterwards, the phthaloyl protecting group was cleaved with hydrazine hydrate to the corresponding amine **16**. 3-[(*p*-Toluenesulfonyl)-amino]-3-phenylpropanoic acid, prepared using TsCl according to [8], reacted readily with **16** under *Mukaiyama* conditions [2] to the *N*-tosyl derivative of **17**. Finally, ring closure according to [9] by *N*-alkylation of the corresponding alkali-metal tosylamides should give the desired 13-membered macrocycle. However, unfortunately, no *N*(7)-(*p*-

toluenesulfonyl)-protected cyclocelabenzine (**1**) could be isolated. Even the exchange of the chloride to the more reactive bromide or iodide gave no better results.

Therefore, the ring closure to the macrocyclic 13-membered lactam was performed by reductive amination of the formyl derivative **20** [2] [10]. To obtain the appropriately substituted compound **20**, the amine **16** was condensed with (−)-(*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoic acid, synthesized by using Boc-S in aqueous DMF in the presence of Et_3N according to [2] [11], using 2-chloro-1-methylpyridinium iodide as coupling agent to yield **17**. The chloro compound **17** was converted into the iodo derivative **18** by treatment with NaI (*Finkelstein* reaction), followed by hydrolysis of **18** with H_2O in HMPA to give the corresponding alcohol **19**. Oxidation of **19** with pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature gave the formyl derivative **20**. Cleavage of the Boc group with CF_3COOH generated the amine salt which was dissolved in MeOH, after removal of the acid. The solution was neutralized with Et_3N to pH 8 to give the *Schiff* base **21** which was subsequently reduced with $NaBH_3CN$ to afford (8*S*,13*S*/*R*)-cyclocelabenzine as a mixture of C(13)-epimers. The ratio of the two epimers, **1a**/**1b**, could be determined by ^{1}H-NMR spectroscopy to be 4:1. Finally, the epimers were separated into the natural, albeit oily, (+)-isomer and the crystalline, synthetic (−)-isomer by repeated column chromatography. All analytical data ($[\alpha]_D$, 300-MHz NMR, IR, MS, and TLC) of the synthesized (+)-isomer **1a** were identical to those published for cyclocelabenzine isolated from natural sources. The relative configuration of the (−)-isomer **1b** was determined by an X-ray crystal-structure analysis, and, on the basis of the known absolute configuration of the employed (+)-(3*S*)-3-amino-3-phenylpropanoic acid, the absolute configuration of the two chiral centers could be assigned. Thus, **1b** is (−)-(8*S*,13*S*)-4,5,6,7,8,9,12,13-octahydro-8-phenyl-2,13-methano-2*H*-2,7,11-benzotriazacyclopentadecine-1,10-(3*H*,11*H*)-dione (see *Fig. 2*).

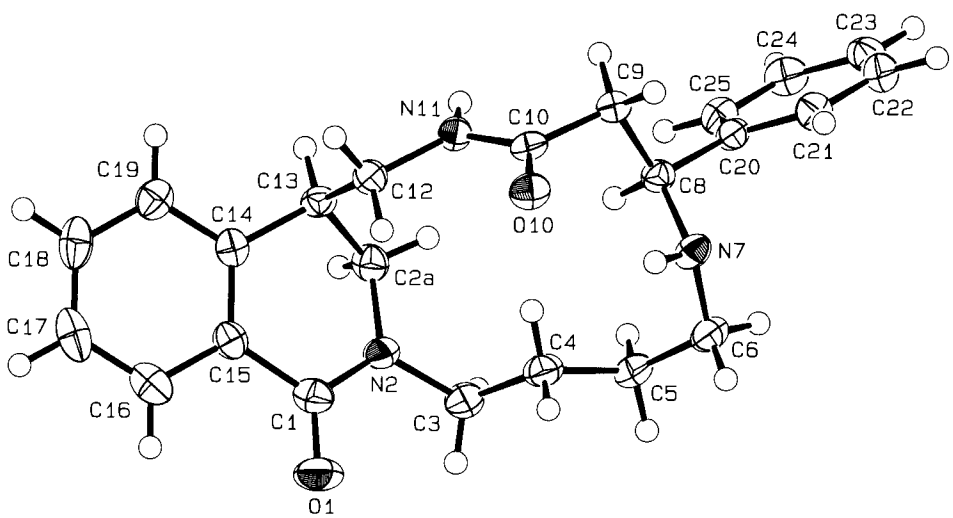


Fig. 2. *ORTEP Plot* [12] *of the molecular structure of* **1b**

Considering these results, we could finally assign the absolute configuration of the natural cyclocelabenzine (**1a**) to be (8*S*,13*R*).

