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TOTAL SYNTHESIS OF THE SPERMIDINE ALKALOID (+)-(9*S*,13*S*)-ISOCYCLOCELABENZINE

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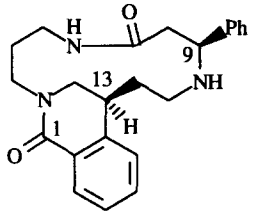
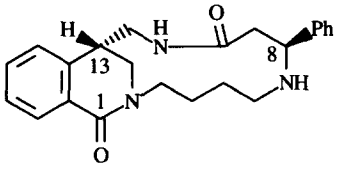
ABSTRACT: An asymmetric synthesis of the spermidine alkaloid (+)-isocyclocelabenzine (**1a**) is reported using (3*S*)-3-amino-3-phenylpropanoic acid as the chiral building block. The 1,2,3,4-tetrahydro-isoquinolin-1-one fragment **9** was synthesized by a modified *Bischler-Napieralski* reaction. The resulting C(13)-epimers were separated by semi-preparative HPLC. The relative configuration of the naturally occurring alkaloid was determined by an X-ray crystal structure analysis, which enabled us to determine the absolute configuration of natural (+)-**1a** at both chiral centers to be (9 *S*) and (13 *S*).

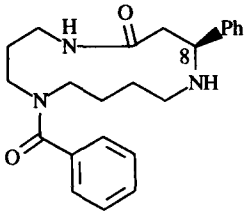
Among the macrocyclic spermidine alkaloids isolated from the leaves and the twigs of *Maytenus mossambicensis* (Klotzsch) Blakelock var. *mossambicensis* (Celastraceae) by *H. Wagner* and coworkers[1] in 1978 were (+)-isocyclocelabenzine (**1a**) and (+)-cyclocelabenzine (**2**).



1a (+)-(9*S*,13*S*)-isocyclocelabenzine



2 (+)-(8*S*,13*R*)-cyclocelabenzine



3 (8*S*)-celabenzine

The structures of the two alkaloids **1a** and **2** may be deduced from (8*S*)-celabenzine (**3**), a *N*-benzoyl substituted 13-membered macrocyclic lactam incorporating spermidine and (3-phenyl)-propenyl-precursorial units whereby the ortho position of the benzoyl group is additionally linked either to the butyl or the propyl unit of the spermidine moiety. Hereby, an additional six-membered ring is formed which leads to a 1,2,3,4-tetrahydroisoquinolin-1-one heterocycle. Although a synthesis of racemic (±)-isocyclocelabenzine has been reported by Kikuchi[2] and coworkers in 1986, no asymmetric synthesis of **1a** has been made so far.

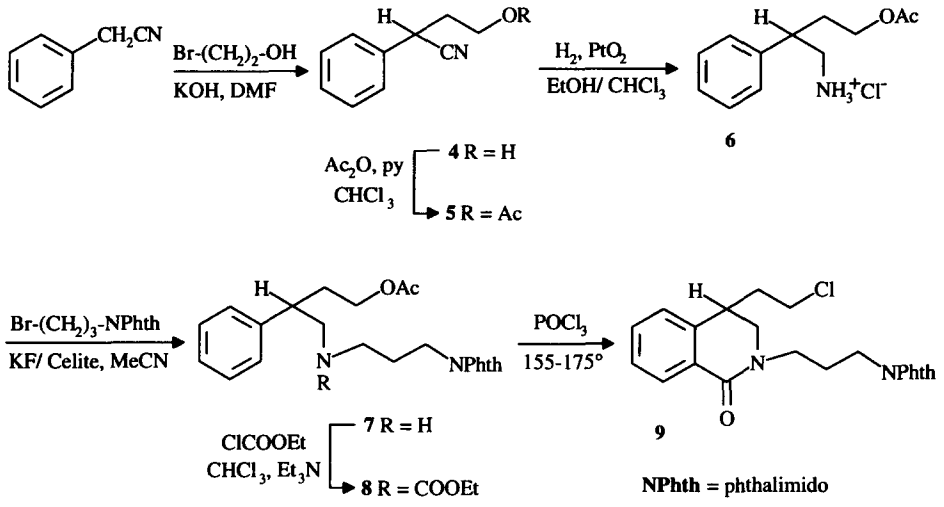
We recently developed an efficient method for the synthesis of substituted 1,2,3,4-tetrahydroisoquinolin-1-one derivatives by a modified *Bischler-Napieralski* reaction; this method was then applied to the synthesis of

(+)-(8*S*,13*R*)-cyclocelabenzine (**2**).[3] On the basis of this methodology, we now describe a short and highly efficient asymmetric synthesis of **1a** which allows the determination of its hitherto unknown absolute configuration by an X-ray crystal structure analysis.

The strategy used here is outlined in Schemes 1 and 2. The retrosynthetic analysis of **1a** suggested an appropriately substituted 1,2,3,4-tetrahydroisoquinolin-1-one derivative and (+)-(3*S*)-3-amino-3-phenylpropanoic acid as useful intermediates.

The key step of the synthesis leading to (+)-isocyclocelabenzine (**1a**) was the formation of the suitably substituted 1,2,3,4-tetrahydroisoquinolin-1-one fragment **9** which basically contains the functionalized spermidine residue. Thus, 4-hydroxy-2-phenyl-butanenitrile (**4**) seemed to be a suitable starting material. The latter could be synthesized by α-monoalkylation of the activated methylene group of phenylacetonitrile with 1 eq. of 2-bromoethanol in the presence of KOH[4] as base affording **4** in a yield of 41% (*Scheme 1*).

