Total Synthesis of the Spermidine Alkaloid 13-Hydroxyisocyclocelabenzine

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A convergent total synthesis of 13-hydroxyisocyclocelabenzine was developed. (3*S*)-Methyl 3-amino-3-phenylpropanoate (**4**) was used as the chiral building block. The 3,4-dihydro-4-hydroxyisoquinolin-1(2*H*)-one derivative (**5**), the key fragment for the total synthesis, was prepared by a novel base-catalyzed lactone-lactam ring enlargement (*Scheme 3*). The resulting target C(13) epimers **3a**/**3b** from macrocyclization (*Scheme 4*) were separated by repeated flash chromatography. The absolute configuration of the synthetic alkaloid was determined by an X-ray crystal-structure analysis, which enabled us to determine the absolute configuration (9*S*,13*R*) for natural **3a** with positive $[\alpha]_D$.

Introduction. – The macrocyclic spermidine alkaloid (+)-13-hydroxyisocyclocelabenzine (**3**), together with (+)-cyclocelabenzine (**1**) and (+)-isocyclocelabenzine (**2**) was isolated from *Maytenus mossambicensis* (KLOTZSCH) BLAKELOCK *var. mossambicensis* (Celastraceae) by *Wagner* and co-workers [1] (*Fig. 1*).

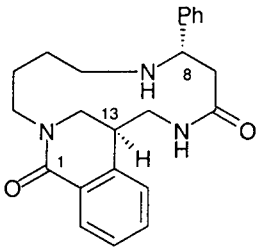
The three alkaloids **1**–**3** show the 13-membered lactam ring of celabenzine being linked to the benzoyl residue within the spermidine unit to form an appended six-membered ring (*Fig. 1*). The 13-hydroxyisocyclocelabenzine is the first known spermidine alkaloid with a hydroxy function at the macrocyclus.

The structures of these alkaloids were elucidated by spectroscopic methods, especially ^{1}H- and ^{13}C-NMR spectroscopy. The absolute configurations of cyclocelabenzine and isocyclocelabenzine were determined by asymmetric syntheses and X-ray crystal-structure analysis [2][3].

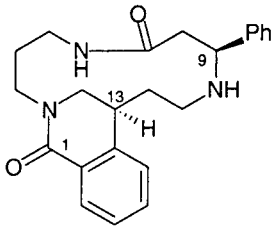
We now describe a short and efficient asymmetric synthesis of (+)-13-hydroxyisocyclocelabenzine, which allows the determination of its unknown relative and absolute configuration by an X-ray crystal-structure analysis. Our *retro*-synthetic consideration leads to the building blocks **4** and **5** and further to the starting compound phthalaldehydic acid *via* **6**–**8** (*Scheme 1*). Although the absolute configuration at C(9) is unknown, it was assumed that this centre probably has the (*S*)-configuration like all other structurally known spermidine alkaloids from this source [4]. Therefore, (*S*)-β-phenyl-β-alanine ester **4** was used as the chiral building block.

Results and Discussion. – The chiral building block, methyl (3*S*)-3-amino-3-phenylpropanoate (**4**) was synthesized according to reported procedures by resolution of racemic β-phenyl-β-alanine [5][6] or by direct asymmetric synthesis [7]. The crucial step of the synthesis leading to 13-hydroxyisocyclocelabenzine was the formation of a suitably substituted 3,4-dihydroisoquinolin-1(2*H*)-one fragment. Although a *modified*

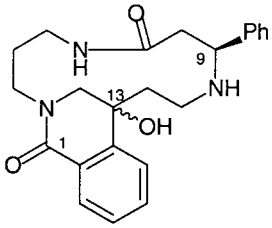
[1]) Part of Ph. D. Thesis of *Y. L.*, Universität Zürich, 2002.



1 (+)-(8*S*,13*R*)-cyclocelabenzine



2 (+)-(9*S*,13*S*)-isocyclocelabenzine



3 (+)-13-hydroxyisocyclocelabenzine

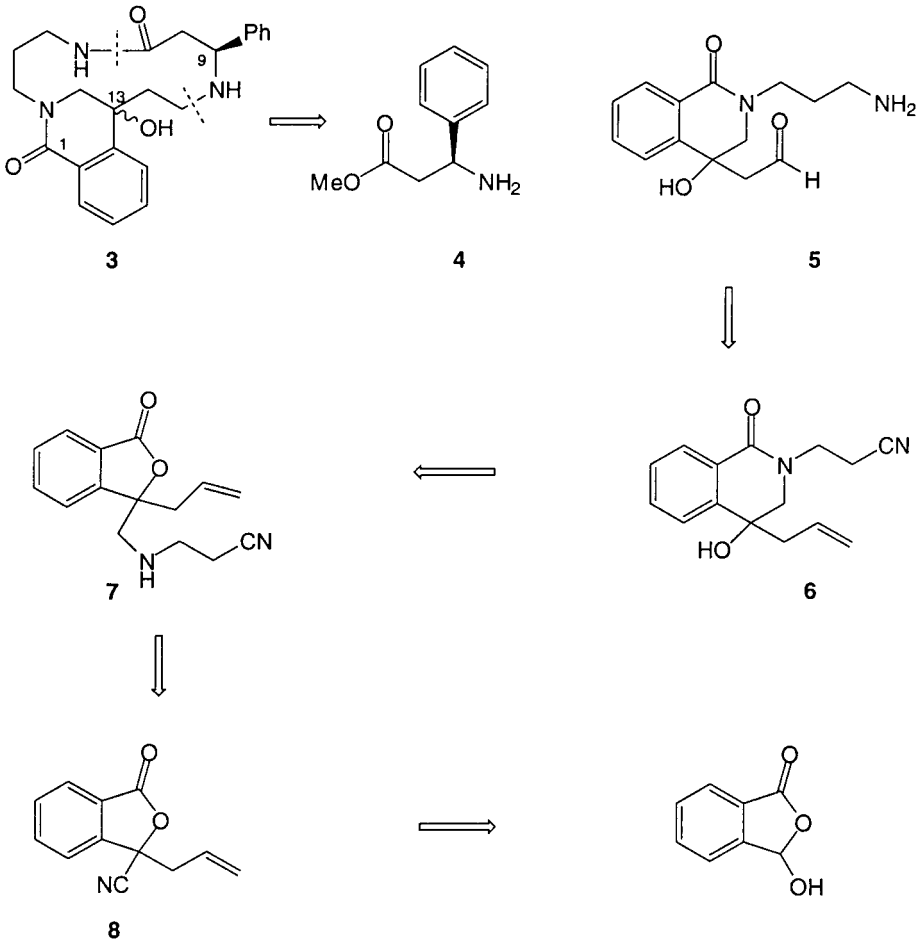
Fig. 1. *Spermidine alkaloids isolated from* Maytenus mossambicensis

Bischler-Napieralski reaction was used by us to construct the similar 3,4-dihydroisoquinolin-1(2*H*)-one derivatives in the syntheses of isocyclocelabenzine and cyclocelabenzine [2][3], the strong acidic reaction conditions employed make this method inapplicable in the present case due to the susceptible benzylic OH group. In fact, there is no general procedure available so far giving access to this structure. Our synthetic strategy to 3,4-dihydro-4-hydroxyisoquinolin-1(2*H*)-one was based on a novel lactone-lactam transformation, which took advantage of the relative spatial arrangement of the O- and N-atom in this fragment.

