150. Fragmentation of Optically Active (1-Phenylethyl)- and (1-Naphthylethyl)ureas in Refluxing Alcohols: Easy Preparation of Optically Active Amines of High Optical Purity[1])[2])

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(1-Phenylethyl)- and (1-naphthylethyl)ureas, obtained in the reaction of racemic amines with optically pure isocyanates, are separated and then decomposed in refluxing alcohols, to afford optically pure secondary amines and optically pure alkyl carbamates in quantitative yields. The scope of this fragmentation for the resolution of racemic mixtures of amines is illustrated by several examples of biologically important compounds. Carbamates obtained by this fragmentation can readily be recycled.

Introduction. – Chemical resolution of racemic amines with optically active acids is the method most widely used to prepare optical isomers and frequently has been applied to prepare alkaloids of unnatural configuration (many examples of successful chemical resolutions are reported in [1b]). Racemic-amine drugs such as mefloquine [2] and mecamylamine [3] have been resolved in an analogous fashion and studied as optical isomers. However, there are cases where chemical resolution proved difficult or afforded the desired optical isomer only after tedious crystallization of salts, resulting in low yield of optically pure material. Such a case is represented by (±)-5-*O*-methyl-1-noreseroline ((±)-**8**; see below, *Scheme 2*), readily available from the racemic oxindole (±)-**7** [4], and required for the synthesis of unnatural (+)-physostigmine [5] [6]. Also chemical resolution of (±)-eserethole (the ethyl-ether analog of (±)-**11**), a key intermediate in the *Julian* total synthesis of natural (−)-physostigmine is tedious [7], affording optically pure isomers in low yield only.

Thus, we decided to look for another way. Racemic secondary amines afford with optically active isocyanates two diastereoisomeric ureas, readily separated by TLC or HPLC [8] and differentiated by ^{1}H-NMR [9], methods frequently used to determine optical purity of optically active amines. The easy separation, together with reports that ureas with at least one NH group are dissociated by heating [10] [11], exemplified with the conversion of urea into pentyl carbamate in refluxing pentanol [12], led to the solution of our problem, *i.e.* to the chemical resolution of (±)-5-*O*-methyl-1-noreseroline ((±)-**8**). We now report details of this resolution[2]) which in the meanwhile has been extended to the following amines: (±)-salsolidine, (±)-salsoline-1-carboxylic acid, (±)-mecamylamine,

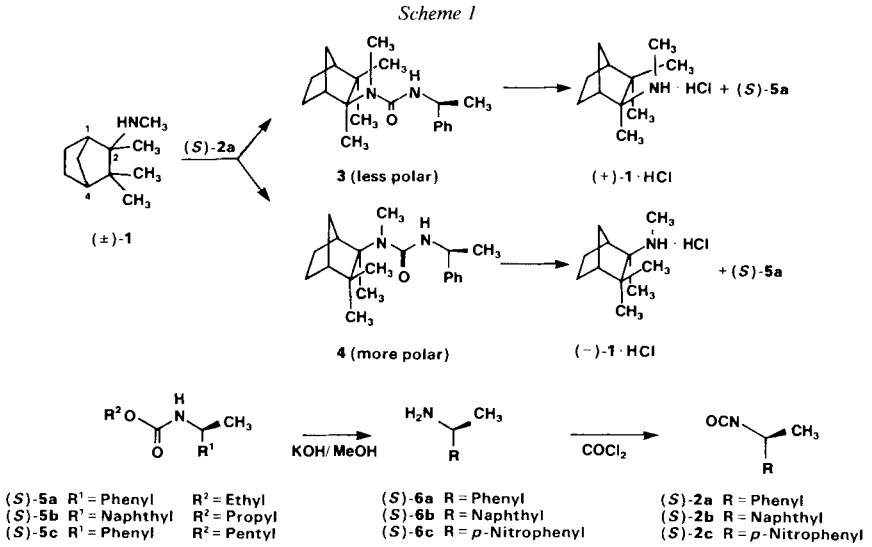
[1]) The thermal decomposition of phenylethyl- and naphthylethylureas in alcohols is covered by a pending patent application.

[2]) Preliminary communication, see [1a].

and (±)-tetrahydroharmine. Successful resolution of (±)-*N*-vanillylamphetamine by the isocyanate method suggests that similar results with analogs having removable N-protecting groups would allow the preparation of optically active primary amines, making the latter class of compounds also amenable by this route.

Chemistry. – Chemical resolution of the drug (±)-mecamylamine ((±)-**1**) [13] by the published procedure [3], in our hands, afforded optically impure hydrochlorides of (+)- and (−)-mecamylamine ((+)- and (−)-**1**), which could not be further purified by crystallization. Reaction of mecamylamine (±)-**1** with (−)-(*S*)-(1-phenylethyl)isocyanate ((*S*)-**2a**) afforded, after chromatographic separation on silica gel, the less polar urea **3** and the more polar urea **4** in 34 and 37% yield, respectively *(Scheme 1)*. Refluxing ureas **3** and **4**

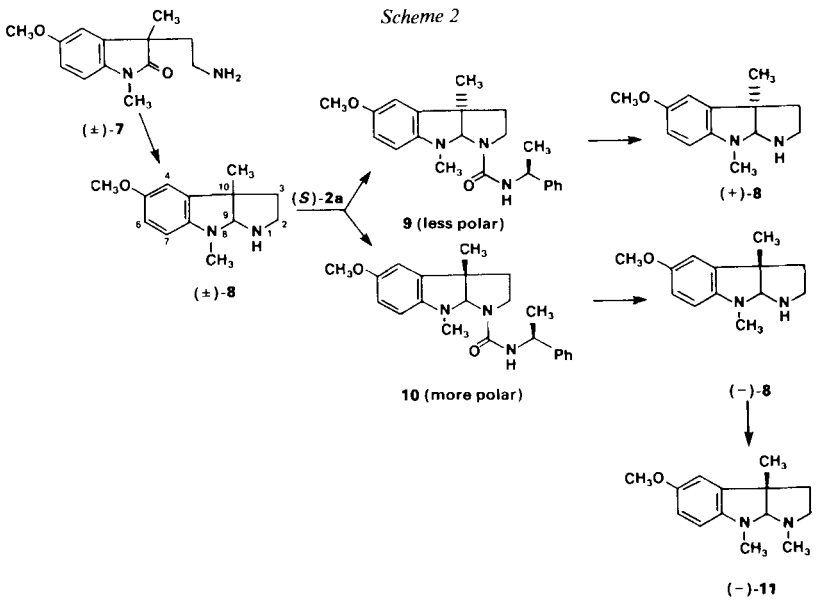
Scheme 1



with 2M NaOEt in EtOH for 45 min gave, after usual workup and transformation to the hydrochlorides, 63% of optically pure (+)- and (−)-**1** · HCl, respectively. The neutral material obtained in both cases was the ethyl carbamate (*S*)-**5a**, readily hydrolyzed with KOH/MeOH to (1-phenylethyl)amine ((*S*)-**6a**) and converted into isocyanate (*S*)-**2a** by reaction of (*S*)-**6a** with phosgene in the presence of Et_3N [14] *(Scheme 1)*. Carbamate (*S*)-**5a** having identical optical properties was prepared from amine (*S*)-**6a** and ethyl chloroformate [15]. *Scheme 1* also lists carbamates obtained in reactions described later. Reaction of **3** in refluxing propanol without addition of base also afforded (+)-mecamylamine ((+)-**1**), but at a slower rate.