Scheme 1



Afterwards the hydroxyl group of **4** was protected with Ac_2O yielding the corresponding 3-cyano-3-phenylpropyl acetate (**5**) almost quantitatively. The complicated purification scheme for **4** (column chromatography followed by bulb-to-bulb distillation) and the low yields were discouraging and for this reason we tried to avoid the isolation of **4**. Therefore, the crude workup of **4** was followed immediately by acetylation of the hydroxyl group. The acetyl derivative **5** could then be purified by distillation giving **5** in a yield of 47% over two steps. Even though this procedure did not substantially improve the overall yield of **5**, it circumvented the time consuming purification step of **4**. Catalytic reduction of the nitrile **5** with H_2/PtO_2 in EtOH containing a small amount of $CHCl_3$[5] led to the corresponding 4-acetoxy-2-phenylbutylammonium chloride (**6**). These mild hydrogenation conditions are advantageous. They permit the preparation of amine hydrochlorides in the

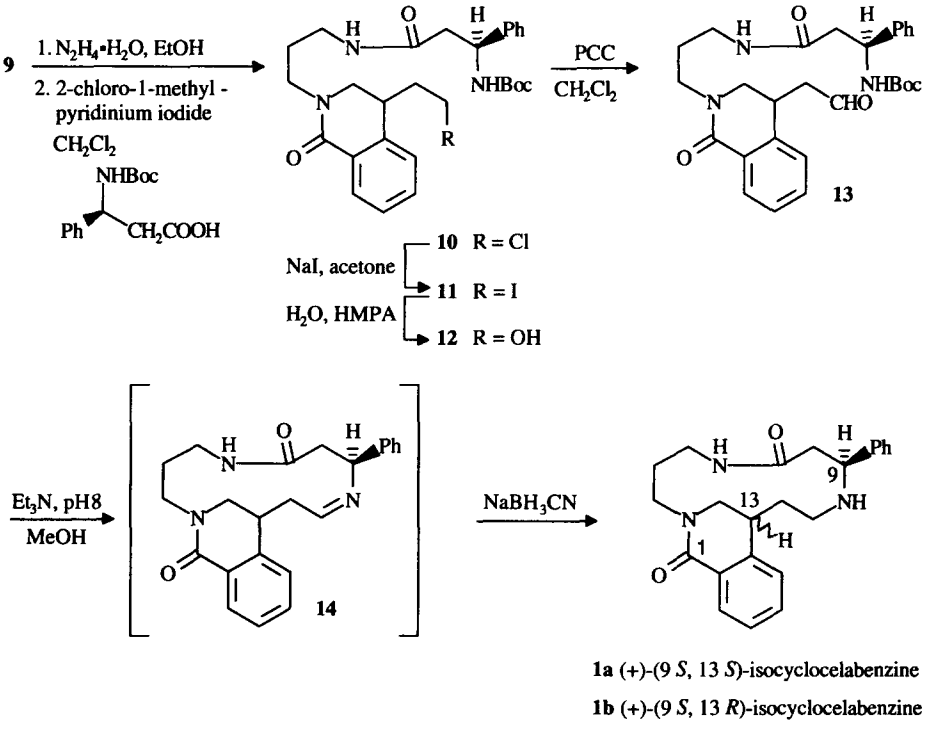
presence of functional groups which are susceptible to reducing conditions in strongly acidic or basic solvents. In our case, the acetyl group was not affected by the conditions outlined above. Nevertheless, irrespective of the very mild reaction conditions, the reaction time had to be observed very precisely. Prolonged reaction times led to a partial hydrogenation of the aromatic residue. This problem may be easily overcome by tracing the progress of the reaction by TLC. The hydrogenation has to be stopped as soon as the nitrile **5** is no longer detectable by TLC (after about 2-3 h) and the wanted hydrochloride **6** could then be isolated in a yield 95%. The hydrochloride **6** was alkylated with *N*-(3-bromopropyl)phthalimide using KF/Celite[6] as a base giving *N*-(8-acetoxy-6-phenyl-4-azaoct-1-yl)phthalimide (**7**) in a yield of 57%. The reaction sequence was continued by conversion of **7** with ClCOOEt in the presence of 1.1 eq. Et_3N yielding the carbamate **8**. The latter could be cyclized as expected according to the previously developed and described modified *Bischler-Napieralski* reaction[3] affording 4-(2-chloroethyl)-(3-phthalimidopropyl)-1,2,3,4-tetrahydroisoquinolin-1-one (**9**) in a yield of 58%. As already observed during the elaboration of the synthesis for **2**, the aggressive reaction conditions not only promoted the cyclization of **8** to the respective 1,2,3,4-tetrahydroisoquinolin-1-one but also caused the substitution of the acetyl group by a chlorine atom. This substitution is an unwanted one because in the following reaction sequence, which proceeds to the formyl derivative **13** necessary for the macrocyclic ring closure by reductive amination, the chloride has to be replaced by the corresponding alcohol. However, based on our experience with different substituents in the cyclization reaction of similar compounds, which also yielded only the corresponding chloro derivatives, we did not attempt to further modify the *O*-protecting group.

In the next step, the phthalimido group was cleaved with $N_2H_4 \cdot H_2O$ in EtOH to generate the corresponding amine (*Scheme 2*). Because of its instability, the amine was not isolated, but was condensed directly with (-)-(3*S*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-3-phenylpropanoic acid,[2,7] synthesized by using Boc-S in aqueous DMF in the presence of Et_3N, with 2-chloro-1-methylpyridinium iodide as a coupling agent. In this way compound **10** was obtained in a yield of 54% over the two step reaction. The chloro compound **10** was subsequently converted into the respective iodo derivative **11** by treatment with NaI in acetone (*Finkelstein* reaction). The iodide **11** was then hydrolyzed with H_2O in HMPA[8] to the corresponding alcohol **12**. Oxidation of **12** with PCC in CH_2Cl_2 at r.t. finally yielded the formyl derivative **13**, which is the immediate precursor to the macrocyclization reaction. The ring closure to the macrocyclic 13-membered lactam was carried out by reductive amination of the aldehyde **13** (*Scheme 2*). Consequently, the Boc protecting group was cleaved with trifluoroacetic acid to give the corresponding amine salt which, after removal of the acid, was dissolved in MeOH. The resulting solution was adjusted to pH 8 with Et_3N to form the intermediate *Schiff* base **14** which was subsequently reduced with $NaBH_3CN$ to afford (9*S*, 13*S*/*R*)-isocyclocelabenzine (**1a/1b**) as a mixture of C(13)-epimers in a yield of 63%.