The commercially available phthalaldehydic acid was treated with potassium cyanide and HCl at 0°. Without isolation, the cyanohydrine generated was subjected to dehydration in the presence of dicyclohexylcarbodiimide (DCC) to afford the phthalide-derived nitrile **9** in an excellent yield (*Scheme 2*) [8]. Alkylation of the nitrile-stabilized anion derived from **9** with allyl bromide provided **8** in 75% yield. Allyl bromide was chosen as the electrophilic reagent in the hope that the C=C bond could be transformed to an aldehyde group for the coupling with the amino acid building block. When 2-(bromomethyl)-1,3-dioxolane, the electrophile with an already protected aldehyde group, was used, no substitution product could be obtained due to the lower reactivity and higher steric hindrance of this reagent.

The presence of a C=C bond and ester function in compound **8** made the selective reduction of the CN group quite thorny. Among methods available for the reduction of nitriles, catalytic hydrogenation over a metal catalyst such as Pt, Pd, or *Raney*-Ni would reduce the C=C bond simultaneously. On the other hand, the lactone could not survive

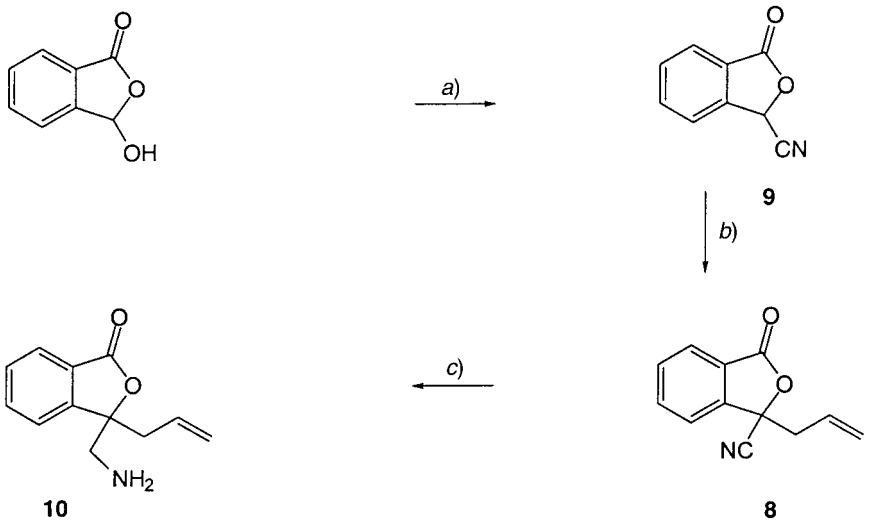
Scheme 1. *Retrosynthetic Analysis of (+)-13-Hydroxyisocyclocelabenzine* (**3**)



the hydride reduction of nitriles to amines by those traditional hydride reagents such as $LiAlH_4$ and $LiAlH_4 \cdot AlCl_3$.

Umino et al. [9] reported that both aliphatic and aromatic nitriles can be reduced to the corresponding amines with sodium trifluoroacetoxy borohydride ($NaBH_3(OCOCF_3)$) in THF. The application of this reagent to our case was examined. When compound **8** was treated with 1 equiv. of $NaBH_3(OCOCF_3)$, generated from $NaBH_4$ and CF_3COOH *in situ*, the desired product **10** was obtained in 40% yield, with recovery of 20% of starting material. The yield decreased sharply on addition of more reducing agent; no reduction product could be isolated, and all starting material was destroyed when 3 equiv. of reducing agent per mol of nitrile were employed. It is well known that $NaBH_4$ in conjunction with various strong acids is an effective hydroboration agent [10]. *Marshall* and *Johnson* [11] have reported the hydroboration of hex-1-ene with $NaBH_4$ and AcOH in THF. The vital role played by the acid would be either to

Scheme 2



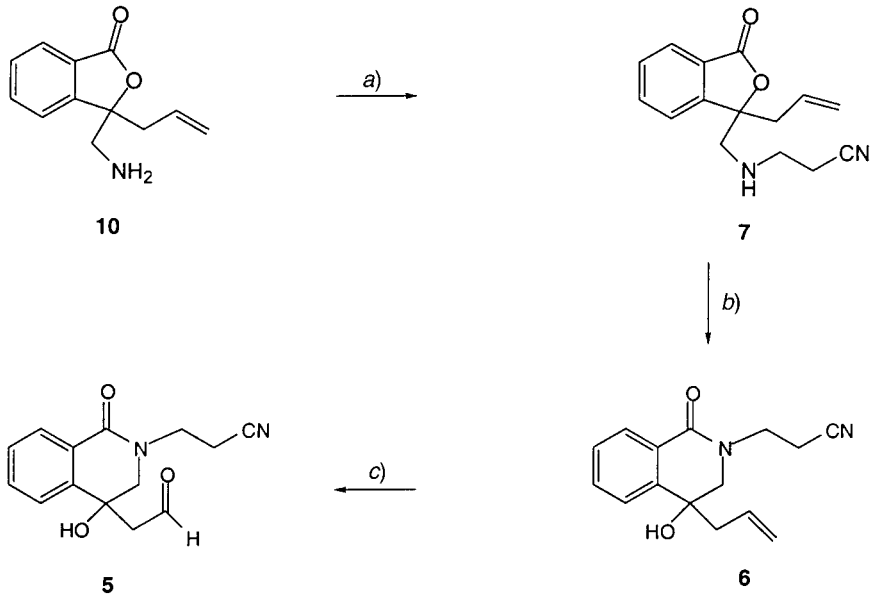
a) 1. KCN, HCl, 0°; 2. DCC, r.t., 8 h; 85%. *b*) Lithium diisopropylamide, allyl bromide, THF, −78°, 8 h; 75%. *c*) $NaBH_3(OCOCF_3)$, THF, r.t. 40%.

protonate the substrate, thus rendering it more susceptible to attack by hydride, as appears to be the case with nitriles, or to produce diborane or a related species, which, in turn, attacks the substrate. The analogous reaction between $NaBH_4$ and CF_3COOH in our case may produce a species which, perhaps by its decomposition into diborane, is capable of effecting hydroboration. So, the reasonable explanation for this reaction could be that the reduction of the cyano group happened prior to the hydroboration of the C=C bond, but excess amount of $NaBH_3(OCOCF_3)$ converted the reduction product into alkylboranes.