We thank the *Swiss National Science Foundation* for generous support, Dr. *A. Linden* for performing the X-ray analysis, the analytical department of the University of Zurich for MS and IR spectra as well as microanalyses, and Prof. *H. Wagner* of the University of Munich for providing a sample of natural (+)-cyclocelabenzine.

Experimental Part

General. Merck precoated plates *60* F_{257} were used for TLC and *Merck* PF_{254} silica gel for flash column chromatography (FC). M.p. (not corrected): *Mettler FP-5/FP-52*. Optical rotation: *Perkin-Elmer 241* polarimeter at 20° and 589 nm (Na_D). UV/VIS Spectra (λ_{max} in nm, MeOH, ($\log\varepsilon$)): *Hewlett Packard* diode-array spectrometer *8452 A*. IR: $\tilde{\nu}_{max}$ in cm^{-1} in KBr, unless otherwise stated; *Perkin-Elmer 297* or *781* spectrometer. NMR Spectra: *Bruker AM 400* and *ARX 300*, chemical shifts in δ (ppm), using the appropriate solvent as internal standard. ^{1}H-NMR at 300.1 MHz and ^{13}C-NMR at 75.5 MHz in $CHCl_3$ unless otherwise stated; multiplicities from DEPT experiments; multiple signals observed in the ^{1}H- and the ^{13}C-NMR spectra are due to the two epimers resulting from the opposite configuration at C(13). CI- and EI-MS: *Finnigan-MAT 90*; 70 eV (EI), NH_3 (CI). ESI-MS: *Finnigan TSQ 700* mass spectrometer. Microanalyses were performed at the Mikrolabor of the University of Zurich.

N-*(2-Phenyl-3-aminopropyl)phthalamic Acid* (**9**). To a soln. of 5 g (33.3 mmol) *2-phenylpropane-1,3-diamine* (**8**) in 300 ml of dry toluene was added, dropwise, under stirring, a soln. of 5 g (33.3 mmol) phthalic anhydride in 100 ml dry THF, whereby a white precipitate appeared. When the addition was complete, the mixture was refluxed for 4 h and finally cooled for 12 h at 4°. The precipitate of fine white needles was collected, washed with Et_2O, and dried under vacuum yielding 8.67 g (87%) of **9**. M.p. 175°. TLC ($CHCl_3$/MeOH/25% aq. NH_4OH 7:3:1): R_f 0.4. IR: 3390*s* (br.), 3280, 3030*s* (br.), 2930 (br.), 2650 (br.), 2180, 1650*s*, 1620, 1585, 1570, 1520*s*, 1455, 1445, 1405, 1390, 1310, 1180, 1150, 1010, 760, 700, 695. ^{1}H-NMR (DMSO): 8.75 (br. *s*, OH); 7.65, 7.40–7.05 (*m*, 9 arom. H, NH); 3.55–3.20 (*m*, 2 CH_2); 2.45 (*m*, CH). ^{13}C-NMR (DMSO): 171.31, 171.13 (2*s*, 2 CO); 141.56, 139.28, 137.03 (3*s*, 3 arom. C); 129.26, 129.02, 128.83, 128.35, 128.03, 127.32 (6*d*, 9 arom. C); 44.19 (*t*, CH_2); 43.62 (*d*, CH); 42.79 (*t*, CH_2). ESI-MS: 298.7 ($[M + 1]^+$).

N-*[3-(Ethoxycarbonyl)-2-phenyl-3-aminopropyl]phthalamic Acid* (**10**). A mixture of 0.5 g (1.78 mmol) of **9**, 25 ml of dry MeOH, 0.27 ml (1.96 mmol) of Et_3N, and 0.18 ml (1.96 mmol) of ClCOOEt was stirred for 3 h at r.t., and the soln. was concentrated to a small volume. After addition of H_2O (100 ml), the soln. was extracted twice with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4) and evaporated under vacuum yielding 0.46 g (74%) of **10**. TLC ($CHCl_3$/MeOH 5:1): R_f 0.4. IR: 3320 (br.), 2980, 2930, 1710*s*, 1650, 1600, 1540, 1450, 1380, 1260*s*, 1140, 1030, 710 (br.), 700. ^{1}H-NMR: 9.45 (br. *s*, OH); 7.85, 7.45–7.15 (*m*, 9 arom. H); 6.82–6.70 (*m*, NH); 5.20–5.05 (*m*, NH); 4.05–3.40 (*m*, CH_2O, 2 CH_2); 3.15–3.00 (*m*, CH); 1.05 (*t*, J = 7.2, Me). ^{13}C-NMR: 171.26 (*s*, COOH); 169.29 (*s*, CONH); 158.00 (*s*, COOEt); 140.64, 137.60 (2*s*, 3 arom. C); 132.49, 131.55, 130.46, 130.33, 129.37, 128.32, 128.14, 127.78 (8*d*, 9 arom. C); 61.68 (*t*, CH_2O); 45.85 (*d*, CH); 43.93, 43.07 (2*t*, 2 CH_2); 14.97 (*q*, Me). ESI-MS: 393.1 ($[M + Na]^+$), 763.8 ($[2M + Na]^+$).