The ratio of the two epimers **1a/1b** was determined by ^1H NMR spectroscopy to be 6:5. Due to their identical R_f-values the two C(13)-epimers could not be distinguished by TLC, i.e. a separation of the epimers by column chromatography was impossible. This is in contrast to the corresponding C(13)-epimers of the cyclocelabenzine (**2**), which could be separated by repeated colum chromatography. Furthermore, fractional crystallization of one epimer from AcOEt/hexane was attempted. Yet again, only a crystalline mixture of **1a**

and **1b** in a ratio of 1:1 was obtained. The preparative separation of the isocyclocelabenzine epimers was finally accomplished by semi-analytical HPLC using hexane/2-propanol (3:1) as eluent. This way the two epimers could be separated in 3 - 5 mg batches into the natural **1a** and the unnatural **1b**. Both epimers have a positive optical rotation and are crystalline compounds.

Scheme 2



1a (+)-(9 *S*, 13 *S*)-isocyclocelabenzine

1b (+)-(9 *S*, 13 *R*)-isocyclocelabenzine

For characterization, the synthetic mixture was compared with a sample of natural isocyclocelabenzine by TLC as well as by HPLC, proving the identity of synthetic **1a** and the natural isolate. Furthermore, all analytical data ($[\alpha]_D$, 300 MHz NMR, IR, and MS) of **1a** are identical to those published for (+)-isocyclocelabenzine isolated from the plant. The assignment of the absolute configuration of the synthetic products was carried out using the natural isomer **1a** which could be crystallized from AcOEt/pentane.

Afterwards, the relative configuration of **1a** was determined by X-ray crystal structure analysis *(Fig. 1.)*. On the basis of the known absolute configuration of the employed (+)-(3*S*)-3-amino-3-phenylpropionic acid, the absolute configuration of the two chiral centers could be assigned to be (9*S*) and (13*S*).

Thus, **1a** is (+)-(9*S*,13*S*)-3,4,5,6,8,9,10,11,12,13-decahydro-9-phenyl-2,13-methano-2*H*-2,6,10-benzotriaza-cyclopentadecine-1,7-dione, and the absolute configuration of the unnatural synthetic isomer **1b** was assigned to be (9*S*, 13*R*).

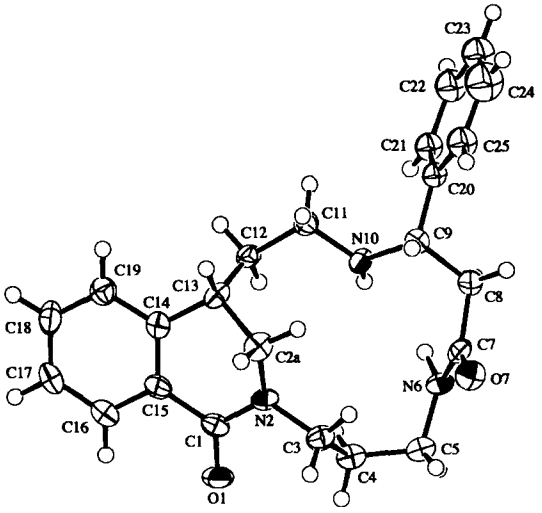


Fig.1 ORTEP plot[9] of **1a**

Experimental

General. Merck precoated plates $60F_{257}$ were used for TLC experiments and *Merck* PF_{254} silica gel for flash column chromatography (FC). Mp (not corrected): *Mettler* FP-5/FP-52. Optical rotation: *Perkin-Elmer* 241 Polarimeter at 589 nm (Na_D). UV/Vis spectra (λ_{max} in nm, MeOH, (logε)): *Hewlett Packard* diode-array spectrometer 8452 A. CD Spectra (λ in nm, MeOH, $\Delta\varepsilon$): *JASCO J-500 A*. IR: $\tilde{\nu}_{max}$ in cm^{-1} in KBr unless otherwise stated; *Perkin-Elmer* 297 or 781 spectrometer. NMR Spectra (in $CHCl_3$ unless otherwise stated): *Bruker* AM 400 and ARX 300. Chemical shifts in δ (ppm), using the appropriate solvent as internal standard. Multiplicities from DEPT experiments; multiple signals observed in the ^1H NMR and the ^{13}C NMR spectra are due to the two epimers resulting from the opposite enantiomeric configuration at C(13). CI-MS: *Finnigan-MAT* 90; 70 eV, NH_3. ESI-MS: *Finnigan* TSQ 700. Microanalyses: Mikrolabor of the University of Zürich.

