CD OF PRIMARY AMINES AND 1- OR 3-SUBSTITUTED TETRAHYDROISOQUINOLINES IN PRESENCE OF $[Rh_2(O_2CCH_3)_4]$*

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Dedicated to the memory of Professor František Šorm.

The syntheses of (*S*)-(−)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (*IX*) and (*S*)-(+)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (*XVI*) [via (*S*)-1-benzoyl-N-ethoxycarbonyl ethylamine (*XI*)] in optically pure form and with known absolute configuration is described. The CD and NMR spectra of these compounds and of most of their intermediates are given, and from these data could be deduced, that the N-methyl groups of the two bases *IX* and *XVI* adopt different conformations in solution, but the same (viz. axial) in their complexes with $[Rh_2(OAc)_4]$.

Transition metal complexes of the type $[M_2(O\text{–Acyl})_4]^{k+}$ $k Cl^-$ have been extensively used by us[1] to determine the absolute configuration of non-absorbing optically active compounds, if they can act as mono or bidentate ligands, provided such complexes are kinetically labile. Whereas in solution the molybdenum complexes in general need exchange of the acetates by chiral ligands, we have good indication from our investigations of amino acids and aminols[1–3] that in case of Rh- or Ru--complexes unidentate ligation in axial position involving the d_{z^2}-orbitals of these metal atoms is also possible. The neutral nitrogen atom of amines obviously binds through its lone pair to this axial position. In this paper we describe our results with some primary and tertiary model amines in the presence of dirhodium tetraacetate.

The primary amines *I*, *II*, and *III* are known in optically active form, the common starting material for their synthesis being commercially available (*S*)-(−)-2-methyl-1--butanol. Its oxidation to the corresponding acid was best achieved with $KMnO_4$ under the reaction conditions described by Freudenberg and Lwowski.[4] This acid was then transformed into the corresponding azide by the standard procedure, and

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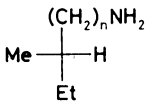
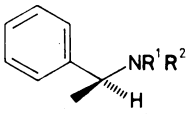
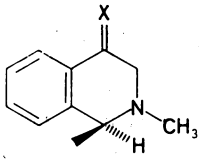
this azide was subjected to Curtius degradation. The optical purity of *I* was 93%. Amine *II* was prepared by standard Gabriel synthesis using the Mitsunobu modification[5] for the synthesis of the intermediate phthalimide from the same methylbutanol (92% optical purity, cf. also ref.[6]). For the synthesis of *III* the methylbutanol was first transformed into its tosylate, which was not further purified but directly treated with sodium cyanide to give the corresponding nitrile. Reduction of the latter to the amine *III* was achieved with diborane.[7] Its specific rotation was +7·8, whereas the reported one[8] was given as +4·27 (both neat). By NMR criteria ("chiral" shift reagents) all three amines prepared by us were at least 90% optically pure.



I, n = 0
II, n = 1
III, n = 2

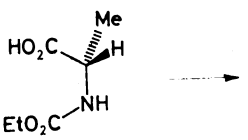


IV, R^1 = R^2 = H
V, R^1 = Me ; R^2 = H
VI, R^1 = Me ; R^2 = CH_2—CO_2Et
VII, R^1 = Me ; R^2 = CH_2—CO_2H

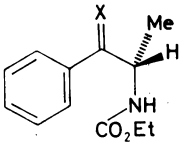


VIII, X = O
IX, X = H_2

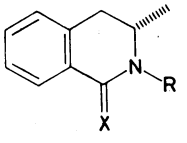
Racemic *IX* is known[9,10]. In order to avoid resolution and determination of its absolute configuration we used (*S*)-(−)-1-phenylethylamine (*IV*) as starting material. Its N-methyl derivative *V* was transformed into the glycine derivative *VI*, which was then saponified to *VII*. Ring closure of its acid chloride to *VIII* was achieved with $AlCl_3$. Since this aminoketone decomposed quickly, the raw material was hydrogenated to *IX* without further purification. Compound *VI* could also be cyclized directly with polyphosphoric acid, but the product obtained in this way was very impure. After the publication[11,*] of the synthesis of optically pure (*S*)-(−)-1-methyl-1,2,3,4-tetrahydroisoquinoline we also methylated that product to *IX*; both methods gave the same optical purity.



X



XI, X = O
XII, X = H_2



XIII, R = H ; X = O
XIV, R = H ; X = H_2
XV, R = CO_2Et ; X = H_2
XVI, R = Me ; X = H_2

* This paper was not yet published when we had prepared (−)-*IX* for the first time.

The optically active (−)-(3*S*)-methyltetrahydroisoquinoline derivatives *XIV* and *XVI* were both synthesized from the known[12] compound *XII*, which can be obtained from L-alanine via its N-ethoxycarbonyl derivative *X* and subsequent reduction of the keto group of *XI*. In our hands this oily product was laevorotatory, whereas a positive rotation was published[13] albeit for much higher concentration. Ring closure of *XII* to *XIII* was performed with polyphosphoric acid, and the carbonyl group was then reduced with lithium aluminium hydride to *XIV*. Ethoxycarbonylation of *XIII* to *XV* and subsequent reduction gave the N—Me derivative *XVI*.