Ethyl N-*(2-Phenyl-3-phthalimidopropyl)carbamate* (**11**). A mixture of 7.2 g (24.2 mmol) of **10**, 360 ml of dry MeOH, 3.6 ml (7.37 mmol) of Et_3N, and 2.5 ml (7.37 mmol) of ClCOOEt was stirred for 3 h at r.t. and then concentrated to a small volume. After addition of H_2O (100 ml), the soln. was extracted twice with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4) and evaporated under vacuum. After addition of toluene (25 ml), the soln. was refluxed overnight, the solvent was evaporated and the residue co-evaporated twice with EtOH. Recrystallization from EtOH afforded 1.42 g (61%) of **11**. M.p. 128–130°. TLC (toluene/AcOEt 7:3): R_f 0.42. IR: 3460, 3360*s*, 3100, 3060, 3025, 2980, 2940, 1770*s*, 1715*s*, 1685*s*, 1610, 1530*s*, 1495, 1470, 1440, 1400*s*, 1365, 1355, 1340, 1330, 1305, 1280*s*, 1260*s*, 1245*s*, 1190, 1170, 1140, 1090, 1050, 1020, 980, 955, 840, 800, 760, 730*s*, 705. ^{1}H-NMR: 7.95, 7.85 (2*m*, 4 phthaloyl-H); 7.50–7.30 (*m*, 5 arom. H); 4.95 (*s*, NH); 4.15 (*q*, J = 7.1, CH_2O); 4.10–4.05 (*m*, CH_2NPhth); 3.90–3.70 (*m*, CH); 3.65–3.45 (*m*, CH_2NH); 1.30 (*t*, J = 7.1, Me). ^{13}C-NMR: 168.15 (*s*, 2 CO); 156.36 (*s*, COOEt); 138.93 (*s*, 1 arom. C); 133.97 (*d*, 2 arom. C); 131.74 (*s*, 2 arom. C); 128.71, 127.88, 127.40, 123.21 (4*d*, 7 arom. C); 60.72 (*t*, CH_2O); 44.51 (*d*, CH); 43.45, 40.81 (*t*, 2 CH_2); 14.44 (*q*, Me). CI-MS: 353.3 ($[M + 1]^+$), 370.3 ($[M + NH_4]^+$). Anal. calc. for $C_{20}H_{20}N_2O_4$ (352.38): C 68.17, H 5.72, N 7.95; found: C 68.05, H 5.88, N 7.89.

Ethyl N-*(4-Chlorobutyl)*-N-*(2-phenyl-3-phthalimidopropyl)carbamate* (**14**). To a soln. of 4 g (11.35 mmol) of **11** in DMF (54 ml) at 0°, 0.60 g NaH (suspension in oil *ca.* 50%) were added. After stirring 30 min at 0°, the mixture was stirred at r.t. for another 3 h. Then, 2.73 ml (24 mmol) of 1-bromo-4-chlorobutane were added, the soln. was stirred at r.t. for 5 d, quenched with H_2O (100 ml), and extracted twice with Et_2O (100 ml). The org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (100 g silica gel; toluene/AcOEt 7:1.5) yielding 3.5 g (70%) of **14** as an oil and 0.4 g (10%) of **11**. *Data of* **14**: TLC (toluene/AcOEt 7:3): R_f 0.60. IR (film): 3600 (br.), 3560, 3080, 3020, 2980*s*, 2925*s*, 2880, 1770*s*, 1720*s*, 1690*s*, 1610, 1540, 1470, 1420, 1400*s*, 1350, 1325, 1230*s*, 1190, 1170, 1130, 1105*s*, 1070, 1020, 1000, 980, 960, 890, 790, 770, 765, 720*s*, 700*s*. ^{1}H-NMR: 7.95, 7.80 (2*m*, 4 phthaloyl-H); 7.50–7.20 (*m*, 5 arom. H); 4.30–4.00 (*m*, 3 H); 4.05 (*q*, J = 7.1, CH_2O); 3.90–3.65 (*m*, 1 H); 3.60 (*t*, J = 6.4, CH_2Cl); 3.55–3.25 (*m*, 2 H); 3.00 (br. *s*, 1 H); 1.95–1.70 (*m*, $CH_2CH_2CH_2Cl$); 1.25 (br. *s*, Me). ^{13}C-NMR: 168.54, 168.48 (2*s*, 3 CO); 139.88 (*s*, 1 arom. C); 134.30 (*d*, 1 arom. C); 132.25 (*s*, 2 arom. C); 129.01, 128.53, 127.80, 123.61 (4*d*, 8 arom. C); 61.72 (*t*, CH_2O); 51.06, 47.27, 46.90 (3*t*, 2 C); 44.94 (*t*, CH_2Cl); 43.77 (*d*, CH); 41.76, 41.42, 30.21, 30.07, 25.43 (5*t*, 3 C); 14.90 (*q*, Me). ESI-MS: 443.4 ($[M + 1]^+$). Anal. calc. for $C_{24}H_{27}ClN_2O_4$ (442.94): C 65.08, H 6.14, N 6.32; found: C 65.08, H 5.92, N 6.14.