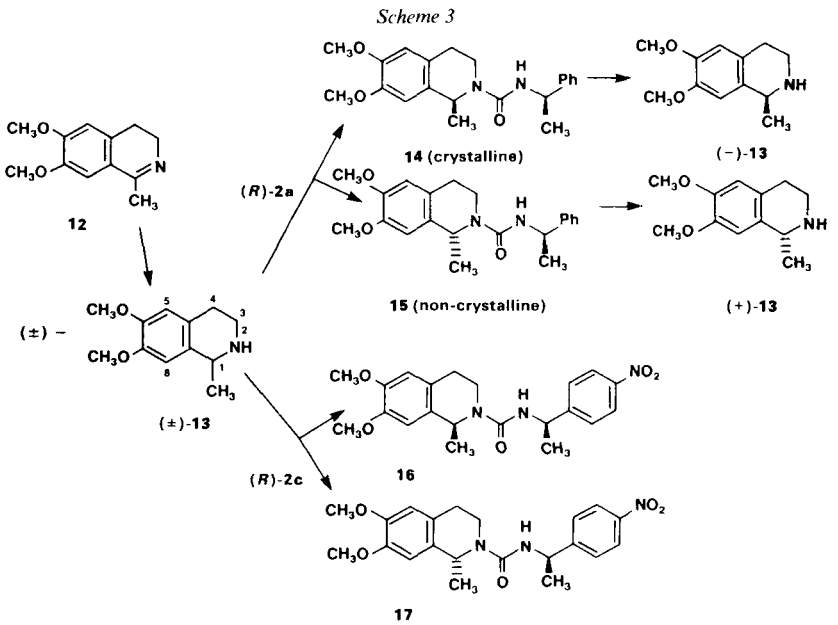
Reductive ring closure of oxindole (±)-**7**, prepared by the *Julian* synthesis [4], was best accomplished with Na in EtOH and afforded 5-*O*-methyl-1-noreseroline ((±)-**8**; *Scheme 2*). Reaction of (±)-**8** with isocyanate (*S*)-**2a** afforded after chromatographic separation of the mixture of diastereoisomers, the less polar urea **9** and the more polar urea **10** in 37 and 40% yield, respectively. Ureas **9** and **10** decomposed in refluxing 1M sodium pentoxide in pentanol within 1 h, affording as basic materials the optically pure amines (+)-

Scheme 2



and (−)-**8**, respectively, isolated as oxalate salts. The optical purity of (−)-**8** was established by reductive *N*-methylation with formaldehyde and $NaBH_4$ in the presence of Et_3N, affording the known eseroline *O*-methyl ether (−)-**11** [16] [17]. Reductive *N*-methylation of (−)-**8** without addition of base afforded open-ring products which were not further characterized, but their ^{1}H-NMR spectra, showing the presence of an additional CH_2 group, were similar to those of indoline compounds of established structure [17].

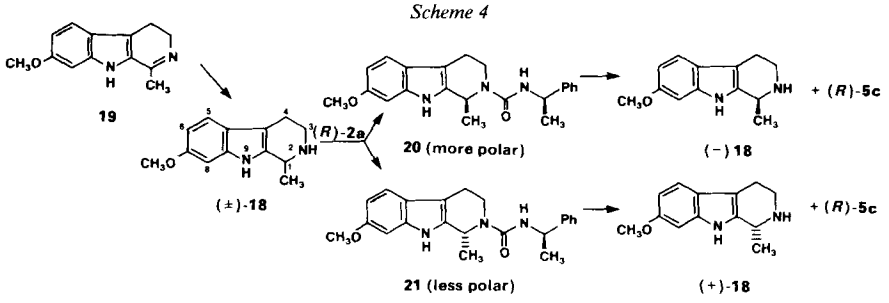
Scheme 3



(±)-Salsolidine ((±)-**13**), an isoquinoline Cactus alkaloid [18], was prepared from readily available 1,2-didehydrosalsolidine (**12**) [19] by reduction with $NaBH_4$ in 2-propanol *(Scheme 3)*. Reaction of (±)-**13** with (+)-(*R*)-(1-phenylethyl)isocyanate ((*R*)-**2a**) afforded the crystalline urea **14** and from its mother liquor the amorphous urea **15**. Both **14** and **15** decomposed by heating in refluxing 2M NaOBu in BuOH to afford (−)- and (+)-**13**, respectively, isolated as hydrochlorides and identical in every respect with materials prepared from (±)-**13** by standard resolution [20]. Ureas **16** and **17**, obtained from (±)-**13** with (*R*)-[1-(*p*-nitrophenyl)ethyl]isocyanate ((*R*)-**2c**; prepared from known (*R*)-[1-(*p*-nitrophenyl)ethyl]amine [21] with phosgene) and separated by HPLC also represent intermediates for preparing optical isomers of (±)-**13**.

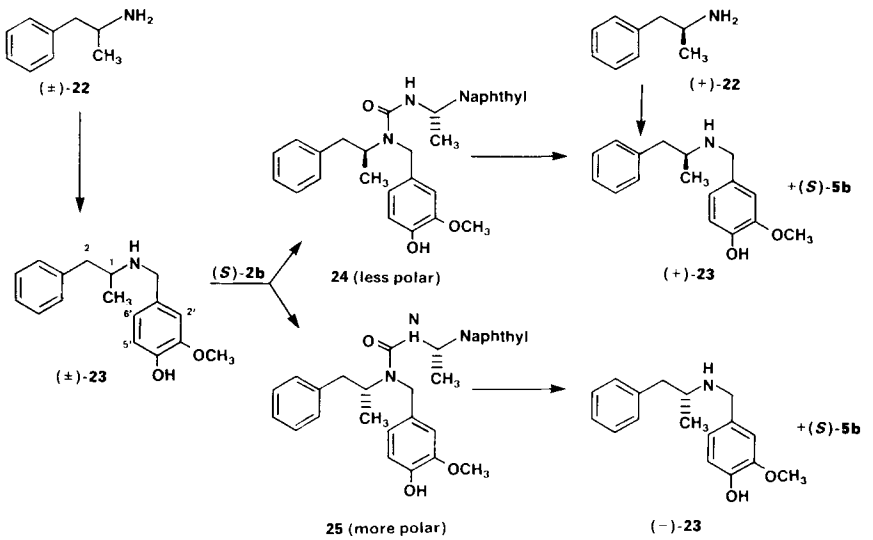
(±)-1,2,3,4-Tetrahydroharmine ((±)-**18**), prepared from harmaline **19** by $NaBH_4$ reduction in MeOH, is a well known carboline alkaloid [22] and occurs in nature as the (+)-(*R*)-isomer [23] of established configuration [24]. Reaction of (±)-**18** with isocyanate (*R*)-**2a** afforded a mixture of diastereoisomeric ureas which were separated by chromatography on silica gel into more polar urea **20** and less polar urea **21** *(Scheme 4)*. These ureas could not be obtained diastereoisomerically pure. After recrystallization, as seen by HPLC, each contained about 25% of its diastereoisomer. Pure **21**, obtained by preparative HPLC, isomerized on standing in acidic $CHCl_3$ solution, suggesting that **20** and **21** are interconvertible. Preparation of optically pure tetrahydroharmines (−)- and (+)-**18**, obtained in impure form by decomposing **20** and **21** in refluxing pentanol, was accomplished by an additional resolution step with (−)- and (+)-camphorsulfonic acid, respectively. Optically pure alkaloids (−)- and (+)-**18** showed considerably higher specific optical rotations than that reported in the literature for the (−)-enantiomer [24], suggesting the latter to be optically impure.

Scheme 4



The resolution technique described above, when applied to (±)-*N*-benzylamphetamine [25], afforded a mixture of diastereoisomeric ureas which could not be separated chromatographically, illustrating that a good separation of urea diastereoisomers is essential to prepare optically pure amines by the urea-fragmentation route. However, (±)-*N*-vanillylamphetamine ((±)-**23**; obtained from (±)-**22** by condensation with vanilline and reduction of the *Schiff* base with $NaBH_4$ in MeOH) afforded by reaction with (*S*)-(1-naphthylethyl)isocyanate ((*S*)-**2b**), a mixture of less polar urea **24** and its more polar diastereoisomer **25**, which could readily be separated by chromatography *(Scheme 5)*. Both **24** and **25** decomposed in refluxing 1M NaOPr in PrOH, affording amines (+)-**23** and (−)-**23**, respectively, beside the carbamate (*S*)-**5b** as neutral constituent. Identity of vanillylamphetamine (+)-**23** with material prepared from amphetamine (+)-**22** by the

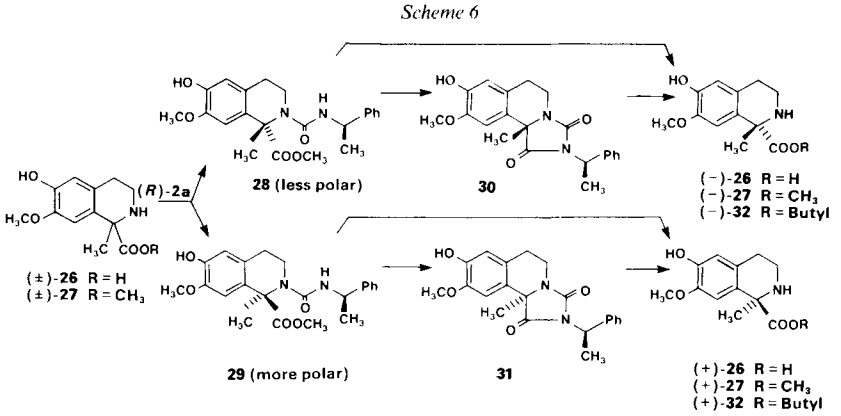
Scheme 5



mentioned procedure was established. The *N*-vanillyl group of amphetamine is not easily removed by catalytic debenzylation [26], but preparation of optical isomers of **23** by the isocyanate method suggests that optically active primary amines are, in principle, accessible, if a removable N-protecting group is introduced.