CD *of Primary Amines in the Presence of* $[Rh_2(OAc)_4]$

Since primary amines ligate quite quickly, several different solvents may be used; the data presented here were obtained for acetonitrile solutions. The CD curves remain constant over several hours, thus no rearrangement of the originally formed axial amino complexes is involved. Since furthermore a (branched) apolar hydrocarbon chain is connected to the N-atom we can assume that the longest (C—C)--chain preferably adopts the antiperiplanar conformation, and that also the N—Rh bond is extending this train of bonds in the same way. The skeleton of this ligand has thus symmetry C_s.

In the CD spectra the strongest Cotton effect shows up around 400 nm. The beginning of another one of same sign can be seen below 350 nm, and between these there must be a third one of opposite sign, because otherwise no such deep apparent minimum would be present. Another Cotton effect between 500 and 450 nm is very pronounced for *III* rather small for *I*, and not detectable for *II*. One to two smaller effects are observable at still longer wavelengths.

For the two Cotton effects below 420 nm we can derive an empirical sector rule in the following way. After unidentate ligation of the antiperiplanar skeleton of the amine to Rh the original D_{4h}-symmetry of the complex is drastically reduced. If the staggered conformation shown in Fig. 1 is the preferred one for steric reasons, only C_s-symmetry remains. According to Schellman[13] and Ruch[14] a halfspace rule* should then be valid as the symmetry determined simplest sector rule. In addition we have to consider the MO-determined nodal planes, and for any antibonding orbital the plane perpendicular to the Rh—Rh bond and cutting this in the middle of that same Rh—Rh bond will have to be added. If MO's built up from *d*-orbitals are involved in the transition, then conical nodes have to be added (cf. Fig. 2 of ref.[1]), with d_{xz}- and d_{yz}-orbitals a horizontal or vertical nodal plane is introduced, d_{xy} needs both these planes, and $d_{x^2-y^2}$ will introduce two planes in the diagonal posi-

* "Halfspace rule" is proposed in the recommendations of IUPAC (to be published) instead of the formerly used "planar" or "planarity rule".

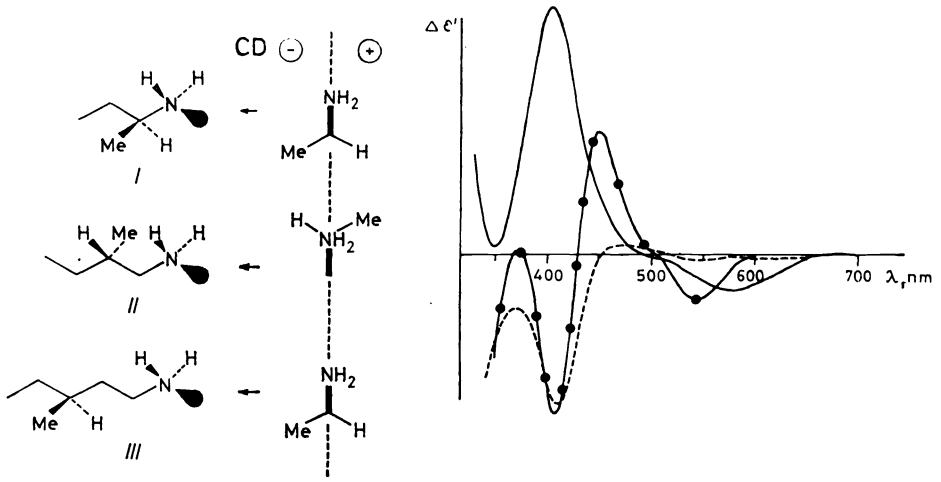


FIG. 1

Complexes between $[Rh_2(OAc)_4]$ and primary amines *I*, *II*, and *III* (left). Middle: Projection along the Rh–N bond. Right: CD-curves: *I* (– – – –); *II* (———); *III* (●—●)