4-Hydroxy-2-phenyl-butanenitrile (4). To a suspension of 11.7 g KOH in 34 ml of DMF, 4.9 ml (0.043 mol) of phenylacetonitrile were added. After stirring the mixture for 30 min at r.t., it was heated to 40-50°. Then, 3.2 ml (0.045 mol) of 2-bromoethanol in 20 ml DMF were added dropwise, during which the temperature may not exceed 50°. After the addition was complete, the mixture was stirred for another 1 h at 50°. The mixture was poured on ice, neutralized with conc. HCl and extracted 3 times with toluene (100 ml). The combined org. phases were washed with aq. HCl (200 ml), H_2O (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. FC (50 g silica gel; toluene/AcOEt 20:1, 7:1) followed by bulb-to-bulb distillation (150°/10^{-2} mbar) yielded 2.8 g (41%) of **4**. TLC (toluene/AcOEt 7:3): R_f 0.38. IR (Film): 3420 (br.), 3060, 3020, 2980, 2960,

2880, 2240, 1600, 1496, 1455, 1435, 1100*s*, 760, 700*s*. ^{1}H NMR: 7.43-7.13 (*m*, 5 arom. H); 4.10 (*dd*, *J* = 8.7, 6.7, CH); 3.88-3.78 (*m*, 1H, C*H*$_2$OH); 3.75-3.62 (*m*, 1 H, C*H*$_2$OH); 2.60 (*s*, OH); 2.23-2.01 (*m*, C*H*$_2$CH$_2$OH). ^{13}C NMR: 135.36 (*s*, arom. C); 128.98, 128.11, 127.32 (3*d*, 5 arom. C); 120.90 (*s*, CN); 58.82 (*t*, CH$_2$OH); 38.13 (*t*, *C*H$_2$-CH$_2$OH); 33.48 (*s*, CH). MS (CI): 162.0 [M+1]$^+$. Anal. calc. for $C_{10}H_{11}NO \cdot 1/8\ H_2O$ (162.20): C 73.47, H 6.78, N 8.57; found: C 73.80, H 7.08, N 8.79.

3-Cyano-3-phenylpropyl Acetate (5). A soln. of 0.5 g (3.1 mmol) of **4**, 0.41 ml of Ac_2O, 0.3 ml of pyridine and 5 ml of $CHCl_3$ was stirred at r.t. overnight. The solution was washed with H_2O (50 ml), the org. phase was dried ($MgSO_4$) and evaporated. Distillation (100°/10^{-2} mbar) yielded 0.63 g (99%) of **5**. TLC (toluene/AcOEt 7:3): R_f 0.66. IR (Film): 3060, 3030, 2980, 2240, 1740, 1495, 1455, 1390, 1370, 1240*s*, 1050*s*, 760, 700*s*. ^{1}H NMR: 7.15-7.10 (*m*, 5 arom. H); 4.08-3.89 (*m*, CH$_2$O); 3.80 (*dd*, *J* = 8.1, 6.8, CH); 2.2-1.92 (*m*, CH$_2$); 1.89 (*s*, Me). ^{13}C NMR: 170.50 (*s*, CO); 134.79 (*s*, 1 arom. C); 129.16, 128.27, 127.23 (3*d*, 5 arom. C); 120.14 (*s*, CN); 60.76 (*t*, CH$_2$O); 34.40 (*t*, 1 C); 34.01 (*d*, CH); 20.65 (*q*, Me). MS (CI): 204.1 [M+1]$^+$. Anal. calc. for $C_{12}H_{13}NO_2$ (203.23): C 70.92, H 6.45, N 6.89; found: C 71.00, H 6.64, N 7.02.

4-Acetoxy-2-phenylbutylammonium Chloride (6). A soln. of 0.63 g (3.1 mmol) of **5** in 1 ml $CHCl_3$ and 30 ml EtOH was hydrogenated over PtO_2 (100 mg) for 3 h at r.t. and 1013 mbar. The catalyst was filtered off and the filtrate concentrated *in vacuo* yielding 0.73 g (97%) of **6** as white needles. TLC ($CHCl_3$/MeOH 10:1): R_f 0.19. IR: 3420 (br.), 2950*s* (br.), 2640, 2040, 1740*s*, 1715*s*, 1605, 1500, 1475, 1455, 1398, 1370, 1250*s* (br.), 1040, 760, 700. ^{1}H NMR (DMSO): 8.15 (*s*, 4 H, NH_4^+); 7.60-7.32 (*m*, 5 arom. H); 4.19 (*m*, CH); 4.02-3.40 (*m*, 1 H, CH$_2$O); 3.86-3.76 (*m*, 1 H, CH$_2$O); 3.26-3.10 (*m*, C*H*$_2$NH$_4^+$); 2.30-2.15 (*m*, 1 H, CH$_2$); 2.05 (*s*, Me); 2.05-1.90 (*m*, 1 H, CH$_2$). ^{13}C NMR (DMSO): 170.53 (*s*, CO); 140.48 (*s*, 1 arom. C); 129.12, 128.26, 127.59 (3*d*, 5 arom. C); 61.96 (*t*, 1C); 44.04 (*t*, 1C); 40.63 (*d*, CH); 32.04 (*t*, 1C); 20.96 (*q*, Me). MS (CI): 208.1 [M+1]$^+$.