In view of our finding, this procedure provided a convenient method for the selective reduction of nitriles to corresponding amines under mild conditions, leaving the olefinic functions intact. The low yield was compensated by the absence of saturated product, which could not easily be separated by column chromatography.

Treatment of the amine **10** with acrylonitrile in refluxing MeOH gave monosubstituted amino derivative **7** in 87% yield (*Scheme 3*). The *N*-alkylation to introduce the butyl unit of the spermidine moiety was carried out now to circumvent the strong-base-catalyzed alkylation of an amide at a later stage. The expected reaction that accomplished the conversion of the intermediate **7** into intermediate **6** took place very smoothly. When **7** was refluxed in EtOH in the presence of 1 equiv. of NaOMe, the amino-phthalide-substituted alkene rearranged to 3,4-dihydro-4-hydroxyisoquinolin-1(2*H*)-one in an excellent yield. This rearrangement reaction is apparently a base-catalyzed one, the driving force is the formation of the more stable six-membered lactam. Ozonolysis of the intermediate **6** at −78° in MeOH and reduction of the ozonolysis product with Me_2S proceeded quite cleanly and in good yield to furnish precursor **5**.

Scheme 3

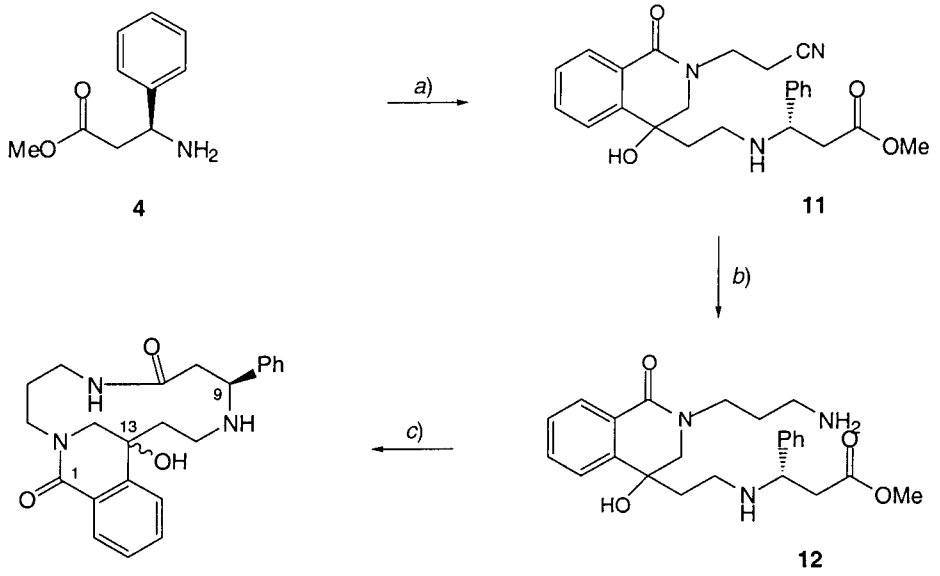


a) Acrylonitrile, MeOH, reflux, 12 h; 87%. *b*) NaOMe, EtOH, reflux, 2 h; 90%. *c)* 1. O_3, MeOH, −78°; 2. Me_2S; 80%.

The coupling of precursor **5** with the chiral building block **4** was attempted by reductive amination [12]. Thus, amino ester **4** and intermediate **5** were dissolved in MeOH, the resulting solution was adjusted to pH 6 with aqueous HCl solution, and the intermediate imine formed was subsequently reduced by $NaBH_3CN$ to give the coupling product **11** in a good yield of 75% (*Scheme 4*). Catalytic reduction of the cyano group of **11** with H_2/PtO_2 in EtOH containing 2 equiv. of HCl led to the corresponding amino ester **12**. These mild reaction conditions are advantageous as they permit the reduction of the cyano group in the presence of functional groups that are susceptible to strongly acidic or basic reagents. In our case, the acetate and benzylic OH group were not affected by the conditions outlined above.

The last step on the way to 13-hydroxyisocyclocelabenzine was the ring closure to the 13-membered macrocycle. Although boron-templated cyclization of triamino esters with tris(dimethylamino)boron has been reported to be highly efficient in the synthesis of macrocyclic spermidine alkaloids containing 13 ring members [13], attempts to obtain target molecule **3** directly by ring closure of amino ester **12** according to the reported procedure [14] only resulted in inseparable mixtures, and no starting material could be recovered. Therefore, an alternative macrocyclization strategy employing the coupling reagent under high-dilution conditions was pursued. To this end, amino ester **12** was converted to the amino acid by saponification with LiOH in THF/MeOH/H_2O 3 : 1 : 1. Without further purification, the amino acid obtained was treated with diethyl phosphorocyanidate [15] in the presence of Et_3N in DMF to furnish (9*S*,13*R*)/(9*S*,13*S*)-13-hydroxyisocyclocelabenzine (**3a**/**3b**) as a mixture of the C(13) epimers in a yield of

Scheme 4



3a (+)-(9*S*,13*R*)-13-hydroxyisocyclocelabenzine

3b (+)-(9*S*,13*S*)-13-hydroxyisocyclocelabenzine

a) **5**, $NaBH_3CN$, HCl, MeOH, r.t., 6 h; 75%. *b*) H_2, PtO_2, EtOH, r.t., 5 h; 90%. *c*) 1. LiOH, THF/MeOH/H_2O 3:1:1, r.t., 3 h; 2. $(EtO)_2POCN$, Et_3N, DMF, r.t.; 60%.

60%. The ratio of the two epimers **3a** and **3b** was determined by ^{1}H-NMR spectroscopy to be 1:1. The cyclization of the amino acid with *Mukaiyama*'s reagent [16] failed in CH_2Cl_2, the optimal solvent for this reagent, due to the very low solubility of the amino acid, but worked out in DMF. The separation of the epimers was accomplished by repeated flash chromatography (see *Exper. Part*). Both epimers have positive optical rotations and are colorless amorphous solids. All analytical data ($[\alpha]_D$, NMR, IR, and MS) of one of the synthesized isomers, *i.e.* of **3a**, are identical to those published for (+)-13-hydroxyisocyclocelabenzine isolated from the plant [1].

The assignment of the absolute configuration was carried out by an X-ray crystal-structure analysis of crystals of **3a** obtained from $CHCl_3$ (*Fig. 2*). On the basis of the known absolute configuration of the employed (3*S*)-methyl 3-amino-3-phenylpropanoate (**4**), the absolute configuration of the two chiral centers could be assigned to be (9*S*,13*R*). Thus, the absolute configuration of the natural 13-hydroxyisocyclocelabenzine was established to be (9*S*,13*R*).