2-(4-Chlorobutyl)-4-[(phthalimido)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**15**). A soln. of 1.2 g (2.7 mmol) of **14** in 1 ml of $POCl_3$ was refluxed at 155° overnight. Then, $POCl_3$ was partly distilled off, and the dark violet mixture was heated at 170–175° for another 8 h. After cooling, H_2O (50 ml) was added, and the residue was extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was dissolved in a small amount of CH_2Cl_2 and adsorbed on silica gel. FC (40 g silica gel; toluene/AcOEt 7:2) afforded 0.59 g (55%) of **15**. A small sample was recrystallized from EtOH: M.p. 124–126°. TLC (toluene/AcOEt 7:3): R_f 0.42. IR: 3480, 3070, 2930, 2870, 1770, 1710*s*, 1645*s*, 1605, 1580, 1480, 1465, 1435, 1395*s*, 1360, 1340, 1310, 1290, 1260, 1190, 1165, 1140, 1120, 1070, 1025, 965, 955, 860, 790, 760, 710, 700*s*. ^{1}H-NMR: 7.95 (*dd*, J = 8.9, 1.6, H–C(8)); 7.70, 7.55 (2*m*, 4 phthaloyl-H); 7.30–7.05 (*m*, 3 arom. H); 4.00–3.75 (*m*, 2 H); 3.64 (*dd*, J = 12.9, 4.4, 2 H–C(3)); 3.42 (*t*, J = 6.0, CH_2Cl); 3.35–3.10 (*m*, 3 H); 1.80–1.60 (*m*, CH_2CH_2). ^{13}C-NMR: 168.17 (*s*, 2 CO); 163.64 (*s*, 1 CO); 137.90 (*s*, 1 arom. C); 134.18, 132.02 (2*d*, 3 arom. C); 131.75, 128.83 (2*s*, 3 arom. C); 128.55, 127.97, 127.17, 123.40 (4*d*, 5 arom. C); 47.63, 46.73 (2*t*, 2 C); 44.69 (*t*, CH_2Cl); 40.30 (*t*, 1 C); 37.15 (*d*, CH); 29.82, 24.54 (2*t*, CH_2CH_2). CI-MS: 397.3/399.3 ($[M + 1]^+$). Anal. calc. for $C_{22}H_{21}ClN_2O_3$ (396.12): C 66.58, H 5.33, N 7.06; found: C 66.41, H 5.16, N 6.89.

4-(Aminomethyl)-2-(4-chlorobutyl)-1,2,3,4-tetrahydroisoquinolin-1-one (**16**). A soln. of 2.0 g (5.04 mmol) of **15**, 110 ml of EtOH, and 4 ml of $N_2H_4 \cdot H_2O$ was heated for 30 min at 60°. After cooling to 0°, the white precipitate was filtered off and the filtrate concentrated under vacuum. The residue was dissolved in CH_2Cl_2, washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated *in vacuo*. Drying in high vacuum afforded 1.04 g (77%) of **16**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.32. IR ($CHCl_3$): 3440 (br.), 3380 (br.), 3000, 2940, 2860, 1640*s*, 1600, 1580, 1480, 1455, 1425, 1375, 1350, 1310, 1260, 1200. ^{1}H-NMR: 8.00 (*dd*, J = 8.9, 1.6, H–C(8)); 7.40–7.15 (*m*, 3 arom. H); 4.30–3.35 (*m*, 6 H); 2.90–2.70 (*m*, CH_2NH_2, H–C(4)); 1.85–1.70 (*m*, CH_2CH_2); 1.53 (*s*, NH_2). ^{13}C-NMR: 163.91 (*s*, CO); 139.61 (*s*, 1 arom. C); 131.60 (*d*, 1 arom. C); 128.79 (*s*, 1 arom. C); 128.44, 127.40, 126.96 (3*d*, 3 arom. C); 47.60, 46.27, 44.65, 44.62 (4*t*, 4 C); 40.85 (*d*, CH); 29.79, 24.82 (2*t*, CH_2CH_2). ESI-MS: 267.4 ($[M + 1]^+$), 533.6 ($[2M + 1]^+$).