Optical resolution was finally investigated with (±)-salsoline-1-carboxylic acid ((±)-**26**), a mammalian alkaloid [27] known only in racemic form [28] (*Scheme 6*). The methyl ester (±)-**27**, prepared from (±)-**26** with thionyl chloride in MeOH, after reaction with isocyanate (*R*)-**2a** and chromatographic separation of the ureas, afforded the less polar urea **28** and its more polar diastereoisomer **29**. Both **28** and **29** converted upon standing into hydantoins **30** and **31**, respectively. Thermal decomposition of **28** and **29** in BuOH in the presence of NaOBu exclusively afforded hydantoins **30** and **31**, respectively, characterized by spectral data. In the absence of base, ureas **28** and **29** decomposed in refluxing BuOH to afford, beside **30** and **31**, methyl esters (−)-**27** and (+)-**27**, respectively, each

Scheme 6



containing considerable amounts of butyl esters (−)-**32** and (+)-**32**, respectively, as shown by TLC. After chromatographic isolation, the latter were characterized by MS and readily converted into the methyl esters by transesterification in MeOH in the presence of NaOMe. Methyl esters (−)- and (+)-**27** were obtained as crystalline hydrochlorides. The salt (+)-**27** · HBr, prepared from the hydrochloride salt in the usual way, was used to determine its absolute configuration by solid-state X-ray diffraction[3]). Acid hydrolysis of (−)- and (+)-**27** with 2N HCl afforded the carboxylic acids (−)- and (+)-**26**, respectively, as crystalline hydrochlorides.

The easy formation of hydantoins from esters **28** and **29** suggests that optical resolution of amino-acid esters by the isocyanate route is conceivable if the hydantoin diastereoisomers obtained from the urea intermediates can by separated.

Conclusions. – Commercially available optically pure isocyanates such as (1-phenylethyl)- or (1-naphthylethyl)isocyanates, possibly complemented by aryl-substituted analogs, may be useful for resolving a wide variety of racemic amines. The resolved amines obtained by urea fragmentation can readily be separated from neutral carbamate esters simultaneously obtained. The latter can be recycled directly [29] or indirectly *via* the corresponding amines into optically active isocyanates with no loss of enantiomeric purity.

Good separation of diastereoisomeric ureas, accomplished by chromatographic techniques or by crystallization, is an essential requirement for preparing optically pure amines, but affords, if successful, both optical isomers in equally good and reproducible yield.

Experimental Part

General. Isocyanates were from *Aldrich Chemical Co.* or *Fluka AG*. The $CHCl_3$ used for reactions was freshly dried and purified through activated, basic Alox. After extraction, all org. phases were dried with $MgSO_4$. TLC: silica gel *GHLF* plates from *Analtech, Inc.* Column chromatography: silica gel *60 (Merck)*, 40–63 μm (flash chromatography); for the chromatography of amines, 1% NH_4OH was added to the eluent. Anal. HPLC: μ-*Porasil* column (silica gel) from *Millipore*, i-PrOH/hexane 10:90 or 5:95 (system *A*); *Axxi Chrom Cyano* column, i-PrOH/hexan 5:95 (system *B*). Prep. HPLC: *Prep LC system 500 (Waters), 1 PrepPak 500 Silica* column. M.p.: *Fisher-Johns* melting-point apparatus. Optical rotations: *Perkin Elmer 241 MC* polarimeter. IR spectra: *Beckman IR 4230*. ^{1}H-NMR spectra: *Varian XL 300* (300 MHz) or *Varian HR 220* (220 MHz) spectrometer. MS: *Hitachi Perkin Elmer RMU-6E* (EI) or *Finnigan 1015D* instrument (CI).

*(1R,2R,4S)-*N*-[((S)-1-Phenylethyl)carbamoyl]mecamylamine*[4]) (**3**) *and its (1S,2R,4R)-Diastereoisomer* **4**. A soln. of 3.19 g (15.66 mmol) of (±)-mecamylamine hydrochloride ((±)-**1** · HCl) in 40 ml of half-sat., aq. Na_2CO_3 soln. was extracted with Et_2O (3 × 30 ml), the org. phase dried and evaporated. The residue was taken up in 30 ml of $CHCl_3$ and mixed at r.t. with 2.30 g (15.65 mmol) of (−)-(*S*)-(1-phenylethyl)isocyanate ((*S*)-**2a**). The soln. was stirred for 1 h, then evaporated and the residue chromatographed on silica gel (column 5 × 30 cm, pressure 5 lbs, Et_2O/hexane 1:5), which gave 2.11 g (43%) of a less polar fraction (oil that crystallized slowly on standing) and 2.62 (53%) of a more polar and mixed fraction (oil that crystallized rapidly on standing). The less polar fraction was recrystallized from hexane to give 1.65 g of **3** as colorless needles. M.p. 91.5–92°. $[\alpha]_D^{r.t.} = -71.8°$ ($c = 0.7$, $CHCl_3$). CI-MS: 315 (92, $M^+ + 1$), 209 (9), 180 (20), 179 (100), 168 (13).

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[3]) The formulae of (−)- and (+)-**26**, (−)- and (+)-**27**, and (−)- and (+)-**32** represent their absolute configuration. Details of the X-ray diffraction analysis, performed by *Judith Flippen-Anderson* at the National Research Laboratory in Washington, D.C., will be reported elsewhere.

[4]) IUPAC name of (1*R*,2*S*,4*S*)-mecamylamine: (1*R*,2*S*,4*S*)-*N*-methyl-(2,3,3-trimethylbicyclo[2.2.1]hept-2-yl)amine ((−)-**1**).

The more polar fraction was recrystallized from (i-Pr)$_2$O to give 1.85 g of **4** as colorless crystals. M.p. 108–108.5°. $[\alpha]_D^{r.t.} = +44.1°$ ($c = 0.9$, $CHCl_3$). CI-MS: 315 (100, $M^+ + 1$), 209 (14), 180 (25), 179 (100), 168 (33).

(+)-Mecamylamine Hydrochloride ((+)-**1**·HCl) *and its Enantiomer* (−)-**1**·HCl[5]). *By Base Catalysis.* A soln. of 2.46 g (7.82 mmol) of **3** in 10 ml of abs. EtOH was mixed with 20 ml of 2M NaOEt in EtOH at r.t. and then refluxed for 45 min. The mixture was cooled to r.t., concentrated *in vacuo* by using a *Vigreux* column, the residue acidified with enough 2M HCl, extracted with Et_2O (2 × 20 ml), then rendered strongly alkaline with 10% NaOH soln., and extracted with Et_2O (3 × 30 ml). The combined org. extracts from the alkaline aq. phase were concentrated, the resulting liquid was mixed with 20 ml of Et_2O, and the crude (+)-**1**·HCl was precipitated by addition of a slight excess of HCl in Et_2O. After filtration, the finely powdered colorless solid was recrystallized from i-PrOH to give 1.02 g (64%) of (+)-**1**·HCl as needles. M.p. 259–260° (dec.). $[\alpha]_D^{r.t.} = +20.1°$ ($c = 1.7$, $CHCl_3$).

The more polar **4** (1.85 g, 5.89 mmol) was treated in exactly the same manner to give 752 mg (63%) of (−)-**1**·HCl as colorless needles. M.p. 259–260° (dec.). $[\alpha]_D^{r.t.} = -20.0°$ ($c = 2.2$, $CHCl_3$; [3]: +20.6° and −20.6° ($CHCl_3$)).