We thank the *Swiss National Science Foundation* for the generous support, *J. Cavegn* for assistance with the determination of the crystal structure, and the analytical department of the University of Zurich for MS and microanalyses.

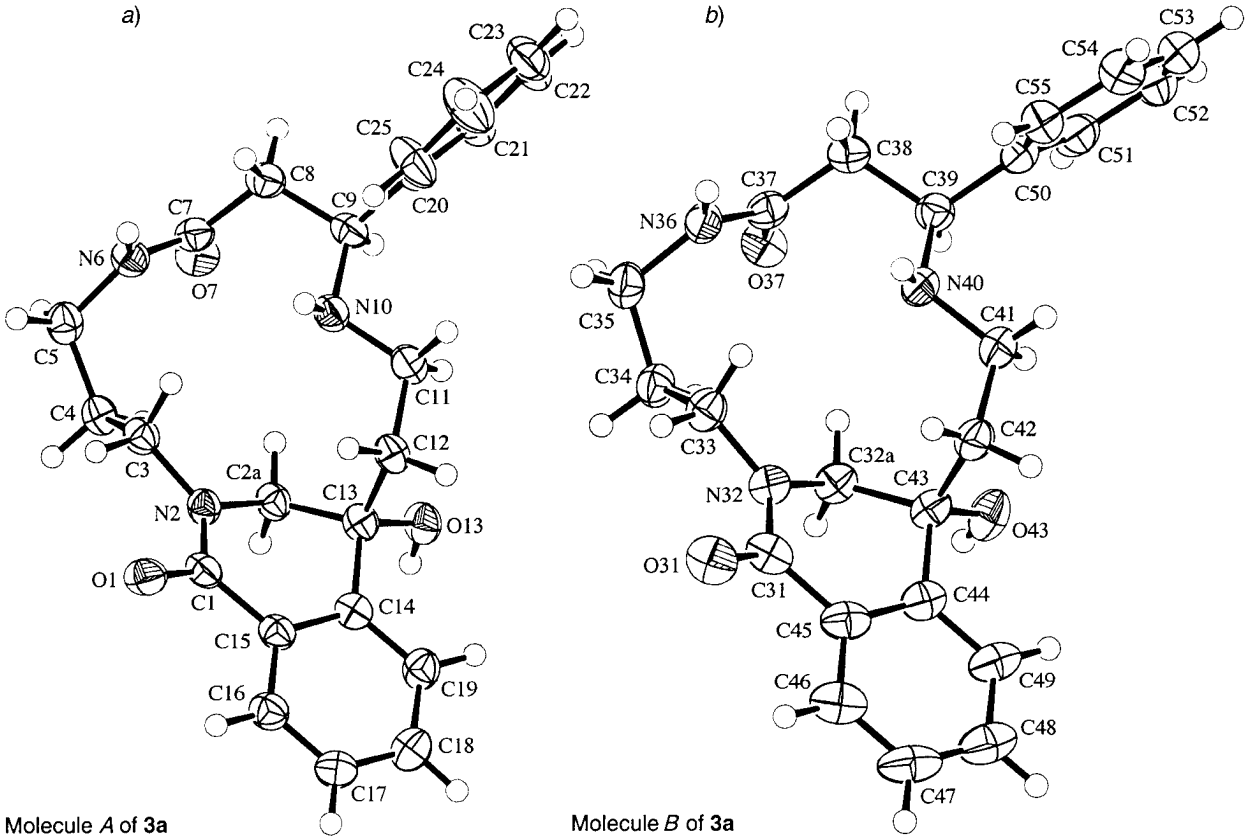


Fig. 2. *ORTEP Plot* [17] *of the two symmetry-independent molecules of* **3a** *in the structure of* **3a** · $CHCl_3$ (50% probability ellipsoids)

Experimental Part

General. All reactions involving air-sensitive reagents were performed under Ar. Solvents and reagents were purchased from *Fluka*. For hydrogenations, an apparatus of *Parr Instruments Company, Inc.* was used. TLC: *Merck* precoated silica gel *60 F-254* plates. Column chromatography (CC): silica gel (*Merck 60*, 230–400 mesh); FC = flash chromatography. M.p.: *Mettler FP-5/FP-52*; uncorrected. IR Spectra: *Perkin Elmer 297* spectrometer. ^{1}H- and ^{13}C-NMR Spectra: *Bruker ARX-300* at 300 and 75 MHz, resp.; chemical shifts δ in ppm rel. to internal $SiMe_4$. MS: chemical ionization (CI) with NH_3 as reactant gas on a *Finnigan MAT-90* and electrospray ionization (ESI) on a *Finnigan TSQ-700* mass spectrometer; *m/z* (rel. %).

1,3-Dihydro-3-oxoisobenzofuran-1-carbonitrile (**9**). To a soln. of phthalaldehydic acid (6.0 g, 0.04 mol) and KCN (3.90 g, 0.06 mol) in H_2O (40 ml) was slowly added 32% aq. HCl soln. (12 ml) at 0° over 1 h. The resulting soln. was maintained at this temp. for 40 min and extracted with AcOEt (2 × 100 ml). The combined extracts were washed with sat. brine (10 ml). After cooling to 0°, the soln. was treated with DCC (10.3 g, 0.05 mol) and stirred for 8 h during which time the mixture was allowed to warm to r.t. Dicyclohexylurea was removed by filtration, and the filtrate was evaporated. The residue was purified by CC (silica gel; CH_2Cl_2): **9** (5.4 g, 85%). Light yellow crystals. A sample was recrystallized from EtOH/hexane to give pure colorless crystals. M.p. 120–121°. IR (KBr): 2940*m*, 2060*w*, 1781*s*, 1602*m*, 1468*m*, 1326*w*, 1273*s*, 1204*s*, 1107*w*, 1044*s*, 1020*s*, 953*m*, 896*w*, 856*w*, 798*w*, 783*w*, 744*s*, 711*w*, 685*m*. ^{1}H-NMR ($CDCl_3$): 8.04–7.95 (*m*, 1 H); 7.90–7.80 (*m*, 1 H); 7.77–7.66 (*m*, 2 H); 6.11 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 167.3, 141.7 (2*s*); 135.5, 131.3, 126.5 (3*d*); 124.3 (*s*); 122.7 (*d*); 113.8 (*s*); 65.6 (*d*). CI-MS: 177 (100, $[M+NH_4]^+$), 150 (25), 133 (10), 105 (40).