*4-{{{3-[(*tert*-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}methyl}-2-(4-chlorobutyl)-1,2,3,4-tetrahydroisoquinolin-1-one* (**17**). To a soln. of 1.3 g (5.04 mmol) of (−)-(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoic acid in 26 ml of dry CH_2Cl_2 and 0.72 ml (5.04 mmol) of freshly distilled Et_3N, 1.33 g (5.04 mmol) 2-chloro-1-methylpyridinium iodide was added. After stirring the mixture for 1 h, a soln. of 1.04 g (3.9 mmol) of freshly prepared **16** in 15 ml of CH_2Cl_2 was added dropwise at r.t. for 2 h. The mixture was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. FC (80 g silica gel; CH_2Cl_2/MeOH 30:1) afforded 1.48 g (75%) of **17**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.68. IR: 3300 (br.), 3080, 2980, 2925, 2885, 1710*s*, 1690*s*, 1640*s*, 1606, 1580, 1550, 1530 (br.), 1495, 1480, 1465, 1430, 1390, 1370, 1320, 1290, 1250, 1170, 1100, 1085, 1050, 1020, 960, 910, 865, 800, 760, 700. ^{1}H-NMR: 8.00–7.92 (*m*, H–C(8)); 7.40–7.10 (*m*, 8 arom. H); 6.05–5.85 (br. 2*m*, 2 NH); 5.00 (br. *m*, CH); 3.60–2.50 (*m*, 11 H); 1.80–1.55 (*m*, CH_2CH_2); 1.30 (*s*, 3 Me). ^{13}C-NMR: 170.92, 163.81, 155.41 (3*s*, 3 CO); 138.75, 138.61 (2*s*, 2 arom. C); 131.92, 131.83, 128.59 (3*d*, 3 arom. C); 128.46 (*s*, 1 arom. C); 128.39, 127.62, 127.27, 127.18, 126.09, 126.00 (6*d*, 6 arom. C); 79.71 (*s*, Me_3C); 47.83, 47.29, 46.22, 44.80, 42.75 (5*t*, 5 C); 37.02, 36.65 (2*d*, 2 C); 29.67 (*t*, 1 C); 28.27 (*q*, Me_3C); 24.72 (*t*, 1 C). ESI-MS: 536.7 ($[M + Na]^+$). Anal. calc. for $C_{28}H_{36}ClN_3O_4$ (514.06): C 65.42, H 7.06, N 8.18; found: C 65.50, H 6.93, N 8.08.

*4-{{{3-[(*tert*-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}methyl}-2-(4-iodobutyl)-1,2,3,4-tetrahydroisoquinolin-1-one* (**18**). A soln. of 1.5 g (2.9 mmol) of **17** and 1.8 g (12 mmol) of NaI in 15 ml of acetone was refluxed for 18 h under protection from light. The solvent was removed under vacuum, and the residual oil was dissolved in 100 ml of CH_2Cl_2, washed twice with H_2O (100 ml), and dried ($MgSO_4$). After filtration, the solvent

was evaporated and the product dried *in vacuo* to yield 1.68 g (95%) of anal. pure **18**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.68. IR: 3300 (br.), 3060, 2980, 2925, 2860, 1715*s*, 1690*s*, 1640*s*, 1605, 1580, 1560 (br.), 1495, 1480, 1460, 1430, 1390, 1370, 1320, 1295, 1170, 1095, 1075, 1050, 1025, 960, 860, 760, 700. ^{1}H-NMR: 8.00–7.90 (*m*, H–C(8)); 7.35–7.10 (*m*, 8 arom. H); 6.20–5.90 (br. 2*m*, 2 NH); 5.10–4.90 (br. *m*, CH); 3.60–2.50 (*m*, 11 H); 1.81–1.69, 1.65–1.50 (2*m*, CH_2CH_2); 1.30 (*s*, 3 Me). ^{13}C-NMR: 170.92, 163.82, 155.35 (3*s*, 3 CO); 138.71, 138.57 (2*s*, 2 arom. C); 131.84, 128.61 (2*d*, 3 arom. C); 128.46 (*s*, 1 arom. C); 128.40, 127.64, 127.39, 127.18, 126.02, 126.00 (6*d*, 6 arom. C); 79.73 (*s*, Me_3C); 47.92, 47.29, 45.98, 42.33, 42.22 (5*t*, 5 C); 37.04, 36.68 (2*d*, 2 C); 30.40 (*t*, 1 C); 28.28 (*q*, Me_3C); 6.80 (*t*, CH_2I). ESI-MS: 628.4 ($[M + Na]^+$). Anal. calc. for $C_{28}H_{36}IN_3O_4$ (605.51): C 55.54, H 5.99, N 6.94; found: C 55.62, H 6.15, N 6.66.