In the Absence of Base. A soln. of 152 mg (0.48 mmol) of **3** in 2 ml of PrOH was refluxed until TLC showed absence of **3** (4 h). The mixture was mixed with 2 ml of 2M HCl, extracted with 5 ml of Et_2O, basified with enough 10% NaOH soln., and extracted with Et_2O (3 × 5 ml). The Et_2O extract was concentrated to *ca.* 5 ml, and enough HCl in Et_2O added to precipitate all (+)-**1**·HCl (56 mg (57%), after recrystallization as described above).

(S)-Ethyl N-(1-Phenylethyl)carbamate ((*S*)-**5a**). The above mentioned Et_2O extract of the concentrated, acidified reaction mixture was evaporated and the residue distilled ('Kugelrohr' oven, 180°/20 Torr) to give 6.08 (96%) of pure (TLC) (*S*)-**5a** as a colorless liquid which turned to a waxy solid on standing in the cold. $[\alpha]_D^{r.t.} = -77.0°$ ($c = 2.6$, benzene); [15]: for (*R*)-**5a**, $[\alpha]_D^{r.t.} = +80.1°$ ($c = 3$, benzene). IR ($CHCl_3$): 3450, 2990, 2940, 2905, 2880, 1710, 1604, 1585, 1497, 1455, 1380, 1335, 1144, 1093, 1060, 1025, 986, 910, 870. ^{1}H-NMR (220 MHz, $CDCl_3$): 7.36–7.15 (*m*, 5 arom. H); 5.02 (*m*, $w_{1/2} = -20$, NH); 4.82 (*m*, $w_{1/2} = 20$, PhC*H*CH_3); 4.09 (*q*, $J = 7$, CH_3CH_2O); 1.45 (*d*, $J = 7$, PhCHCH_3); 1.20 (*t*, $J = 7$, CH_3CH_2O). EI-MS: 194 (100, $M^+ + 1$), 178 (28).

(S)-(1-Phenylethyl)amine ((*S*)-**6a**). A soln. of 640 mg (3.31 mmol) of (*S*)-**5a** in 10 ml of H_2O/EtOH/KOH 10:40:5 was refluxed for 44 h, then acidified with 2M HCl and concentrated to remove the EtOH. The resulting suspension was made alkaline with 10% NaOH soln., extracted with Et_2O (4 × 10 ml), and the extract concentrated to *ca.* 10 ml. Addition of 1 equiv. of HCl in MeOH gave 271 mg (52%) of (*S*)-**6a**·HCl. M.p. 169–171° ([30]: m.p. 171°). From this hydrochloride, (*S*)-**6a** was freed and distilled ('Kugelrohr' oven, 120°/15 Torr). $[\alpha]_D^{r.t.} = -38.4°$ ($c = 1.9$, $CHCl_3$); a reference sample *(Aldrich)* had $[\alpha]_D = -34.7°$ ($c = 2.1$, $CHCl_3$).

(±)-5-O-Methyl-1-noreseroline[6]) ((±)-**8**). The oxindole (±)-**7** was cyclized as already described for its ethyl-ether analog [31]: 7.05 g (30 mmol) of (±)-**7** yielded, after distillation ('Kugelrohr' oven, 200°/1 Torr), 4.48 g (68%) of (±)-**8** as a colorless oil.

(10R)-5-O-Methyl-1-[((S)-1-phenylethyl)carbamoyl]-1-noreseroline (**9**) *and its (10S)-Diastereoisomer* **10**. To a stirred, cold soln. (0°) of 1.20 g (5.49 mmol) of (±)-**8** in 12 ml of $CHCl_3$, 889 mg (6.04 mmol) of (*S*)-**2a** was added dropwise. After 2 h, the mixture was evaporated and the residue chromatographed on silica gel (column 4 × 30 cm, pressure 5 lbs, CH_2Cl_2/MeOH 100:1 to 80:1) which gave 736 mg (37%) of the less polar **9**, 803 mg (40%) of the more polar **10** and 441 mg (22%) of a mixture. The diastereoisomeric purity of **9** and **10** was > 95% according to HPLC (system *A*). The oily **9** crystallized slowly on standing and was recrystallized from CH_2Cl_2/(i-Pr)$_2$O. M.p. 124–125°. $[\alpha]_D^{r.t.} = +215.1°$ ($c = 1.2$, $CHCl_3$). IR ($CHCl_3$): 3470, 3100, 2980, 2940, 2920, 2890, 2850, 1655, 1600, 1487, 1450, 1373, 1282, 1170, 1118, 1093, 1064, 1034, 994, 971, 872. ^{1}H-NMR (300 MHz, $CHCl_3$): 7.4–7.2 (*m*, 5 arom. H); 6.6–6.7 (*m*, H–C(4), H–C(6)); 6.35 (*d*, $J(6,7) = 7.8$, H–C(7)); 5.27 (*s*, H–C(9)); 5.05 (*qd*, J(PhC*H*CH_3,CH_3) = J(PhC*H*CH_3,NH) = 6.8, PhC*H*CH_3); 4.54 (br. *d*, $J = 6.8$, NH); 3.74 (*s*, CH_3O); 3.57–3.45 (*m*, H–C(2)); 3.34–3.21 (*m*, H′–C(2)); 2.89 (*s*, CH_3N); 2.18 (*ddd*, $J_{gem} = 13.0$, $J(2,3) = J(2',3) = 6.7$, H–C(3)); 2.00 (*ddd*, $J_{gem} = 13.0$, $J(2,3') = 5.6$, $J(2',3') = 7.3$, H′–C(3)); 1.52 (*d*, J(CH_3, PhC*H*CH_3) = 6.8, PhCHCH_3); 1.40 (*s*, CH_3–C(10)). EI-MS: 366 (25), 365 (100, M^+), 350 (7), 245 (5), 218 (8), 203 (10), 188 (15), 174 (20).

The more polar **10** remained as a foam. $[\alpha]_D = -40.0°$ ($c = 1.7$, $CHCl_3$). IR ($CHCl_3$): 3460, 2995, 2960, 2930, 2870, 2830, 1645, 1487, 1446, 1373, 1276, 1165, 1112, 1082, 1027, 990, 966, 906. ^{1}H-NMR: very similar to the one of **9**. CI-MS: 366 (55, $M^+ + 1$), 250 (25), 219 (100), 217 (25).

(+)-(10R)-5-O-Methyl-1-noreseroline ((+)-**8**). A soln. of 4.53 g (12.39 mmol) of **9** in 45 ml of 1M sodium pentoxide in Pentanol was refluxed for 1 h, then cooled and rendered acidic by dropwise addition of 6 ml of conc.

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[5]) The optical-rotation sign refers to the hydrochlorides. The corresponding free bases have opposite optical-rotation signs.

[6]) IUPAC name of (10*R*)-5-*O*-methyl-1-noreseroline: (3a*R*)-1,2,3,3a,8,8a-hexahydro-5-methoxy-3a,8-dimethylpyrrolo[2,3-*b*]indol ((+)-**8**).

HCl. The mixture was concentrated at high vacuum, the residue taken up in 50 ml of 0.5M HCl and extracted once with 50 ml of Et_2O. The aq. phase was made alkaline with aq. sat. Na_2CO_3, extracted with $CHCl_3$ (3 × 50 ml), the combined org. phase concentrated, and the residue chromatographed on silica gel (CH_2Cl_2/MeOH 15:1), which gave 2.51 g (93%) of (+)-**8** as an oil. $[\alpha]_D^{r.t.} = +35.2°$ ($c = 1.8$, $CHCl_3$). IR, ^{1}H-NMR, MS: identical with those of (±)-**8**.

An oxalate was precipitated by addition of 1 equiv. of oxalic acid (1M in EtOH) to a soln. of (+)-**8** in EtOAc. Recrystallization from EtOH/(i-Pr)$_2$O yielded fine, colorless crystals. M.p. 151–153°. $[\alpha]_D = +68.0°$ ($c = 0.8$, MeOH). Anal. calc. for $C_{15}H_{20}N_2O_5$ (308.32): C 58.43, H 6.53, N 9.01; found: C 59.20, H 6.78, N 9.21.

(–)-(10S)-5-O-Methyl-1-noreseroline ((–)-**8**). Urea **10** was treated as **9** to give (–)-**8** as an oil: $[\alpha]_D^{r.t.} = -38°$ ($c = 3.0$, $CHCl_3$).