N-(8-Acetoxy-6-phenyl-4-azaoct-1-yl)phthalimide (7). To a suspension of 2.2 g (9.0 mmol) of **6** in 66 ml MeCN was added 11 g of KF/Celite® followed by 2.42 mg (9.0 mmol) of *N*-(3-bromopropyl)phthalimide. After stirring for 2 d at 40°, the suspension was filtered and the filtrate concentrated *in vacuo*. FC (70 g silica gel; CH_2Cl_2/MeOH 20:1) gave 1.3 g (57%) of **7** as an oil. TLC ($CHCl_3$/MeOH 10:1): R_f 0.55. IR (Film): 3060, 3020, 2940 (br.), 1770, 1740*s*, 1710*s*, 1495, 1470, 1450, 1440, 1400*s*, 1367, 1240*s*, 1190, 1130, 1040, 890, 760, 720*s*, 700. ^{1}H NMR: 7.68-7.58 (*m*, 2 arom. H); 7.55-7.44 (*m*, 2 arom. H); 7.10-6.88 (*m*, 5 arom. H); 3.8-3.6 (*m*, CH$_2$O); 3.49 (*t*, *J* = 6.9, CH$_2$NPhth); 2.70-2.55 (*m*, CH, CHRC*H*$_2$NH); 2.40 (*t*, *J* = 6.6, C*H*$_2$NH); 1.90-1.79 (*m*, 1H, CH$_2$); 1.78 (*s*, Me); 1.70-1.50 (*m*, 3H). ^{13}C NMR: 168.48 (*s*, CO); 165.87 (*s*, 2 CO); 139.95 (*s*, 1 arom. C); 131.34 (*d*, 2 arom. C); 129.65 (*s*, 2 arom. C); 126.20, 125.14, 124.25, 120.64 (4*d*, 7 arom. C); 60.18 (*t*, OCH$_2$CH$_3$); 52.94 (*t*, CH$_2$NPhth); 44.95 (*t*, 1 C); 40.40 (*s*, CH); 33.47 (*t*, 1 C); 30.56 (*t*, 1 C); 26.24 (*t*, 1 C); 18.37 (*q*, Me). MS (CI): 395.2 [M+1]$^+$. Anal. calc. for $C_{23}H_{26}N_2O_4 \cdot 3/4\ H_2O$ (394.41): C 67.72, H 6.79, N 6.87; found: C 67.67, H 6.71, N 6.85.

Ethyl N-(4-Acetoxy-2-phenylbutyl)-N-(3-phthalimidopropyl)carbamate (8). To a stirred soln. of 1.3 g (3.3 mmol) of **7** in 18 ml $CHCl_3$ was added 0.5 ml (3.6 mmol) of freshly distilled Et_3N and 0.35 ml (3.6 mmol) of ClCOOEt. After 14 h the soln. was washed twice with H_2O (20 ml), dried ($MgSO_4$) and concentrated *in*

vacuo yielding 1.46 g (95%) of **8** as an oil. TLC (toluene/AcOEt 7:3): R_f 0.40. IR (Film): 2960 (br.), 1770, 1735, 1710s (br), 1470, 1420, 1400*s*, 1370, 1240, 1190, 1145, 1100 (br.), 1040, 890, 770, 720*s*, 700. ^{1}H NMR: 7.90-7.80 (*m*, 2 arom. H); 7.78-7.70 (*m*, 2 arom. H); 7.30-7.05 (*m*, 5 arom. H); 4.18-3.50 (*m*, 7 H); 3.36-2.73 (*m*, 4 H); 2.10-1.70 (*m*, 7 H); 1.30-1.10 (br. *s*, Me). ^{13}C NMR: 172.41, 169.67 (2*s*, 4 CO); 143.06 (*s*, 1 arom. C), 135.44 (*d*, 1 arom. C); 133.58 (*s*, 2 arom. C); 130.10, 129.27, 128.40, 124.70 (4*d*, 8 arom. C); 64.08, 62.74 (2*t*, 2 OCH_2); 54.89, 46.89 (2*t*, 2C); 43.33 (*d*, CH); 37.17, 33.28, 28.77 (3*t*, 3 C); 20.74, 14.67 (2*q*, 2 Me). MS (CI): 467.3 $[M+1]^+$. Anal. calc. for $C_{26}H_{30}N_2O_6$ (394.41): C 66.94, H 6.48, N 6.01; found: C 66.74, H 6.58, N 5.60.

4-(2-Chloroethyl)-2-(3-phthalimidopropyl)-1,2,3,4-tetrahydroisoquinolin-1-one (9). A soln. of 0.56 g (1.2 mmol) of **8** in 1 ml $POCl_3$ was refluxed at 155° overnight. $POCl_3$ was partially 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 3 times with CH_2Cl_2 (20 ml). The combined extracts were washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in small amount of CH_2Cl_2 and adsorbed on silica gel. FC (30 g silica gel; toluene/AcOEt 7:2) afforded 277 mg (58%) of **9**. Mp 97-99°. TLC (toluene/AcOEt 7:3): R_f 0.40. IR: 3460, 2930, 1780, 1710*s* (br.), 1640*s*, 1600, 1568, 1495, 1470, 1440, 1405*s*, 1380, 1315, 1260, 1220, 1170, 1065, 1040*s*, 880, 760, 720*s*, 700. ^{1}H NMR: 8.00 (*dd*, *J* = 7.6, 1.4, H-C(8)); 8.80-7.73 (*m*, 2 phthaloyl-H); 7.68-7.60 (*m*, 2 phthaloyl-H); 7.43-7.00 (*m*, 3 arom. H); 3.85 (*dd*, *J* = 12.7, 4.2, 1 H, H-C(3)); 3.78-3.62 (*m*, 3 H); 3.60-3.30 (*m*, 3 H); 3.27 (*dd*, *J* = 12.7, 2.3, 1 H, H'-C(3)); 3.21-3.19 (*m*, CH); 2.10-1.85 (*m*, 2 CH_2). ^{13}C NMR: 168.16 (*s*, 2 CO); 163.99 (*s*, CO); 140.13 (*s*, 1 arom. C); 133.88 (*d*, 2 arom. C); 132.02 (*s*, 2 arom. C); 131.69 (*d*, 1 arom. C); 128.94 (*s*, 1 arom. C); 128.66, 127.52, 126.95, 123.18 (4*d*, 5 arom. C); 50.38 (*t*, 1 C); 44.96 (*t*, CH_2Cl); 42.58, 35.99, 35.81 (3*t*, 3 C); 34.19 (*d*, CH); 26.84 (*t*, 1C). MS (CI): 397.1 $[M+1]^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_3$ (396.12): C 66.58, H 5.33, N 7.06; found: C 66.49, H 5.37, N 7.12.