*4-{{{3-[(*tert*-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}methyl}-2-(4-hydroxybutyl)-1,2,3,4-tetrahydroisoquinolin-1-one* (**19**). A soln. of 200 mg (0.33 mmol) of **18** and a mixture of 1.7 ml of HMPA and 0.4 ml H_2O was heated at 100° for 2.5 h. The mixture was diluted with H_2O (50 ml) and extracted with AcOEt (3 × 50 ml). The combined org. phases were washed twice with H_2O (50 ml) to remove all HMPA, dried (Na_2SO_4), and concentrated *in vacuo*. FC (50 g silica gel; CH_2Cl_2/MeOH 20:1) afforded 129 mg (79%) of **19**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.42. IR: 3420 (br.), 3300 (br.), 3060, 2980, 2925, 2860, 1700*s*, 1640*s*, 1605, 1580, 1540 (br.), 1495, 1480, 1460, 1430, 1390, 1370, 1320, 1295, 1250, 1165, 1050, 1020, 960, 860, 800, 760, 700. ^{1}H-NMR: 8.00–7.90 (*m*, H–C(8)); 7.40–7.10 (*m*, 8 arom. H); 6.90 (*s*-like *m*, NH); 6.30–6.00 (br. *m*, NH); 5.10–4.90 (*m*, CH); 4.00–2.60 (*m*, 12 H, 1 OH); 1.95–1.50 (*m*, CH_2CH_2); 1.38 (*s*, 3 Me). ^{13}C-NMR: 171.05, 164.27, 155.42 (3*s*, 3 CO); 141.27, 139.20 (2*s*, 2 arom. C); 131.84, 128.55 (2*d*, 3 arom. C); 128.44 (*s*, 1 arom. C); 128.29, 127.53, 127.29, 126.25, 126.05, 126.00 (6*d*, 6 arom. C); 79.80 (*s*, Me_3C); 61.72 (*t*, CH_2OH); 46.27, 45.73, 42.30 (3*t*, 4 C); 36.54, 36.16 (2*d*, 2 C); 29.03 (*t*, 1 C); 28.29 (*q*, Me_3C); 23.87 (*t*, 1 C). ESI-MS: 518.6 ($[M + Na]^+$). Anal. calc. for $C_{28}H_{37}N_3O_5 \cdot 1\ H_2O$ (495.60): C 65.47, H 7.65, N 8.18; found: C 65.44, H 7.38, N 8.18.

*4-{{{3-[(*tert*-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}methyl}-2-(3-formylpropyl)-1,2,3,4-tetrahydroisoquinolin-1-one* (**20**). To a soln. of 0.6 g (1.2 mmol) of **19** in 12 ml of dry CH_2Cl_2 with molecular sieve (3 Å; ~ 0.5 g per mmol **19**), 522 mg (2.4 mmol) of PCC was added in 3 portions during 1 h. After stirring for another 2.5 h at r.t., the mixture was diluted with CH_2Cl_2 (100 ml) and washed with H_2O. The org. phase was dried ($MgSO_4$), filtered over *Florisil*, and the product was eluated with AcOEt (500 ml). The org. phase was concentrated under vacuum, and the residue was purified by FC (30 g silica gel; AcOEt) yielding 445 mg of **20** (75%). TLC ($CHCl_3$/MeOH 10:1): R_f 0.50. IR: 3300 (br.), 3060, 2925, 2980, 2720, 1710, 1690, 1640, 1605, 1530, 1495, 1480, 1455, 1430, 1390, 1370, 1290, 1250, 1170, 1100, 1075, 1050, 1020, 865, 760, 700. ^{1}H-NMR: 9.75 (*s*, COH); 7.90 (*d*, *J* = 8.8, H–C(8)); 7.40–6.95 (*m*, 9 arom. H); 6.70, 6.35, 6.15 (3*s*, 3 NH); 5.05–4.90 (*m*, CH); 3.60–2.45 (*m*, 11 H); 1.89–1.68 (*m*, 2 H); 1.32 (*s*, 3 Me). ^{13}C-NMR: 202.50, 202.05 (2*d*, COH); 170.83, 164.91, 164.02, 155.27 (4*s*, 3 CO); 141.56, 138.87, 138.76 (3*s*, 3 arom. C); 131.99, 131.90, 128.54, 128.32, 127.61, 127.37, 127.26, 127.20, 126.11, 126.0 (10*d*, 9 arom. H); 79.56 (*s*, Me_3C); 47.87, 47.24, 46.58, 46.47, 42.70, 42.17, 42.10, 40.97 (8*t*, 5 C); 37.03, 36.63 (2*d*, 2 C); 28.28 (*q*, Me_3C); 19.85 (*t*, 1 C). ESI-MS: 516.5 ($[M + Na]^+$). Anal. calc. for $C_{28}H_{35}N_3O_5 \cdot \frac{3}{4}\ H_2O$ (493.60): C 66.30, H 7.25, N 8.29; found: C 66.17, H 7.02, N 8.05.