Oxalate: M.p. 156–159°. $[\alpha]_D = -77.2°$ ($c = 0.7$, MeOH). Anal. calc. for $C_{15}H_{20}N_2O_5$ (308.32): C 58.43, H 6.53, N 9.01; found: C 58.42, H 6.58, N 8.90.

(±)-Salsolidine[7]) ((±)-**13**). A soln. of 23.13 g (0.112 mmol) of dihydroisochinoline **12** in 50 ml of i-PrOH was added dropwise to a stirred soln. of 4.0 g (0.11 mmol) of $NaBH_4$ in 100 ml of H_2O/i-PrOH 1:1 at 0°. The mixture was stirred for 5 h and then cautiously acidified with conc. HCl. Most of the i-PrOH was removed *in vacuo*, the remaining soln. made alkaline with 50 ml of 10% NaOH soln., extracted with CH_2Cl_2 (4 × 50 ml), and concentrated. The residue was distilled to give 17.07 g (73%) of a colorless oil which crystallized on standing. M.p. 50–52° ([20]: 53–53.5°). CI-MS: 208 (100, $M^+ + 1$), 192 (7).

(1S)-2-[(R)-1-Phenylethyl)carbamoyl]salsolidine (**14**). To a stirred, cold soln. (0°) of 2.07 g (9.99 mmol) of (±)-**13**) in 20 ml of $CHCl_3$, 1.6 g (10.87 mmol) of (+)-(*R*)-(1-phenylethyl)isocyanate ((*R*)-**2a**) was added dropwise. After 1 h, the mixture was evaporated, the residue dissolved in 2 ml of CH_2Cl_2 and 10 ml of (i-Pr)$_2$O added. This soln. was kept in the refrigerator overnight after addition of a seed crystal of **14**. Filtration and recrystallization of the colorless crystals from CH_2Cl_2/(i-Pr)$_2$O gave 1.61 g (46%) of **14** which was free of its diastereoisomer **15** according to HPLC (system *B*). M.p. 199–202°. $[\alpha]_D^{r.t.} = +48.0°$ ($c = 0.7$, $CHCl_3$). IR (KBr): 3435, 3050, 3010, 2985, 2950, 2840, 1640, 1585, 1527, 1453, 1403, 1374, 1355, 1330, 1317, 1288, 1253, 1225, 1215, 1201, 1173, 1145, 1120, 1065, 1055, 1034, 1020, 997, 985, 950, 915, 897, 868, 807, 780, 757, 749, 706, 660. ^{1}H-NMR (220 MHz, $CDCl_3$): 7.39–7.16 (*m*, 5 arom. H); 6.59, 6.57 (2*s*, H–C(5), H–C(8)); 5.15–4.95 (*m*, H–C(1), PhC*H*CH$_3$); 4.73 (br. *d*, *J*(NH,PhC*H*CH$_3$) = 7.2, NH); 3.95 (*ddd*, $J_{gem} = 13$, *J*(3,4) = *J*(3,4′) = 5, H–C(3)); 3.83 (*s*, 2 CH$_3$O); 3.27 (*ddd*, $J_{gem} = 13$, *J*(3′,4′) = 10, *J*(3′,4) = 4.5, H′–C(3)); 2.85 (*ddd*, $J_{gem} = 16$, *J*(3′,4′) = 10, *J*(3,4′) = 5, H′–C(4)); 2.70 (*ddd*, $J_{gem} = 16$, *J*(3,4) = 5, *J*(3′,4) = 4.5, H–C(4)); 1.51, 1.45 (2*d*, *J*(PhC*H*CH$_3$),CH$_3$) = *J*(1,CH$_3$) = 7, CH$_3$–C(1), PhCHC*H*$_3$. EI-MS: 354 (17, M^+), 339 (30), 249 (13), 206 (43), 192 (100), 176 (23), 147 (37), 132 (74), 105 (25), 77 (38).

(1R)-2-[(R)-1-Phenylethyl)carbamoyl]salsolidine (**15**). The combined mother liquors of **14** were evaporated, the residue chromatographed on silica gel (AcOEt/hexane 1:1), and from the resulting oil a second crop of **14** (133 mg) was crystallized, which was strongly contaminated with **15** according to HPLC (system *B*). The remaining mother liquor contained 1.61 g (44%) of non-crystalline **15** with only traces of **14**. $[\alpha]_D^{r.t.} = -101.5°$ ($c = 0.9$, $CHCl_3$). IR ($CHCl_3$): 3480, 3005, 2950, 2880, 2850, 1735, 1645, 1497, 1465, 1378, 1130, 1060, 1043, 1005, 950, 863. ^{1}H-NMR (220 MHz, $CDCl_3$): 7.36–7.14 (*m*, 5 arom. H); 6.57 (*s*, H–C(5), H–C(8)); 5.17–4.95 (*m*, H–C(1), PhC*H*CH$_3$); 4.70 (br. *d*, *J*(NH,PhC*H*CH$_3$) = 7, NH); 3.95 (*ddd*, $J_{gem} = 13$, *J*(3,4) = *J*(3,4′) = 5, H–C(3)); 3.82 (*s*, 2 CH$_3$O); 3.25 (*ddd*, $J_{gem} = 13$, *J*(3′,4′) = 10, *J*(3′,4) = 4.5, H′–C(3)); 2.84 (*ddd*, $J_{gem} = 16$, *J*(3′,4′) = 10, *J*(3,4′) = 5, H′–C(4)); 2.68 (*dd*, $J_{gem} = 16$, *J*(3,4) = 5, *J*(3′,4) = 4.5, H–C(4)); 1.51, 1.45 (2*d*, *J*(CH$_3$,1) = *J*(CH$_3$, PhC*H*CH$_3$) = 7, CH$_3$–C(1), PhCHC*H*$_3$). EI-MS: identical with the one of **14**.

(–)-(1S)-Salsolidine Hydrochloride ((–)-**13**·HCl). A suspension of 1.58 g (4.46 mmol) of **14** in 10 ml of 2M NaOBu in BuOH was heated to boiling temp. and the resulting soln. refluxed for 2 h. The mixture was then cooled to r.t., 15 ml of 2M HCl was added and the acidic soln. concentrated *in vacuo* to *ca.* 10 ml. After addition of a few drops of conc. HCl, the resulting 2-phase system was kept overnight in the refrigerator which gave, after filtration, a first crop of (–)-**13**·HCl. Extraction of the acidic aq. phase with 10 ml of Et_2O, rendering alkaline by the addition of enough 10% NaOH soln., extraction of the aq. soln. with CH_2Cl_2 (3 × 10 ml), and dissolution of the residue of the CH_2Cl_2 extract in 10 ml of 2M HCl gave, after addition of a seed crystal, a second crop of (–)-**13**·HCl. Total yield: 810 mg (74%). Recrystallization from 2M HCl gave colorless crystals. M.p. 238–240°. $[\alpha]_D^{r.t.} = -25.6°$ ($c = 2.1$, H_2O; [20]: –24.8°). IR, ^{1}H-NMR, and MS of the free base (–)-**13** were identical with the one of (±)-**13**.

(+)-(1R)-Salsolidine Hydrochloride ((+)-**13**·HCl). The non-crystalline urea **15** was treated in exactly the same way as **14** to give (+)-**13**·HCl. M.p. 240–242°. $[\alpha]_D^{r.t.} = +24.1°$ ($c = 1.8$, H_2O; [20]: +25.3°).

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[7]) IUPAC name of (1*S*)-salsolidine: (1*S*)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline ((–)-**13**).