2-{{3-{3-[(tert-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}propyl}-4-(2-chloroethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (10). A soln. of 2.0 g (5.04 mmol) of **9**, 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 *in vacuo*. The residue was dissolved in CH_2Cl_2, washed with sat. aq. NaCl soln., dried ($MgSO_4$) and concentrated *in vacuo*. The intermediate amine was dried *in vacuo* and dissolved in 15 ml CH_2Cl_2. The soln. was added dropwise, at r.t. to a stirred mixture of 1.3 g (5.04 mmol) of (-)-(3*S*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-3-phenylpropanoic acid and 1.33 g (5.04 mmol) of 2-chloro-1-methylpyridinium iodide in 26 ml dry CH_2Cl_2 and 0.72 ml (5.04 mmol) of freshly distilled Et_3N. After 3 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) yielded 1.4 g (54%) of **10**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.67. IR: 3330 (br.), 2980, 2930, 1710*s*, 1645*s*, 1600, 1530 (br.), 1490, 1480, 1455, 1440, 1365, 1250, 1165, 1045, 1020, 760, 700. ^{1}H NMR: 8.03 (*d*, *J* = 7.7, H-C(8)); 7.50-7.12 (*m*, 8 arom. H); 6.96 (br. *s*, NH); 6.50-6.30 (br. *s*, NH); 5.04 (br. *s*, CH); 3.86-3.10 (*m*, 8 H); 3.00-2.85 (*m*, 1 H); 2.80-2.60 (*m*, 2 H); 2.12-1.90 (*m*, 2 H); 1.67-1.48 (*m*, 2 H); 1.38 (*s*, 3 Me). ^{13}C NMR: 170.32, 164.72, 155.21 (3*s*, 3 CO); 140.07 (*s*, 2 arom. C); 132.03, 128.61, 128.54, 128.33 (4*d*, 4 arom. C); 127.96 (*s*, 1

arom. C); 127.66, 127.02, 126.95, 126.03, (4*d*, 5 arom. C); 78.68 (*s*, *C*Me$_3$); 50.48, 44.81, 42.22, 35.99, 35.86, 35.13, 34.95 (7*t*, 6 C); 34.11, 34.02 (2*d*, 2 C); 28.28 (*q*, 3 Me), 26.70, 26.56 (2*t*, 1 C). MS (CI): 514.3 $[M+1]^+$.

2-{[3-{3-[(tert-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}propyl]-4-(2-iodoethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (11). A soln. of 0.93 g (1.8 mmol) of **10** and 1.12 g (7.5 mmol) of NaI in 10 ml of acetone was refluxed for 18 h under the exclusion of light. The solvent was removed *in vacuo* and the residual oil was dissolved in 80 ml CH_2Cl_2, washed twice with H_2O (60 ml) and dried ($MgSO_4$). After filtration the solvent was evaporated and the product was dried *in vacuo* to yield 1.07 g (98%) of **11**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.69. IR: 3300 (br.), 2980, 2930, 1700, 1645*s*, 1605, 1530 (br.), 1490, 1480, 1455, 1430, 1365, 1250, 1170*s*, 1045, 1020, 760, 700*s*. ^{1}H NMR: 7.95 (*dd*, *J* = 7.6, 1.5, H-C(8)); 7.46-7.04 (*m*, 8 arom. H); 6.98-6.85 (*m*, NH); 6.40 (br. *s*, NH); 5.00 (br. *s*, CH); 3.75-3.61 (*m*, 1 H); 3.30-2.51 (*m*, 10 H); 2.10-1.90 (*m*, 2H); 1.60-1.38 (*m*, 2 H); 1.30 (*s*, 3 Me). ^{13}C NMR: 169.38, 163.76, 154.25 (3*s*, 3 CO); 139.05 (*s*, 2 arom. C); 131.10, 127.67, 127.58, 127.41 (4*d*, 4 arom. C); 127.07 (*s*, 1 arom. C); 126.79, 126.02, 125.87, 125.07 (4*d*, 5 arom. C); 78.22 (*s*, *C*Me$_3$); 49.22, 43.14, 42.95, 41.85 (4*t*, 3 C); 36.39, 36.30 (2*d*, 2 CH); 35.90, 35.78, 34.09, 33.91 (2*t*, 1 C); 2.84 (*t*, CH_2I). MS (ESI): 628.3 $[M+Na]^+$.

2-{[3-{3-[(tert-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}propyl]-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (12). A soln. of 1.0 g (1.65 mmol) of **11** and a mixture of 9 ml of HMPA and 2 ml of H_2O was heated at 100° for 2.5 h. The mixture was diluted with H_2O (100 ml) and extracted 3 times with AcOEt (100 ml). The combined org. phases were washed twice with H_2O (100 ml) to remove all HMPA, dried (Na_2SO_4) and concentrated *in vacuo*. FC (100 g silica gel; CH_2Cl_2/MeOH 20:1) afforded 0.56 g (76%) of **12**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.40. IR: 3300 (br.), 2965, 1695, 1640*s*, 1640, 1600, 1530 (br.), 1490, 1480, 1455, 1430, 1390, 1370, 1300 (br.), 1250, 1170*s*, 1050, 760, 700*s*. ^{1}H NMR: 7.94 (*d*, *J* = 7.7, H-C(8)); 7.40-6.95 (*m*, 8 arom. H, 1 NH); 6.30 (br. *s*, NH); 4.96 (br. *s*, CH); 3.70-2.51 (*m*, 11 H); 2.24 (br. *s*, OH); 1.84-1.68, 1.60-1.40 (2 *m*, 4 H); 1.35 (*s*, 3 Me). ^{13}C NMR: 170.63, 164.99, 155.26 (3*s*, 3 CO); 141.27 (*s*, 2 arom. C), 131.93, 128.36 (2*d*, 3 arom. C); 127.98 (*s*, 1 arom. C); 127.21, 127.03, 126.87, 126.01 (4*d*, 6 arom. C); 79.38 (*s*, *C*Me$_3$), 59.90 (*t*, CH_2OH); 44.03, 36.01, 35.85, 35.24 (4*t*, 5 C); 34.24, 34.16 (2*d*, 2 CH); 28.29 (*q*, 3 Me); 26.61 (*t*, 1 C). MS (ESI): 518.3 $[M+Na]^+$. Anal. calc. for $C_{28}H_{37}N_3O_5 \cdot 3/4\ H_2O$ (495.60): C 66.06, H 7.62, N 8.25; found: C 66.07, H 7.36, N 8.20.