3-Allyl-1,3-dihydro-3-oxoisobenzofuran-1-carbonitrile (**8**). To a soln. of ^{i}Pr$_2$NH (1.78 g, 17.6 mmol) in THF (15 ml) was added 1.6M BuLi in hexane (11.0 ml, 17.6 mmol) at −5°. The mixture was stirred at this temp. for 30 min. After cooling to −78°, **9** (2.52 g, 15.8 mmol) in THF (15 ml) was added dropwise over 30 min and then treated with hexamethylphosphoric triamide (HMPA; 5 ml) to afford a reddish-brown soln. A soln. of allyl bromide (2.40 g, 19.7 mmol) was slowly added. After stirring for 2 h at −78°, the mixture was allowed to warm to r.t. and then quenched with AcOH. The mixture was diluted with Et_2O, the soln. washed with H_2O and brine, dried (Na_2SO_4) and evaporated, and the residue purified by CC (hexane/Et_2O 3:1): **8** (2.38 g, 75%). Colorless crystals. M.p. 76–77°. IR (KBr): 2985*w*, 1988*w*, 1779*s*, 1641*w*, 1602*m*, 1467*s*, 1430*m*, 1409*w*, 1341*w*, 1324*w*, 1290*m*, 1246*s*, 1194*m*, 1147*w*, 1113*w*, 1064*s*, 1015*m*, 987*m*, 957*s*, 927*s*, 884*w*, 802*w*, 758*s*, 736*s*, 697*s*, 683*m*, 654*w*. ^{1}H-NMR ($CDCl_3$): 8.01–7.90 (*m*, 1 H); 7.87–7.77 (*m*, 1 H); 7.74–7.60 (*m*, 2 H); 5.80–5.63 (*m*, 1 H); 5.38–5.21 (*m*, 2 H); 3.06–2.86 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 166.9, 145.4 (2*s*); 135.3, 131.2, 127.3, 126.4 (4*d*); 124.7 (*s*); 123.2 (*t*); 122.2 (*d*); 43.3 (*t*). CI-MS: 217 (100, $[M+NH_4]^+$), 158 (15).

*3-Allyl-3-(aminomethyl)isobenzofuran-1(3*H*)-one* (**10**). To a stirred suspension of $NaBH_4$ (0.19 g, 5 mmol) in THF (5 ml) was added CF_3COOH (0.57 g, 5 mmol) in THF (1 ml) within 10 min at 20°. To this soln. of $NaBH_3(OCOCF_3)$ was added **8** (1.0 g, 5 mmol) in THF (2 ml). The mixture was stirred at r.t. for 30 min and then quenched with H_2O below 10°. The resulting mixture was evaporated, the residue extracted with CH_2Cl_2, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue was submitted to CC (CH_2Cl_2/MeOH 30:1): **10** (0.40 g, 40%) as a colorless oil and starting material **8** (0.205 g). **10**: IR (film): 3391*w*, 2918*w*, 1759*s*, 1669*w*, 1642*w*, 1613*w*, 1466*m*, 1433*w*, 1333*w*, 1287*m*, 1224*m*, 1086*m*, 997*w*, 972*w*, 923*w*, 765*w*, 699*w*. ^{1}H-NMR ($CDCl_3$): 7.95–7.82 (*m*, 1 H); 7.77–7.65 (*m*, 1 H); 7.60–7.50 (*m*, 1 H); 7.49–7.40 (*m*, 1 H); 5.63–5.45 (*m*, 1 H); 5.15–4.90 (*m*, 2 H); 3.35–3.01 (*m*, 2 H); 2.88–2.65 (*m*, 2 H); 1.07 (br., 2 H). ^{13}C-NMR ($CDCl_3$): 169.7, 150.2 (2*s*); 133.9, 130.3, 129.1 (3*d*); 127.3 (*s*); 125.5, 121.4 (2*d*); 120.0 (*t*); 89.7 (*s*); 48.7, 40.2 (2*t*). CI-MS: 407 (40, $[2M+1]^+$), 221 (15, $[M+NH_4]^+$), 204 (100, $[M+1]^+$).

3-[[(1-Allyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)methyl]amino]propanenitrile (**7**). A soln. of **10** (0.180 g, 0.883 mmol) and acrylonitrile (0.070 g, 1.33 mmol) in MeOH (10 ml) was heated to reflux for 12 h. After cooling, the soln. was evaporated and the residue purified by CC (CH_2Cl_2/MeOH 30:1): **7** (0.197 g, 87%). Colorless oil. IR (film): 3348*w*, 2919*w*, 2850*w*, 2247*w*, 1759*s*, 1642*w*, 1614*w*, 1466*m*, 1418*w*, 1350*w*, 1286*m*, 1223*w*, 1134*w*, 1078*w*, 996*w*, 925*w*, 767*w*, 700*w*. ^{1}H-NMR ($CDCl_3$): 7.92–7.84 (*m*, 1 H); 7.70–7.63 (*m*, 1 H); 7.57–7.50 (*m*, 1 H); 7.47–7.40 (m, 1 H); 5.63–5.48 (*m*, 1 H); 5.13–4.99 (*m*, 2 H); 3.11 (*q*, *J* = 13.1, 2 H); 2.92–2.83 (*m*, 2 H); 2.82–2.68 (*m*, 2 H); 2.44–2.26 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 169.6, 150.6 (2*s*); 133.9, 130.4, 129.2 (3*d*); 126.9 (*s*); 125.6, 121.5 (2*d*); 120.2 (*t*); 118.3, 88.7 (2*s*); 55.0, 45.3, 40.3, 18.9 (4*t*). CI-MS: 274 (100, $[M+NH_4]^+$), 257 (25, $[M+1]^+$).

*4-Allyl-3,4-dihydro-4-hydroxy-1-oxoisoquinoline-2(1*H*)-propanenitrile* (**6**). A soln. of **7** (0.62, 2.42 mmol) in EtOH (20 ml) containing NaOMe (prepared from Na (56 mg, 2.42 mmol) and MeOH) was heated to reflux for 2 h. After cooling, the soln. was evaporated and the residue purified by CC (CH_2Cl_2/MeOH 45:1): **6** (0.55 g, 90%). Slightly yellow oil. IR (film): 3396*s*, 2936*w*, 2252*w*, 1643*s*, 1603*m*, 1577*m*, 1488*s*, 1429*m*, 1369*w*, 1325*w*, 1242*w*, 1162*w*, 1113*w*, 1046*w*, 998*w*, 924*w*, 767*m*, 705*m*. ^{1}H-NMR ($CDCl_3$): 8.06–7.96 (*m*, 1 H); 7.60–7.49

(*m*, 2 H); 7.48–7.35 (*m*, 1 H); 5.92–5.75 (*m*, 1 H); 5.35–5.10 (*m*, 2 H); 3.94–3.72 (*m*, 2 H); 3.71–3.51 (*m*, 2 H); 3.07 (br., 1 H); 2.80–2.68 (*m*, 2 H); 2.67–2.58 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 164.3, 143.5 (2*s*); 132.6, 132.1, 128.2, 128.1 (4*d*); 126.6 (*s*); 123.7 (*d*); 120.0 (*t*); 118.1, 70.2 (2*s*); 57.0, 44.5, 43.9, 16.4 (4*t*). CI-MS: 274 (100, $[M+NH_4]^+$), 257 (21, $[M+1]^+$).