(1S)-2-[(R)-1-(p-Nitrophenyl)ethyl]carbamoyl]salsolidine (**16**) *and its (1R)-Diastereoisomer* **17**. A soln. of 392 mg (2.36 mmol) of (*R*)-1-(*p*-nitrophenyl)ethylamine ((*R*)-**6c**) in 5 ml of $CHCl_3$ was mixed dropwise with 2.2 ml of a $COCl_2$-soln. (12.5% in toluene) at 0°. The resulting suspension was stirred at r.t. for 2 h, refluxed for 1 h, and then evaporated. $CHCl_3$ (5 ml) was added and then, at r.t., a soln. of 476 mg (2.36 mmol) of (±)-**13** in 2 ml of $CHCl_3$. After 15 min, the resulting clear soln. was mixed with 5 ml of H_2O, the aq. phase extracted with $CHCl_3$ (2 × 5 ml), and the org. extract evaporated. The residue was chromatographed on silica gel (column 3 × 20 cm, pressure 3 lbs, AcOEt/hexan 2:1) to give 230 mg of a 1:1 mixture of **16**/**17** as a slowly crystallizing oil from which **16** could be crystallized in pure form (according to HPLC, system *A*). M.p. 221–224° from CH_2Cl_2/hexane. ^{1}H-NMR (220 MHz, $CDCl_3$): 8.17, 7.46 (2*d*, J_o = 8.5, $NO_2C_6H_4$); 6.60, 6.57 (2*s*, H–C(5), H–C(8)); 5.16–4.95 (*m*, H–C(1), ArC*H*H_3); 4.82 (*d*, *J*(ArC*H*CH_3,NH) = 7, NH); 4.02–3.82 (*m*, H–C(3)); 3.84 (*s*, CH_3O); 3.32 (*ddd*, J_{gem} = 13, *J*(3′,4) = 9, *J*(3′,4′) = 5, H′–C(3)); 2.98–2.64 (*m*, 2 H–C(4)); 1.51, 1.46 (2*d*, *J*(ArC*H*CH_3,CH_3) = *J*(1,CH_3) = 7, ArCHC*H*$_3$, CH_3–C(1)). CI-MS: 400 (M^+ + 1).

(±)-1,2,3,4-Tetrahydroharmine[8] ((±)-**18**). To a cold (0°), stirred suspension of 4.05 g (14.12 mmol) of harmaline hydrochloride dihydrate (**19** · HCl · 2 H_2O) in 40 ml of i-PrOH/CH_3OH/H_2O 1:1:1, a soln. of 600 mg (15 mmol) of $NaBH_4$ in 20 ml of H_2O was added dropwise. After 1 h, the mixture was cautiously acidified with 2M HCl (clear soln.), then made alkaline with 10% aq. NaOH soln. and extracted with $CHCl_3$ (3 × 50 ml). After evaporation the residue was crystallized from EtOH to give 2.93 g (96%) of colorless crystals. M.p. 198–200° ([32]: 199°).

(1S)-2-[(R)-1-Phenylethyl)carbamoyl]-1,2,3,4-tetrahydroharmine (**20**) *and its (1R)-Diastereoisomer* **21**. A suspension of 2.93 g (13.54 mmol) of (±)-**18** in 20 ml of $CHCl_3$ was mixed dropwise with 2.19 g (14.90 mmol) of (*R*)-**2a**. After 1 h, the resulting soln. was shaken with 100 ml of 0.1M H_2SO_4 and extracted with $CHCl_3$ (4 × 50 ml) which gave, after concentration, a solid residue (quant.). Prep. HPLC (silica gel, AcOEt/hexane 1:3) gave 1.26 g (26%) of the less polar **21** with an optical purity of 75% (anal. HPLC, system *A*). Repurification of an anal. sample with semiprep. HPLC gave pure, crystalline **21**. M.p. 111–114° (from CH_2Cl_2/Et_2O). $[\alpha]_D^{r.t.} = -158.5°$ (*c* = 0.6, $CHCl_3$). IR ($CHCl_3$): 3460, 3280, 2910, 2830, 1620, 1144. CI-MS: 364 (40, M^+ + 1), 217 (100), 213 (50).

Besides a mixed fraction of 0.83 g (17%), the more polar **20** was obtained as a solid, which was recrystallized from CH_2Cl_2/Et_2O to give 1.53 g (31%) with an optical purity of 75% (anal. HPLC, system *A*). Further recrystallization did not improve this ratio.

(1S)-1,2,3,4-Tetrahydroharmine ((−)-**18**). A soln. of 0.79 g (2.17 mmol) of **20** (contaminated with 25% of **21**) in 10 ml of 1M sodium pentoxide in Pentanol was refluxed for ½ h, then acidified with 2M HCl, extracted with Et_2O (1 × 10 ml), made alkaline with 10% NaOH soln., and extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ extract was evaporated and the solid residue recrystallized from EtOH to give 0.21 g (45%) of (−)-**18** with an optical purity of 74% according to $[\alpha]_D^{r.t.}$. M.p. 192–194° ([24]: 190–194°). Repurification by a method described [24] with α-camphorsulfonic acid gave optically pure (−)-**18**. M.p. 199–200°. $[\alpha]_D^{r.t.} = -58.6°$ (*c* = 0.8, $CHCl_3$); optical purity was checked by HPLC (system *A*) after urea formation with (*S*)-**2a**.

(R)-Pentyl N-*(1-Phenylethyl)carbamate* ((*R*)-**5c**). The above Et_2O extract of the acidified reaction mixture was concentrated *in vacuo* to *ca.* 5 ml, a part of it chromatographed on silica gel (column 2 × 20 cm, 1 lbs pressure, Et_2O/hexane 1:2), and the desired fraction distilled ('Kugelrohr' oven, 230°/1 Torr) to give (*R*)-**5c** as a colorless oil. $[\alpha]_D^{r.t.} = +52.8°$ (*c* = 4.4, $CHCl_3$). IR ($CHCl_3$): 3440, 2950, 2920, 2865, 1700, 1485, 1445, 1375, 1325, 1070, 1050. CI-MS: 236 (95, M^+ + 1), 153 (100).

(1R)-1,2,3,4-Tetrahydroharmine ((+)-**18**) was obtained from **21** and repurified as described above for (−)-**18**. M.p. 199–201°. $[\alpha]_D^{r.t.} = +60.7°$ (*c* = 1.2, $CHCl_3$).

*(±)-*N-*Vanillylamphetamine*[9] ((±)-**23**). To a stirred soln. of 1.36 g (10.04 mmol) of amphetamine ((±)-**22**) in 10 ml of benzene at r.t., a soln. of 1.83 g (12.02 mmol) of vanilline in 5 ml of CH_2Cl_2 and 2 g of freshly activated 4-Å molecular sieve was added. After 2 h, the mixture was cooled to 0°, and a soln. of 380 mg (10 mmol) of $NaBH_4$ in 5 ml of CH_3OH was added dropwise. After 30 min, the mixture was cautiously acidified with 2M HCl, passed through *Celite*, made alkaline to pH 8 with 10% aq. NaOH soln., and extracted with CH_2Cl_2 (4 × 30 ml). The residue of the org. phase was taken up in 7 ml of acetone and 1 equiv. of HBr in MeOH added. This soln. was mixed with enough Et_2O until turbid and then seeded, which gave 2.93 g (83%) of (±)-**23** · HBr as colorless crystals which were recrystallized from acetone. M.p. 173–175°. Anal. calc. for $C_{17}H_{22}BrNO_2$ (352.25): C 57.96, H 6.29, N 6.29; found: C 58.04, H 6.35, N 3.93.

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[8]) IUPAC name of (1*S*)-1,2,3,4-tetrahydroharmine: (1*S*)-1,2,3,4-tetrahydro-7-methoxy-1-methyl-1*H*-pyrido-[3,4-*b*]indol ((−)-**18**).

[9]) IUPAC name of (*S*)-*N*-vanillylamphetamine: (*S*)-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]-1-methyl-2-phenylethylamine ((+)-**23**).

(S)-N-[((S)-1-Naphthylethyl)carbamoyl]-N-vanillylamphetamine (**24**) *and its (R)-Diastereoisomer* **25**. To a soln. of 1.84 g (6.78 mmol) of (±)-**23** at 0°, 1.38 ml (7.89 mmol) of (+)-(*S*)-(1-naphthylethyl)isocyanate ((*S*)-**2b**) was added dropwise. After 1 h, the mixture was evaporated and the residue chromatographed on silica gel (column 5 × 25 cm, 1 lbs pressure, CH_2Cl_2/MeOH 100:1 to 80:1) to give 0.76 (24%) of the less polar **24**, 1.45 g (47%) of mixed fraction, and 0.79 g (26%) of the more polar **25** as a foam. Ureas **24** and **25** were 95% pure according to anal. HPLC (system *A*). **24**: IR ($CHCl_3$): 3560, 3440, 2995, 2945, 2885, 1640, 1500, 1455, 1435, 1380, 1327, 1145, 1125, 1035, 960. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.1–7.0 (several *m*, 7 H of Naph, 5 H of Ph); 6.74 (*d*, J(5',6') = 8.2, H–C(5')); 6.64 (*dd*, J(5', 6') = 8.2, J(2',6') = 1.6, H–C(6')); 6.56 (*d*, J(2',6') = 1.6, H–C(2')); 5.75 (*qd*, J(NaphC*H*CH_3, CH_3) = 6.9, J(NaphC*H*CH_3, NH) = 7.8, NaphC*H*CH_3); 5.50 (*s*, O–H); 4.80 (*m*, $w_{½}$ = 23, H–C(1)); 4.59 (*d*, J(NaphC*H*CH_3, NH) = 7.8, NH); 4.23 (*d*, J_{gem} = 17.1, H–C(α)); 4.11 (*d*, J_{gem} = 17.1, H'–C(α)); 3.57 (*s*, CH_3O); 2.98 (*dd*, J_{gem} = 13.7, J(1,2) = 7.1, H–C(2)); 2.70 (*dd*, J_{gem} = 13.7, J(1,2') = 7.8, H'–C(2)); 1.42, 1.16 (2*d*, J(NaphC*H*CH_3, CH_3) = J(1,CH_3) = 6.9, NaphCHC*H*$_3$, CH_3–C(1)). CI-MS: 469 (1, M^+ + 1), 33 (3), 272 (20), 155 (100), 136 (60).