(+)-(8S,13R)- and (−)-(8S,13S)-4,5,6,7,8,9,12,13-Octahydro-8-phenyl-2,13-methano-2H-2,7,11-benzotriazacyclopentadecine-1,10(3H,11H)-dione (**1a** and **1b**, resp.). A soln. of 1 g (0.4 mmol) of **20** in 10 ml of CF_3COOH (TFA) was stirred for 30 min at r.t. The solvent was evaporated under vacuum and the residue dissolved in 350 ml of MeOH. The pH value was adjusted to pH 8 with Et_3N. After the addition of 150 mg (2.34 mmol) of $NaBH_3CN$, the soln. was stirred at r.t. for 2.5 d, quenched with H_2O (20 ml), and the MeOH was evaporated under vacuum. The residue was dissolved in CH_2Cl_2, and the org. phase was washed twice with H_2O. After drying ($MgSO_4$), the solvent was evaporated under vacuum and the residue purified by FC (80 g silica gel; CH_2Cl_2/MeOH 40:1) yielding 312 mg (41%) of a mixture of two diastereoisomers in a ratio of 4:1 according to ^{1}H-NMR data. TLC ($CHCl_3$/MeOH 10:1): R_f 0.57 (**1a**) and 0.62 (**1b**). IR: 3440 (br.), 3280, 3080, 3020, 2920, 2860, 1640*s*, 1600, 1585, 1550, 1490, 1480, 1455, 1430, 1360, 1300, 1260, 1220, 1160, 1120, 1070, 1030, 800, 760, 730, 700. ESI-MS: 378.3 ($[M + 1]^+$). Anal. calc. for $C_{23}H_{27}N_3O_2$ (377.48): C 73.18, H 7.21, N 11.13; found: C 73.29, H 6.94, N 11.16.

The two epimers were separated by repeated FC (80 g silica gel; $CHCl_3$/MeOH 40:1, 7 times) yielding 66 mg of optically pure, natural *(+)-cyclocelabenzine* (**1a**) and *ca.* 80 mg of the unnatural (−)-isomer **1b**.

Data of **1a**: $[\alpha]_D^{20} = +29.2$ (*c* = 0.94, $CHCl_3$). UV: 263 (3.65), 252 (3.73). ^{1}H-NMR: 9.45 (*d*, H–N(11)); 8.11 (*dd*, *J* = 7.3, 1.1, 1 arom. H); 7.50–7.00 (*m*, 8 arom. H); 4.37 (*ddd*, *J* = 14, 9.2, 1.6, H–C(3)); 4.05 (*m*, H–C(12)); 3.80 (*dd*, *J* = 13, 5.7, H–C(2′)); 3.55 (*d*, *J* = 13, H′–C(2′)); 3.50 (*dd*, *J* = 11.7, 2.7, H–C(8)); 3.31 (*m*, H′–C(12)); 3.10 (*m*, H–C(13)); 2.70 (*m*, H–C(3), H–C(6)); 2.45 (*m*, H′–C(6)); 2.35 (*dd*, *J* = 16.7, 11.5, H–C(9)); 2.15 (*dd*, *J* = 16.8, 2.7, H′–C(9)); 2.00–1.40 (*m*, H–C(4), H–C(5), H–N(7)). ^{13}C-NMR: 170.75 (*s*, C(10)); 163.38 (*d*, C(1)); 141.25 (*s*, C(20)); 137.03 (*s*, C(14)); 131.25 (*d*, C(18)); 128.25 (*s*, C(15)); 127.69, 127.05, 126.63, 126.44,

125.18 (5*d*, 8 arom. C); 58.39 (*d*, C(8)); 48.88 (*t*, C(2')); 44.44, 43.59, 42.53, 41.53 (4*t*, 5 C); 35.69 (*d*, C(13)); 27.18, 23.29 (2*t*, 2 C).