*3,4-Dihydro-4-hydroxy-1-oxo-4-(2-oxoethyl)isoquinoline-2(1*H*)-propanenitrile* (**5**). A soln. of **6** (0.530 g, 2.07 mmol) in MeOH (30 ml) was cooled to $-78°$, and then an excess of ozone was passed through the mixture ($\rightarrow$ deep blue soln. when saturated with ozone). After the mixture was purged with N_2 for 20 min at $-78°$, it was treated with Me_2S (2 ml). The cold bath was removed, and the mixture was allowed to warm to r.t. and stirred for 2 h. Evaporation provided crude **5**, which was purified by CC (CH_2Cl_2/MeOH 30:1): **5** (0.43 g, 80%). Colorless oil. IR (film): 3382*s*, 2928*w*, 2251*w*, 1717*s*, 1650*s*, 1603*m*, 1578*m*, 1487*m*, 1424*m*, 1324*m*, 1297*m*, 1237*w*, 1162*w*, 1130*w*, 1094*w*, 1030*m*, 953*w*, 768*w*, 704*w*. ^{1}H-NMR ($CDCl_3$): 9.77 (*t*, 1 H); 7.99–7.91 (*m*, 1 H); 7.64–7.50 (*m*, 2 H); 7.44–7.36 (*m*, 1 H); 4.80 (br., 1 H); 3.89–3.75 (*m*, 2 H); 3.72–3.59 (*m*, 2 H); 2.90 (*d*, 2 H); 2.78–2.65 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 201.5 (*d*); 164.2, 143.1 (2*s*); 132.9, 128.3, 128.2 (3*d*); 126.3, 123.6, 118.3, 69.9 (4*s*); 56.9, 51.1, 44.1, 16.3 (4*t*). CI-MS: 276 (100, $[M+NH_4]^+$), 259 (10, $[M+1]^+$), 248 (15), 232 (44), 215 (11).

*Methyl (β*S*)-β-{[2-[2-(2-Cyanoethyl)-1,2,3,4-tetrahydro-4-hydroxy-1-oxoisoquinolin-4-yl]ethyl}amino}benzenepropanoate* (**11**). To a soln. of **4** (0.316 g, 1.76 mmol) in dry MeOH (15 ml) was added 5N HCl/MeOH (0.71 ml, 3.53 mmol), followed by **5** (0.455 g, 1.76 mmol) and $NaBH_3CN$ (0.138 g, 2.20 mmol). The mixture was stirred at r.t. for 12 h. The residue obtained after evaporation was purified by CC (CH_2Cl_2/MeOH 30:1): **11** (0.564 g, 75%). Colorless oil. IR (film): 3291*s*, 2952*m*, 2855*m*, 2250*w*, 1732*s*, 1651*s*, 1603*m*, 1578*w*, 1477*m*, 1435*m*, 1366*w*, 1317*m*, 1293*m*, 1195w, 1164*m*, 1130*w*, 1082*w*, 1029*w*, 919*w*, 845*w*, 766*m*, 702*m*. ^{1}H-NMR ($CDCl_3$): 8.01–7.98 (*m*, 1 H); 7.66–7.55 (*m*, 1 H); 7.49–6.98 (*m*, 7 H); 4.12–3.98 (*m*, 1 H); 3.95–3.10 (*m*, 8 H); 2.92–2.45 (*m*, 6 H); 2.04–1.78 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 171.8, 164.5, 145.2, 144.8, 140.8, 140.7 (6*s*); 132.4, 131.9, 128.7, 128.0, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0 (10*d*); 126.1 (*s*); 124.3, 124.1 (2*d*); 118.2, 118.0, 72.0, 71.8 (4*s*); 59.7, 59.6 (2*d*); 58.8, 56.9 (2*t*); 51.8 (*q*); 44.3, 44.2, 43.1, 42.8, 41.5, 41.1, 37.5, 37.1, 16.5, 16.4 (10*t*). CI-MS: 422 (100, $[M+1]^+$), 404 (15), 306 (35), 260 (12), 232 (26), 206 (28), 180 (11).

*Methyl (β*S*)-β-{[2-[2-(3-Aminopropyl)-1,2,3,4-tetrahydro-4-hydroxy-1-oxoisoquinolin-4-yl]ethyl}amino}-benzenepropanoate* (**12**). To a soln. of **11** (0.535 g, 1.27 mmol) in EtOH was added 32% aq. HCl soln. (0.32 g, 2.81 mmol) and PtO_2 (0.100 g). The hydrogenation was carried out at r.t./50 psi H_2 for 6 h. Then the mixture was filtered through a pad of *Celite*®. The filtrate was evaporated and the residue purified by CC (CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 90:10:1): **12** (0.471 g, 87%). Colorless oil. IR ($CHCl_3$): 3300*m*, 3000*m*, 2940*m*, 2880*m*, 1730*s*, 1640*s*, 1600*m*, 1580*m*, 1490*m*, 1475*m*, 1440*m*, 1300*m*, 1260*w*, 1160*w*, 1120*s*, 1010*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.99–7.88 (*m*, 1 H); 7.62–7.47 (*m*, 1 H); 7.44–6.96 (*m*, 7 H); 4.09–3.94 (*m*, 1 H); 3.72, 3.67 (2*s*, 3 H); 3.65–3.36 (*m*, 4 H); 3.30–2.94 (*m*, 3 H); 3.24, 2.98 (2*d*, 1 H); 2.88–2.40 (*m*, 6 H); 1.95–1.46 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 171.9, 171.8, 164,1, 164.0, 144.8, 144.0, 140.8, 140.7 (8*s*); 131.8, 131.4, 128.7, 128.7, 127.9, 127.8, 127.3, 127.2, 127.1, 127.0 (10*d*); 126.9 (*s*); 123.9, 123.7 (2*d*); 71.9, 71.7 (2*s*); 59.8, 59.7 (2*d*); 56.8, 55.3 (2*t*); 51.7 (*q*); 44.2, 44.1, 43.0, 42.7, 41.6, 41.2, 38.8, 37.4, 37.1, 30.8 (10*t*). CI-MS: 426 (100, $[M+1]^+$), 408 (15), 292 (10), 278 (30), 264 (90), 246 (75).