25: IR ($CHCl_3$): 3560, 3450, 3000, 1635, 1495, 1450, 1400, 1380, 1330, 1140, 1120, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.15–7.00 (several *m*, 7 H of Naph, 5 H of Ph); 6.78 (*d*, J(5',6') = 8.2, H–C(5')); 6.67 (*dd*, J(5',6') = 8.2, J(2',6') = 1.6, H–C(6')); 6.56 (br. *s*, H–C(2')); 5.78–5.65 (*m*, NaphC*H*CH_3); 5.51 (*s*, OH); 4.94–4.80 (*m*, H–C(1)); 4.53 (*d*, J(NaphC*H*CH_3, NH) = 7.3, NH); 4.22 (*d*, J_{gem} = 17.0, H–C(α)); 4.14 (*d*, J_{gem} = 17.0, H–C(α)); 3.58 (*s*, CH_3O); 2.93 (*dd*, J_{gem} = 13.8, J(1,2) = 7.4, H–C(2)); 2.72 (*dd*, J_{gem} = 13.8, J(1,2') = 7.5, H'–C(2)); 1.41 (*d*, J(NaphC*H*CH_3, CH_3) = 6.8, NaphCHC*H*$_3$); 1.19 (*d*, J(1,CH_3) = 6.8, CH_3–C(1)). CI-MS: 469 (0.1), 468 (0.2, M^+), 333 (8), 270 (7), 155 (75), 136 (100).

(+)-(S)-N-Vanillylamphetamine ((+)-**23**). A soln. of 760 mg (1.62 mmol) of **24** in 8 ml of 1M NaOPr in PrOH was refluxed for 4 h, then concentrated at high vacuum, and the residue taken up in 20 ml of H_2O. Then, enough 2M HCl was added until pH 8, and this aq. soln. was extracted with CH_2Cl_2 (3 × 15 ml). After concentration, the residue was taken up in acetone, and 1 equiv. of HBr in MeOH and then Et_2O added until beginning turbidity. After standing overnight, 473 mg (80%) of (+)-**23** · HBr was collected and recrystallized from MeOH/acetone. M.p. 204–206°. $[\alpha]_D^{t.}$ = +19.1° (*c* = 0.7, MeOH). The base (+)-**23** was freed: colorless oil. IR ($CHCl_3$): 3650, 3475, 2970, 2940, 1615, 1505, 1465, 1450, 1425, 1375, 1335, 1265, 1150, 1120, 1030, 905, 850. ^{1}H-NMR (220 MHz, $CDCl_3/D_2O$): 7.32–7.09 (*m*, 5 H of Ph); 6.80 (*d*, J(5',6') = 8, H–C(5')); 6.73 (*d*, J(2',6') = 1.5, H–C(2')); 6.67 (*dd*, J(5',6') = 8.0, J(2',6') = 1.5, H–C(6')); 3.80 (*s*, CH_3O); 3.79 (*d*, J_{gem} = 12.8, H–C(α)); 3.65 (*d*, J_{gem} = 12.8, H'–C(α)); 3.02–2.90 (*m*, H–C(1)); 2.80 (*dd*, J_{gem} = 13.2, J(1,2) = 7.0, H–C(2)); 2.66 (*dd*, J_{gem} = 13.2, J(1,2') = 7.0, H'–C(2)); 1.11 (*d*, J(1,CH_3) = 6.3, CH_3–C(1)). CI-MS: 272 (100), 271 (25, M^+), 212 (30).

(S)-Propyl N-((S)-1-Naphthylethyl)carbamate ((*S*)-**5b**). The mother liquor of the above crystallization was concentrated and the residue chromatographed on silica gel (Et_2O/hexane 1:2) to give, after recrystallization from hexane, 146 mg (35%) of colorless crystals as fine needles. M.p. 105–106°. $[\alpha]_D^{t.}$ = –21.5° (*c* = 1.7, $CHCl_3$). CI-MS: 258 (10, M^+ + 1), 242 (7), 155 (100), 130 (100).

(–)-(R)-N-Vanillylamphetamine ((–)-**23**). Urea **25** (790 mg, 1.69 mmol) was treated in exactly the same way as described for **24** to give 320 mg (54%) of (–)-**23** · HBr, after recrystallization. M.p. 201–203°. $[\alpha]_D$ = –19.9° (*c* = 0.7, $CHCl_3$).

Methyl (RS)-Salsoline-1-carboxylate[10] ((±)-**27**). To a stirred suspension of 4.95 g (20.9 mmol) of the acid (±)-**26** in 50 ml of MeOH at 0°, 8 ml (100 mmol) of $SOCl_2$ was added dropwise. Then the soln. was refluxed for 5 h, cooled down and taken up in 50 ml of aq. sat. $NaHCO_3$ soln. Enough aq. sat. Na_2CO_3 soln. was added to beginning alkalinity, and then this aq. soln. extracted with $CHCl_3$ (3 × 50 ml). After evaporation the solid residue was recrystallized from CH_2Cl_2/hexane to give 4.02 g (80%) of (±)-**27**. M.p. 156–157°. IR ($CHCl_3$): 3570, 3355, 2970, 2865, 1730, 1630, 1597, 1500, 1450, 1380, 1360, 1335, 1155, 1140, 1110, 1060, 1045, 1020, 980, 875. ^{1}H-NMR (220 MHz, $CDCl_3/D_2O$): 6.86, 6.57 (2*s*, H–C(5), H–C(8)); 3.84, 3.70 (2*s*, CH_3OCO, CH_3O); 3.15–3.04 (*m*, 2 H–C(3)); 2.80 (*ddd*, J_{gem} = 16, J(3,4) = J(3',4) = 7, H–C(4)); 2.60 (*ddd*, J_{gem} = 16, J(3,4') = J(3',4') = 4.5, H'–C(4)); 1.66 (*s*, CH_3–C(1)). CI-MS: 252 (100, M^+ + 1), 192.

Methyl (1S)-2-[((R)-1-Phenylethyl)carbamoyl]salsoline-1-carboxylate (**28**) *and its (1R)-Diastereoisomer* **29**. To a stirred soln. of 2.49 g (9.92 mmol) of (±)-**27** in 28 ml of $CHCl_3$ at 0°, 1.46 ml (10.9 mmol) of (*R*)-**2a** was added dropwise. After 2 h, the mixture was evaporated and the residue chromatographed by prep. HPLC (AcOEt/hexane 1:3, flow 0.1 l/min) to give 1.03 g (26%) of the less polar **29** as a foam, 0.83 g (21%) of the more polar **28** as crystals and 0.78 g (20%) of mixed fraction. **29**: $[\alpha]_D$ = +56.1° (*c* = 1.5, $CHCl_3$). IR ($CHCl_3$): 3540, 3460, 2995, 2940, 2870, 2845, 1735, 1645, 1597, 1495, 1445, 1375, 1340, 1270, 1150, 1117, 1052, 1018, 905, 870.

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[10]) IUPAC name of methyl (*S*)-salsoline-1-carboxylate: methyl (*S*)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-1-methylisoquinoline-1-carboxylate ((–)-**27**).