Data of **1b**: M.p. 242–243°. $[\alpha]_D^{20} = -165.1$ ($c = 0.99$, $CHCl_3$). UV: 263 (3.70), 252 (3.78). ^{1}H-NMR: 9.94 (br. *s*, H–N(11)); 8.15 (*dd*, $J = 7.5$, 1.2, 1 arom. H); 7.55–7.10 (*m*, 8 arom. H); 4.70–4.55 (*m*, H–C(3)); 3.95–3.70 (*m*, H–C(12), H–C(2'), H'–C(2')); 3.60 (*dd*, $J = 12.8$, 1.1, H–C(8)); 3.31–3.10 (*m*, H'–C(12), H–C(13)); 2.75 (*m*, H–C(3)); 2.65–2.35 (*m*, H–C(6), H'–C(6), H–C(9)); 2.20 (*m*, H'–C(9)); 1.85–1.50 (*m*, H–C(4), H–C(5), H–N(7)). ^{13}C-NMR: 171.79 (*s*, C(10)); 163.95 (*d*, C(1)); 139.11 (*s*, C(20)); 131.9 (*s*, C(14)); 131.23 (*d*, C(18)); 128.84 (*s*, C(15)); 128.31, 127.63, 127.57, 127.24, 125.94 (5*d*, 8 arom. C); 59.81 (*d*, C(8)); 48.06 (*t*, C(2')); 45.35, 44.39, 42.79, 42.45 (4*t*, 5 C); 36.44 (*d*, C(13)); 27.98, 26.53 (2*t*, 2 C).

Crystal-Structure Determination of **1b** (see *Table* and *Fig. 2*)[2]). The intensities were collected on a *Rigaku-AFC5R* diffractometer in the ω-2θ scan mode using graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are listed in the *Table*, a view of the molecule is shown

Table. *Crystallographic Data for Compound* **1b**

	1b		**1b**
Crystallized from	AcOEt/pentane	Z	4
Empirical formula	$C_{23}H_{27}N_3O_2$	D_x [g cm^{-3}]	1.277
Formular weight	377.48	μ (MoK_α) [mm^{-1}]	0.0825
Crystal color, habit	colorless, prism	2θ (max) [°]	60
Crystal dimensions [mm]	0.33·0.38·0.48	Total reflections measured	3805
Crystal temp. [K]	173(1)	Symmetry independent reflections	3675
Crystal system	orthorhombic	R_{int}	0.017
Lattice parameters		Reflections used [$I > 2\sigma(I)$]	2743
Reflections for unit	25	Parameters refined	286
cell determination		Final R	0.0413
2θ range [°]	37–40	wR	0.0338
a [Å]	13.134(2)	Weights	$1/w = \sigma^2(F_0) + (0.005F_0)^2$
b [Å]	15.815(4)	Goodness of fit	1.698
c [Å]	9.448(3)	Final Δ_{max}/σ	0.0002
V [Å^3]	1962.6(5)	$\Delta\rho$ (max, min) [eÅ^{-3}]	0.21; –0.19
Space group	$P2_12_12_1$	$\sigma(d(C-C))$ [Å]	0.003–0.004

in *Fig. 2*. The structure was solved by direct methods using SHELXS86 [13], which revealed the position of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms bonded to the N-atoms were placed in the position indicated by a difference electron-density map, and their position were allowed to refine. The H-atoms bonded to the C-atoms were fixed in geometrical calculated positions with a C–H distance of 0.95 Å. Individual isotropic temp. factors were refined for all H-atoms. All refinements were carried out on F using full-matrix least-squares procedures. Neutral atom-scattering factors for non-H-atoms were taken from [14a] and the scattering factors for H-atoms from [15]. Anomalous dispersion effects were included in F_{calc} [16]; the values for f' and f'' were those of [14b]; all calculations were performed using the TEXSAN crystallographic software package [17].

N(7)–H forms a weak intramolecular H-bond with the C=O group at C(10), while N(11)–H forms an intermolecular H-bond with the same C=O O-atom of an adjacent molecule. The intermolecular interaction links the molecule into indefinite one-dimensional chains.

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[2]) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-10/4. Copies of the data can be obtained, free of charge, on application to the Director, CDCC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-334033 or e-mail: teched@chemcrys.cam.ac.uk).

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