2-{[3-{3-[(tert-Butoxycarbonyl)amino]-1-oxo-3-phenylpropyl}amino}propyl]-4-(formylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (13). To a soln. of 0.42 g (1.1 mmol) of **12** in 9 ml dry CH_2Cl_2 with molecular sieve (3 Å; ~0.5 g per mmol **12**), 375 mg (1.7 mmol) of PCC was added in 3 portions over a period of 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 eluted with AcOEt (500 ml). The org. phase was concentrated *in vacuo* and the residue was purified by FC (30 g silica gel; AcOEt) yielding 280 mg (67%) of **13**. TLC ($CHCl_3$/MeOH 10:1): R_f 0.43. IR: 3320 (br.), 2970, 2920, 1710*s* (br.), 1640*s* (br.), 1600, 1540, 1490, 1480, 1450, 1430, 1390, 1365, 1310, 1250, 1170*s*, 1150, 1020, 760, 700*s*. ^{1}H NMR: 9.80 (*s*, COH); 8.05 (*d*, *J* = 7.7, H-C(8)); 7.53-7.28 (*m*, 8 arom. H); 6.93 (3 *s*, NH); 6.41 (br. *s*, NH); 5.08 (br. *s*, CH); 3.81-2.60 (*m*, 11 H); 1.70-1.42 (*m*, 2 H); 1.40 (*s*, 3 Me). ^{13}C NMR: 199.50 (2*d*, COH); 170.27, 164.83, 155.84

(3*s*, 3 CO); 140.31 (*s*, 3 arom. C); 132.37, 128.49, 128.34, 128.19, 127.69, 126.96, 126.34, 126.02 (8*d*, 9 arom. H); 79.20 (*s*, CMe_3); 51.83, 49.91, 47.03, 46.93, 44.05, 43.98, 42.81, 35.18, 35.01 (9*t*, 5 C); 31.52 (*d*, 2 C); 28.29 (*q*, 3 Me); 26.61 (*t*, 1 C). MS (ESI): 516.3 $[M+Na]^+$. Anal. calc. for $C_{28}H_{35}N_3O_5 \cdot 3/4\ H_2O$ (493.60): C 66.30, H 7.25, N 8.29; found: C 66.32, H 7.14, N 8.33.

(+)-(9S,13S)- and (+)-(9S,13R)-Isocyclocelabenzine (≡ 3,4,5,6,8,9,10,11,12,13-Decahydro-9-phenyl-2,13-methano-2*H*-2,6,10-benzotriazacyclopentadecine-1,7-dione **1a** and **1b**, respectively). A soln. of 236 mg (0.49 mmol) of **12** in 10 ml of TFA was stirred for 30 min at r.t. The solvent was evaporated *in vacuo* and the residue was dissolved in 85 ml of MeOH. The pH value was adjusted to pH 8 with Et_3N. After the addition of 36 mg (0.57 mmol) of $NaBH_3CN$ the soln. was stirred at r.t. for 2.5 d, quenched with H_2O (10 ml) and the MeOH was evaporated *in vacuo*. 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 *in vacuo* and the residue was purified by FC (50 g silica gel; CH_2Cl_2/MeOH 40:1) yielding 114 mg (63%) of a mixture of two diastereoisomers in a ratio of 1.2:1 according to ^1H NMR data. TLC ($CHCl_3$/MeOH 10:1): R_f 0.36. IR: 3430 (br.), 3300, 3060, 3020, 2920, 2940, 1640*s* (br.), 1600, 1570, 1550, 1495, 1475, 1455, 1435, 1350, 1305, 1250, 1160, 1115, 760, 700*s*. MS (ESI): 378.5 $[M+1]^+$.

HPLC separation (*Hewlett Packard* 1090; UV-detection at 254 nm; solvent system: hexane/2-propanol 3:1, Semi-preparative column: 250/10 *Nucleosil 100-5NH*$_2$ (*Machery-Nagel* AG), flow-rate 3.5 ml/min.) of 60 mg yielded 27.35 mg of natural **1a** and 21.70 mg of the unnatural isomer **1b**.