^{1}H-NMR (220 MHz, $CDCl_3$): 7.36–7.18 (*m*, 5 H of Ph); 6.68, 6.64 (2*s*, H–C(5), H–C(8)); 4.99 (*qd*, *J*(PhC*H*CH$_3$, NH) = 7.5, *J*(PhC*H*CH$_3$, CH$_3$) = 7, PhC*H*CH$_3$); 4.77 (*d*, *J*(PhC*H*CH$_3$, NH) = 7.5, NH); 3.79, 3.41 (2*s*, CH$_3$OCO, CH$_3$O); 3.58 (*ddd*, J_{gem} = 11.5, *J*(3,4′) = 6.5, *J*(3,4) = 4.5, H–C(3)); 3.47–3.34 (*m*, H′–C(3)); 2.92 (*ddd*, J_{gem} = 15, *J*(3′,4) = 8, *J*(3,4) = 4.5, H–C(4)); 2.76 (*ddd*, J_{gem} = 15, *J*(3,4′) = 6.5, *J*(3′,4′) = 4, H′–C(4)); 1.82 (*s*, CH$_3$–C(1)); 1.50 (*d*, *J*(PhCH*CH*$_3$,CH$_3$) = 7, PhCHC*H*$_3$). CI-MS: 399 (25, M^+ + 1), 367 (35), 252 (100).

28: Recrystallization from AcOEt/hexane gave long needles. M.p. 139–140°. $[\alpha]_D^{r.t.}$ = −34.3° (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): 3540, 3460, 2980, 2940, 2840, 1730, 1640, 1485, 1440, 1367, 1103, 1045, 898, 862. ^{1}H-NMR (220 MHz, $CDCl_3/D_2O$): 7.36–7.23 (*m*, 5 H of Ph); 6.70, 6.65 (2*s*, H–C(5), H–C(8)); 5.03 (*qd*, *J*(PhC*H*CH$_3$,NH) = *J*(PhC*H*CH$_3$,CH$_3$) = 7, PhC*H*CH$_3$); 4.68 (*d*, *J*(PhC*H*CH$_3$,NH) = 7, NH); 3.82, 3.64 (2*s*, CH$_3$OCO, CH$_3$O); 3.66–3.52 (*m*, H–C(3)); 3.33 (*ddd*, J_{gem} = 12, *J*(3′,4) = 8.5, *J*(3′,4′) = 4, H′–C(3)); 2.95 (*ddd*, J_{gem} = 15.5, *J*(3′,4) = 8.5, *J*(3,4) = 4.5, H–C(4)); 2.73 (*ddd*, J_{gem} = 15.5, *J*(3,4′) = 5.5, *J*(3′,4′) = 4, H′–C(4)); 1.88 (*s*, CH$_3$–C(1)); 1.50 (*d*, *J*(PhCH*CH*$_3$,CH$_3$) = 7, PhCHC*H*$_3$). CI-MS: 398 (15, M^+ + 1), 367 (30), 252 (100), 192 (8).

Hydantoin **30**[11]) was obtained from the Et_2O extract in the thermal decomposition of the less polar **28**, as described for hydantoin **31** (see below). The 414 mg of material obtained after chromatography through silica gel (AcOEt/hexane 1:2) was an oil. CI-MS: 367 (100, M^+ + 1), 351 (5), 337 (7), 120 (45).

Methyl (−)-Salsoline-1-carboxylate ((−)-**27**). A soln. of 760 mg (1.91 mmol) of **28** in 16 ml of BuOH was refluxed for 2 h and then kept at 100° for 14 h. Then, the mixture was evaporated and the residue refluxed for 30 min in 10 ml of 1M NaOMe in MeOH. This mixture was acidified with 10 ml of 2M HCl, the MeOH removed *in vacuo*, and the remaining aq. phase extracted with Et_2O (1 × 10 ml). The aq. phase was made alkaline with aq. sat. Na_2CO_3 to pH 8 and extracted with $CHCl_3$ (4 × 5 ml). This org. phase was concentrated, the residue taken up in some acetone, and 73 mg (13%) of (−)-**27** · HCl precipitated by addition of 1 equiv. of HCl in MeOH. Recrystallization from EtOH/(i-Pr)$_2$O gave fine, colorless crystals. M.p. 221–223°. $[\alpha]_D^{r.t.}$ = −60.2° (*c* = 0.8, MeOH). The base was freed and crystallized from CH_2CH_2/hexane: M.p. 61–63°. $[\alpha]_D^{r.t.}$ = −28.3° (*c* = 0.9, $CHCl_3$). ^{1}H-NMR and MS are identical with those of (±)-**27**.

Butyl (−)-Salsoline-1-carboxylate ((−)-**32**). A small part of the above mentioned reaction mixture, before refluxing with NaOMe, was taken, chromatographed on silica gel (CH_2Cl_2/MeOH 24:1), and the side product (−)-**32** with a slightly higher R_f than (−)-**27** was isolated. CI-MS: 294 (17, M^+ + 1), 223 (65), 177 (100).

Methyl (+)-Salsoline-1-carboxylate ((+)-**27**). Urea **29** (960 mg, 2.41 mmol) was treated in the same way as **28** to yield 72 mg (10%) of (+)-**27** · HCl. M.p. 215–218°. $[\alpha]_D$ = +59.7° (*c* = 0.9, MeOH). From the free base, the hydrobromide (+)-**27** · HBr was crystallized from MeOH by addition of 1 equiv. of HBr in MeOH and then AcOEt. M.p. 228–230°. $[\alpha]_D^{r.t.}$ = +48.6° (*c* = 0.5, MeOH). Anal. calc. for $C_{13}H_{18}BrNO_4$ (332.17): C 47.00, H 5.46, N 4.29; found: C 47.06, H 5.51, N 4.19.

Hydantoin **31**[11]). The Et_2O extract of the above acidified reaction mixture from (−)-**27** was concentrated and the solid residue recrystallized from CH_2Cl_2/(i-Pr)$_2$O to give 279 mg (32%) of **31** as brownish crystals. M.p. 159–161°. $[\alpha]_D^{r.t.}$ = +138.8° (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): 3550, 2990, 2950, 2855, 1765, 1705, 1590, 1490, 1445, 1410, 1370, 1350, 1370, 1300, 1270, 1125, 1010, 960, 925, 880, 865. ^{1}H-NMR (220 MHz, $CDCl_3$): 7.43–7.18 (*m*, 6 arom. H); 6.61 (*s*, I arom. H); 5.68 (br. *s*, OH); 5.34 (*q*, *J*(PhC*H*CH$_3$,CH$_3$) = 7.5, PhC*H*CH$_3$); 4.30 (*ddd*, J_{gem} = 13.5, *J*(3,4) = 6.5, *J*(3,4′) = 1.5, H–C(3)); 3.17 (*ddd*, J_{gem} = 13.5, *J*(3′,4) = 12, *J*(3′,4′) = 4.5, H′–C(3)); 2.92 (*ddd*, J_{gem} = 16, *J*(3′,4) = 12, *J*(3,4) = 6.5, H–C(4)); 2.57 (*ddd*, J_{gem} = 16, *J*(3′,4′) = 4.5, *J*(3,4′) = 1.5, H′–C(4)); 1.80 (*d*, *J*(PhC*H*CH$_3$, CH$_3$) = 7.5, PhCHC*H*$_3$); 1.61 (*s*, CH$_3$–C(1)). CI-MS: 367 (100, M^+ + 1), 351 (3), 222 (5).

(+)-Salsoline-1-carboxylic Acid ((+)-**26** · HCl). A soln. of 16 mg (0.06 mmol) of (+)-**27** · HCl in 2 ml of 2M HCl was refluxed for 16 h (starting material disappeared in favor of a much more polar compound) and then evaporated. The colorless, solid residue was taken up in little EtOH and precipitated with (i-Pr)$_2$O to give (+)-**26** · HCl as a colorless powder. M.p. 245–250° (dec.). $[\alpha]_D^{r.t.}$ = +48.9° (*c* = 0.5, MeOH). IR (KBr): 3600–1900, 1600 (br.), 1505, 1455, 1387, 1345, 1280, 1260, 1235, 1205, 1170, 1135, 1112, 1065, 1053, 1040, 1000, 960, 935, 882, 867, 795, 775, 736, 697, 620.

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[11]) IUPAC name: (10b*S*)-6,10b-dihydro-8-hydroxy-9-methoxy-10b-methyl-2-((*R*)-1-phenylethyl)-5*H*-imidazo-[4,3-*a*]isoquinoline-1(2*H*),3(4*H*)-dione (**30**).

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