*(+)-(9*S*,13*R*)- and (+)-(9*S*,13*S*)-13-Hydroxyisocyclocelabenzine (=(9*S*,13*R*)- and (9*S*,13*S*)-3,4,5,6,8,9,10,11,12,13-Decahydro-13-hydroxy-9-phenyl-2,13-methano-2*H*-2,6,10-benzotriazacyclopentadecine-1,7-dione*, resp.; **3a** and **3b**, resp.). A soln. of **12** (0.330 g, 0.776 mmol) and $LiOH \cdot H_2O$ (35.8 mg, 0.853 mmol) in THF/MeOH/H_2O 3:1:1 (10 ml) was stirred at r.t. for 4 h, and the solvent was evaporated. The residue was dissolved in EtOH (10 ml) and the soln. evaporated; this process was repeated twice. After further drying under h.v., the residue was dissolved in dry DMF (50 ml) and added to a soln. of $(EtO)_2POCN$ (0.190 g, 1.16 mmol) and Et_3N (2 ml) in DMF (100 ml) at r.t. within 5 h. The mixture was stirred at r.t. for another 24 h and evaporated. The residue was dissolved in sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The combined org. phase was evaporated and the residue purified by CC (CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 90:10:1): **3a**/**3b** (185 mg, 60%), 1:1 by NMR. IR ($CHCl_3$): 3306*s*, 3064*w*, 2926*m*, 2853*m*, 1728*w*, 1638*s*, 1603*w*, 1550*w*, 1492*w*, 1449*w*, 1430*w*, 1309*m*, 1236*w*, 1160*w*, 1113*m*, 1038*w*, 877*w*, 765*m*, 702*m*. ESI-MS: 416 ($[M+Na]^+$).

The two epimers were separated by repeated FC (CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 94:6:0.6): optically pure, natural 13-hydroxyisocyclocelabenzine (**3a**; 80 mg) and **3b** (85 mg).

Data of **3a**: Colorless solid. M.p. 136–138°. $[\alpha]_D = +108$ ($c = 0.93$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.03 (*d*, $J =$ 7.7, 1 H): 7.88 (*t*, 1 H); 7.58 (*d*, $J = 7.1$, 1 H); 7.50 (*t*, $J = 7.5$, 1 H); 7.34 (*t*, $J = 7.6$, 1 H); 7.12–7.03 (*m*, 3 H); 6.73–6.66 (*m*, 2 H); 4.05–3.91 (*m*, 3 H); 3.90–3.78 (*m*, 2 H); 3.60 (*d*, $J = 12.3$, 1 H); 2.98–2.82 (*m*, 1 H); 2.71 (*t*, $J =$ 11.2, 1 H); 2.48–2.35 (*m*, 1 H); 2.34–2.23 (*m*, 2 H); 2.17 (*t*, $J = 12.4$, 1 H); 1.85–1.55 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 172.4, 164.9, 145.9, 142.9 (4*q*); 132.5, 128.4, 127.8, 126.9, 125.9, 123.6 (7*d*); 70.3 (*q*); 61.5 (*d*); 53.7, 45.5, 43.6, 42.9, 40.9, 38.2, 24.1 (7*t*).

Crystals of **3a** suitable for the X-ray crystal-structure analysis were grown from $CHCl_3$.

Data of **3b**: Colorless solid. M.p. 121–125°. $[\alpha]_D = +48.7$ ($c = 1.35$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.00 (t, 1 H); 7.94 (d, $J = 7.4$, 1 H); 7.38–7.09 (m, 2 H); 7.28–7.20 (m, 1 H); 7.17–7.07 (m, 3 H); 7.05–7.00 (m, 2 H); 3.96 (t, $J = 7.4$, 1 H); 3.86–3.74 (m, 1 H); 3.71–3.64 (m, 2 H); 3.42–3.10 (m, 3 H); 3.08–2.94 (m, 3 H); 2.53–2.38 (m, 1 H); 2.36 (d, $J = 7.3$, 2 H); 2.13–1.87 (m, 3 H); 1.85–1.72 (m, 1 H). ^{13}C-NMR ($CDCl_3$): 172.4, 164.7, 143.2, 142.2 (4q); 132.1, 128.7 (2d); 128.4 (q); 128.0, 127.9, 127.4, 126.1, 123.1 (5d); 70.1 (q); 61.9 (d); 56.4, 47.1, 45.3, 43.3, 38.2, 35.8, 28.0 (7t).

X-Ray Crystal-Structure Determination of **3a** (see *Table* and *Figs. 2* and *3*)[2]). All measurements were made on a *Nonius-KappaCCD* diffractometer [18] with graphite-monochromated Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å)

Table 1. *Crystallographic Data of Compound* **3a**

Crystallized from	$CHCl_3$
Empirical formula	$C_{23}H_{27}N_3O_3 \cdot CHCl_3$
Formula weight [g mol^{-1}]	512.86
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	$0.17 \times 0.17 \times 0.25$
Temperature [K]	160 (1)
Crystal system	monoclinic
Space group	$C2$ (#5)
Z	8 (2 formula units per asymmetric unit)
Reflections for cell determination	50789
2θ Range for cell determination [°]	4–50
Unit cell parameters a [Å]	42.5469 (6)
b [Å]	9.0286 (2)
c [Å]	13.2181 (2)
α [°]	90
β [°]	97.6897 (8)
γ [°]	90
V [Å^3]	5031.9 (2)
$F(000)$	2144
D_x [g cm^{-3}]	1.354
μ(Mo$K\alpha$) [mm^{-1}]	0.394
Scan type	ω
$2\theta_{(max)}$ [°]	50
Transmission factors (min; max)	0.795; 0.971
Total reflections measured	43491
Symmetry-independent reflections	8846
R_{int}	0.072
Reflections with $I > 2\sigma(I)$	7669
Reflections used in refinement	8843
Parameters refined; restraints	576; 1
Final	$R(F)$ ($I > 2\sigma$ (I) reflections)
0.0415	
$wR(F^2)$ (all data)	0.1016
Weights:	$w = [\sigma^2(F_o^2) + (0.0602P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness-of-fit	1.052
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.28; −0.29
σ (d(C–C)) [Å]	0.003–0.005

[2]) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-203556 Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