Data of 1a (≡ natural (+)-isocyclocelabenzine): Mp 226-227° (recrystallized from AcOEt/pentane). $[\alpha]_D$ = +139.3 (c = 0.505, $CHCl_3$). UV: 266 (3.69), 254 (3.77). CD: ($1.54 \cdot 10^{-4}$M): 282.6 nm (Δε +3.59), 269.4 nm (Δε +2.14), 243.0 nm (Δε +6.43), 232.0 (Δε 0), 219.2 (Δε -7.33). ^1H NMR: 8.41-8.32 (*m*, 1 arom. H); 7.93-7.84 (br. *m*, H-N(6)); 7.70-7.60 (*m*, 2 arom. H); 7.40-7.38 (*m*, 3 arom. H); 7.02-6.82 (*m*, 2 arom. H); 4.40-4.20 (*m*, 2 H, H-C(5), H-C(3)); 4.18 (*dd*, *J* = 11.2, 2.7, H-C(9)); 4.1 (*dd*, *J* = 12.8, 5.6, H-C(2')); 3.82 (*dd*, *J* = 12.9, 2.0, H'-C(2')); 3.80-3.70 (*m*, 1 H); 3.39-3.11 (2 *m*, 2 H); 2.92-2.70 (*m*, 2 H, H-C(11)); 2.57 (*dd*, *J* = 13.5, 2.8, H-C(8)); 2.46-2.32 (*m*, H-C(4)); 2.30 (*dd*, *J* = 13.5, 11.2, H'-C(8)); 2.18-1.92 (*m*, 3 H, H'-C(4), H-C(12)). ^{13}C NMR: 170.58 (*s*, C(7)); 164.40 (*s*, C(1)); 142.65 (*s*, C(20)); 140.35 (*s*, C(14); 130.76 (*d*, C(18)); 128.71 (*s*, C(15)); 127.31, 126.82, 126.01, 125.94, 125.89, 125.06 (6*d*, 8 arom. C); 60.38 (*d*, C(9)); 49.34 (*t*, C(2')); 45.63, 45.35, 44.86 (3*t*, 4 C); 37.42 (*t*, 1 C); 35.48 (*t*, 1 C); 35.36 (*d*, C(13)); 24.74 (*t*, C(4)).

Crystal structure determination of **1a**:[10] $C_{23}H_{27}N_3O_2$, M_r = 377.48, orthorhombic, space group $P2_12_12_1$, a = 14.487(6), b = 26.522(9), c = 5.131(2) Å, V = 1972(1) Å^3, Z = 4, D_c = 1.272 g cm^{-3}, T = -100°C, Mo-Kα radiation, λ = 0.71069 Å, μ = 0.0821 mm^{-1}. Intensities were collected in the ω-scan mode on a *Rigaku*-AFC5R diffractometer and were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods (SHELXS86)[11] and refined on F by full-matrix least-squares methods to give R = 0.0602, *wR* = 0.0600, S = 1.967 using 225 refined parameters and 2055 observed reflections with $I > 2\sigma(I)$ from the 3304 collected with 5° < 2θ< 55°. The enantiomorph was fixed by the known configuration at C(9). The phenyl group is disordered with the two equally occupied orientations differing by a rotation of approximately 50° about the C(9)-C(20) bond. The disordered atoms were refined as two rigid groups. A view

of the molecule is shown in *Fig. 1.* All calculations were performed using the TEXSAN crystallographic software package.[12]

Data of 1b: Mp 189-190° (recrystallized from AcOEt/diisopropyl ether). $[\alpha]_D$ = +48.9 (c = 0.1637, $CHCl_3$). UV: 266 (3.68), 252 (3.81). CD: ($1.55 \cdot 10^{-4}$ M): 284.8 nm (Δε +0.38), 275.4 nm (Δε + 0.35), 249.8 nm (Δε +2.05), 240.4 (Δε 0), 229.0 (Δε -4.13), 218.8 (Δε 0), 213.2 (Δε +4.01). ^{1}H NMR: 8.50-8.36 (br. *m*, H-N(6)); 8.25 (*dd*, *J* = 7.6, 1.4, 1 arom. H); 7.62-7.20 (*m*, 8 arom. H); 4.10-4.00 (*m*, 1 H); 3.95 (*dd*, *J* = 10.5, 3.5, H-C(9)); 3.86 (*dd*, *J* = 12.0, 4.3, H-(2')); 3.82-3.70 (*m*, 1 H); 3.62 (*dd*, *J* = 12.0, 8.9, H'-C(2')); 3.60-3.30 (*m*, 2 H); 3.05-2.95 (*m*, 1 H); 2.75-2.58 (*m*, 3 H); 2.30-2.10 (*m*, 3 H); 1.95-1.70 (*m*, 3 H). ^{13}C NMR: 169.89 (*s*, C(7)); 163.90 (*s*, C(1)); 140.58 (*s*, C(20)); 140.06 (s, C(14); 130.06 (*d*, C(18)); 127.56 (*s*, C(15)); 127.06, 126.46, 125.85, 125.23, 124.24, 122.44 (6*d*, 8 arom. C); 59.21 (*d*, C(9)); 48.90 (*t*, C(2')); 45.52, 42.13, 42.05 (3*t*, 4 C); 35.27 (*t*, 1 C); 34.04 (*d*, C(13)); 27.76, 25.96 (2*t*, 2 C).

REFERENCES AND NOTES

1. Wagner, H.; Burghart, J.; Hull, W. E. *Tetrahedron Lett.* **1978**, 3893; Wagner, H.; Burghart, J. *Helv. Chim. Acta* **1982**, *65*, 739.
2. Iida, H.; Fukuhara, K.; Murayama, Y.; Machiba, M.; Kikuchi, T. *J. Org. Chem.* **1986**, *51*, 4701.
3. Schultz, K.; Hesse, M. *Helv. Chim. Acta* **1996**, *79*, 1295.
4. Bulat, A. D.; Grishin, V. V.; Kuznetsova, T. E.; Nekrasov, S. V.; Passet, B. V. *Chim.-Farm. Zurnal* **1991**, *25*, 60.
5. Secrist, J. A.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335.
6. Ando, T.; Yamawaki, J. *Chem. Letters* **1979**, *1*, 45.
7. Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269.
8. Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360.
9. Johnson, C. K. 'ORTEP II'. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge Tennessee, 1976.
10. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. 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).
11. Sheldrick, G. M. 'SHELXS86', *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
12. TEXSAN. 'Single Crystal Structure Analysis Software', Version 5.0, *Molecular Structure Corporation*, The Woodlands, Texas, 1989.

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