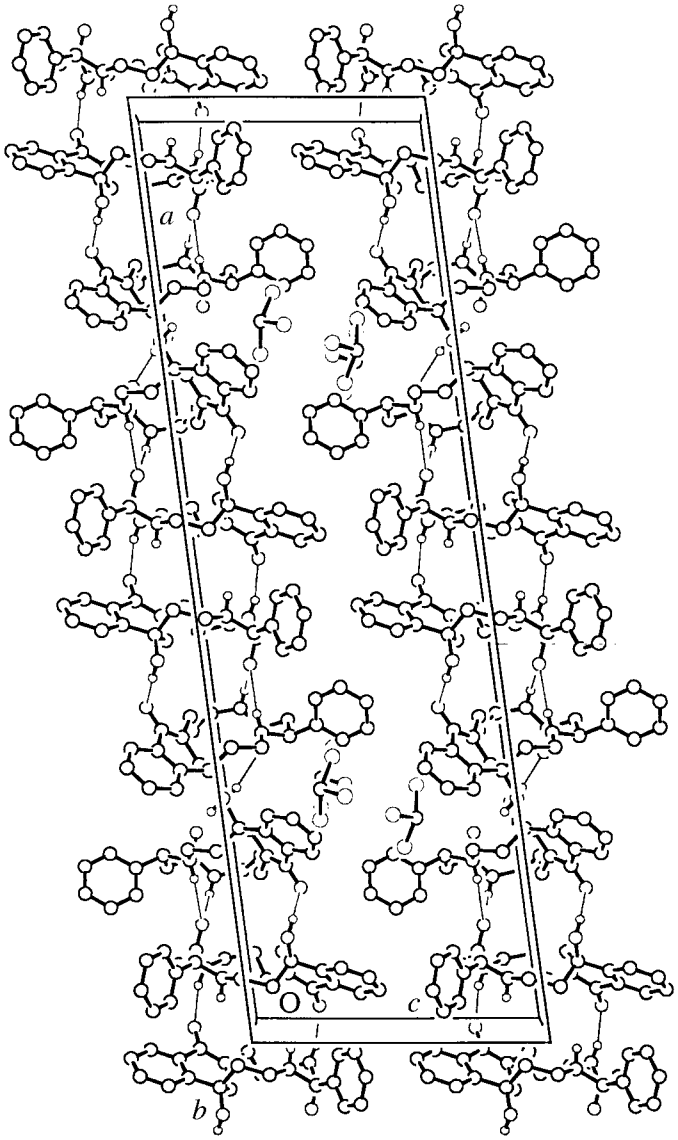


Fig. 3. *Crystal packing of* **3a**

and an *Oxford-Cryosystems-Cryostream-700* cooler. The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [19] was applied. Data collection and refinement parameters are given in the *Table*. A view of the molecule is shown in *Fig. 2*.

The structure was solved by direct methods using SHELXS97 [20], which revealed the positions of all non-H atoms. The non-H atoms were refined anisotropically. The hydroxy and amine H-atoms were placed in the positions indicated by a difference electron density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated

positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. Refinement of the structure was carried out on F^2 by means of full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied.

Neutral-atom scattering factors for non-H-atoms were taken from [21a] and the scattering factors for H-atoms from [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f''were those of *Creagh* and *McAuley* [21b]. The values of the mass attenuation coefficients are those of *Creagh* and *Hubbel* [21c]. All calculations were performed by using the SHELXL97 [24].

There are two symmetry-independent polycyclic substrate molecules and two $CHCl_3$ molecules in the asymmetric unit. The need to model one disordered $CHCl_3$ molecule was overcome by using SQUEEZE [25]. The space group is polar, and the presence of $CHCl_3$ in the structure allowed the absolute structure and absolute configuration of the polycyclic molecule to be determined independently by the diffraction experiment (absolute structure parameter: 0.05(4)). Both symmetry-independent molecules *A* and *B* are of the same enantiomer and have the (9*S*,13*R*) configuration, thus being in agreement with the (*S*) configuration at C(9) known from the synthesis of the compound. The conformations of the two symmetry-independent molecules are quite similar with only small differences in the puckering of the 13-membered rings, shown by differences of up to 12° in the corresponding torsion angles. The most significant difference between the two molecules is the orientation of the OH group, which in molecule *B* is pivoted about the O–C axis by a *ca.* 23° compared with its orientation in molecule *A*. The presence of two symmetry-independent molecules is probably due to packing considerations and differences in the H-bonding pattern of each molecule. A complex system of intermolecular H-bonds links the molecules into infinite two-dimensional networks (*Fig. 3*).

References

[1] H. Wagner, J. Burghart, W. E. Hull, *Tetrahedron Lett*. **1978**, 3893; H. Wagner, J. Burghart, *Helv. Chim. Acta* **1982**, *65*, 739.
[2] K. Schultz, M. Hesse, *Tetrahedron* **1996**, *45*, 14189.
[3] K. Schultz, M. Hesse, *Helv. Chim. Acta* **1996**, *79*, 1295.
[4] K. Schultz, P. Kuehne, U. Häusermann, M. Hesse, *Chirality* **1997**, *9*, 523.
[5] H. H. Wasserman, G. D. Berger, *Tetrahedron* **1983**, *39*, 2459.
[6] K. Schultz, Ph.D. Thesis, University of Zürich, 1996.
[7] S. G. Davies, L. A. S. Walters, *J. Chem. Soc.; Perkin. Trans. I* **1994**, 1129.
[8] R. A. Russell, B. A. Pilley, *Synth. Commun*. **1986**, *16*, 425; J. N. Freskos, G. W. Morrow, J. S. Swenton, *J. Org. Chem*. **1985**, *50*, 805.
[9] N. Umino, T. Iwakuma, N. Itoh, *Tetrahedron Lett*. **1976**, *33*, 2875.
[10] H. C. Brown, in ' Hydroboration', W. A. Benjamin, Inc., New York, 1962.
[11] J. A. Marshall, W. S. Johnson, *J. Org. Chem*. **1963**, *28*, 595.
[12] R. F. Borch, M. Bernstein, H. D. Durst, *J. Am. Chem. Soc*. **1971**, *93*, 2897.
[13] H. Yamamoto, K. Maruoka, *J. Am. Chem. Soc*. **1981**, *103*, 6133.
[14] K. Ishihara, Y. Kuroki, H. Yamamoto, *Synlett* **1995**, 41.
[15] S. Yamada, S. Kasai, T. Shioiri, *Tetrahedron Lett*. **1973**, *18*, 1595; T. Shioiri, Y. Yokoyama, Y. Kasai, S. Yamada, *Tetrahedron* **1976**, *32*, 2211.
[16] E. Bald, K. Saigo, T. Mukaiyama, *Chem. Lett*. **1975**, 1163.
[17] C. K. Johnson, 'ORTEPII, Report ORNL-5138', Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[18] R. Hooft, 'KappaCCD Collect Software', Nonius BV, Delft, The Netherlands, 1999.
[19] R. H. Blessing, *Acta Crystallogr., Sect. A* **1995**, *51*, 33.
[20] G. M. Sheldrick, 'SHELXS97, Program for the Solution of Crystal Structures', University of Göttingen, Germany, 1997.
[21] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, *ibid*., Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, *ibid*., Table 4.2.4.3, p. 200.
[22] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.

[23] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[24] G. M. Sheldrick, 'SHELXL97, Program for the Refinement of Crystal Structures', Universität Göttingen, Germany, 1997.
[25] P. van der Sluis, A. L. Spek, *Acta Crystallogr., Sect. A* **1990**, *46*, 194; A. L. Spek, 'PLATON, Program for the Analysis of Molecular Geometry', University of Utrecht, The Netherlands, 2002.

Received July 31, 2002