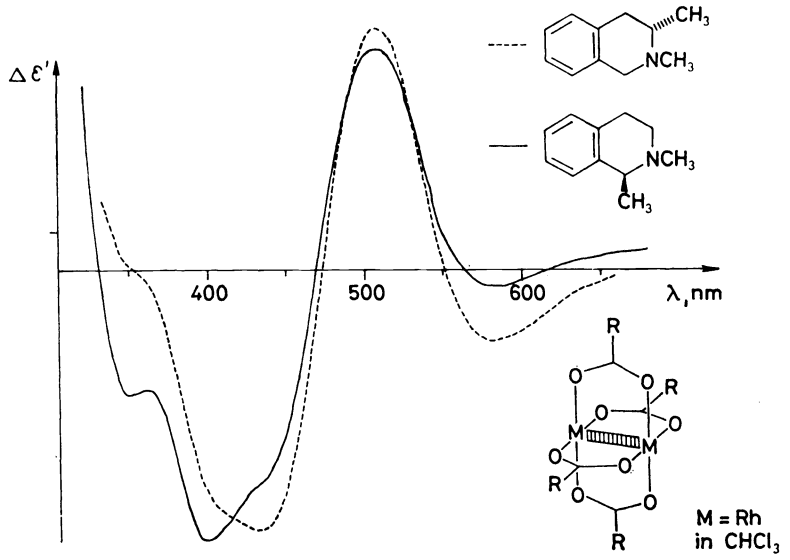


FIG. 2

CD-curves of *IX* (———) and *XVI* (– – – –) in the presence of $[Rh_2(OAc)_4]$ in chloroform

tion. Without knowledge about the parentage of each CD-band we cannot, therefore, further develop this hemisphere rule. We do not know whether additional nodal spheres must be added, but even this simple hemisphere rule can be used as a working tool successfully.[14]

If one projects from the Rh towards the N and draws the projection of the N—C(1) bond upwards, the position of the nodal plane for the halfspace rule is fixed. Figure 1 shows such a projection and indicates also the approximate position of the methyl group for *III* which lies on the right side. The additional methyl group of *I* is also positioned in this same halfspace whereas that of *II* appears on the left side. The contribution to the Cotton effects of these complexes of a group on the right side of the plane is thus negative for the CD-bands around 400 nm and below 330 nm, and positive for that between them.

Even without knowing the positions of eventual further nodal planes this rule should be applicable at least as long as the perturbing substituent is positioned in the upper halves of both halfspaces. Assuming idealized geometry the additional methyl group of *I* and *III* would e.g. fall into sectors of different sign contributions if the plane containing the acetate group is a nodal plane. As for the three most characteristic Cotton effects the CD-curves are similar, the corresponding sector rule should be simple. Differences at longer wavelengths may, however, be explained by the additional MO-determined nodal planes.

CD *of Tetrahydroisoquinolines in the Presence of* $[Rh_2(OAc)_4]$

Compounds *IX* and *XVI* both give two stronger Cotton effects of opposite signs in presence of dirhodium tetraacetate in chloroform, and these and a few other smaller effects can be seen in Fig. 2. In acetonitrile or ethanol similar effects are observed, but they develop slower or need longer heating of the solution. This seems reasonable, because in both axial positions solvent molecules are bound to the complex, and a replacement of ethanol or acetonitrile by a tertiary amine will be much more difficult than that of chloroform.

The two CD-curves are remarkably similar, so the arrangements of atoms in the next neighbourhood of the chromophore should be similar, too. For 1-alkyl substituents on tetrahydroisoquinolines like in *IX* it is known[15], that they preferentially adopt the quasiaxial conformation, however, in *XVI* the methyl group is arranged equatorially, as follows also from its NMR spectrum. Since the complex is diamagnetic, high resolution NMR spectra can be obtained, and it is deduced from the coupling constants that now this same methyl group is arranged in axial conformation. Thus indeed the conformations around the chiral centres next to the nitrogen atoms are identical, as suggested by the CD-curves, but then the nitrogen containing rings have opposite senses of helicity for *IX* and *XVI* after complexing (cf. Fig. 3).

In such a complex the nitrogen atom becomes a center of chirality and there is no easy way to determine, which configuration is the preferred one. From stereomodels we can deduce that for steric reasons in both cases the Rh is connected in equatorial fashion (Fig. 3). This mode of attachment in the Rh-complex explains also, why the conformation with axial position of the 2-methyl of *XVI* is the preferred one. Figure 3 gives furthermore the projection from Rh towards N, and for both, the complexes of *IX* and *XVI*, these are indeed identical in the next neighbourhood of the chromophore, as indicated by the CD curves. Since it is much more difficult to evaluate in such a case the preferred torsional angle around the Rh—N bond we take the projection in Fig. 3 as a working rule: the arrangement of the tertiary amine shown on the right leads to a strong positive CD around 510 nm and to an equally strong negative one between 450 and 400 nm.

The conformations deduced here explain also some other facts. If the alkyl group in 1- or 3-position becomes larger it will tend to bend outwards, and not towards or over the aromatic ring. By this the steric interaction of the amine lone pair with the $[Rh_2(OAc)_4]$ will become very weak or even impossible. On the other hand, if the groups on the nitrogen are pulled back all in one direction, as is e.g. the case with *XVII*, the α-side of this molecule is free for attack of the metal cluster and rather strong Cotton effects can then be observed.[16]

Summarizing these results one can say, that whereas for primary amines other cottonogenic derivatives are known, and they can successfully be used to determine the absolute configuration, as e.g. phthalimides[17] or salicylidene derivatives[18], no

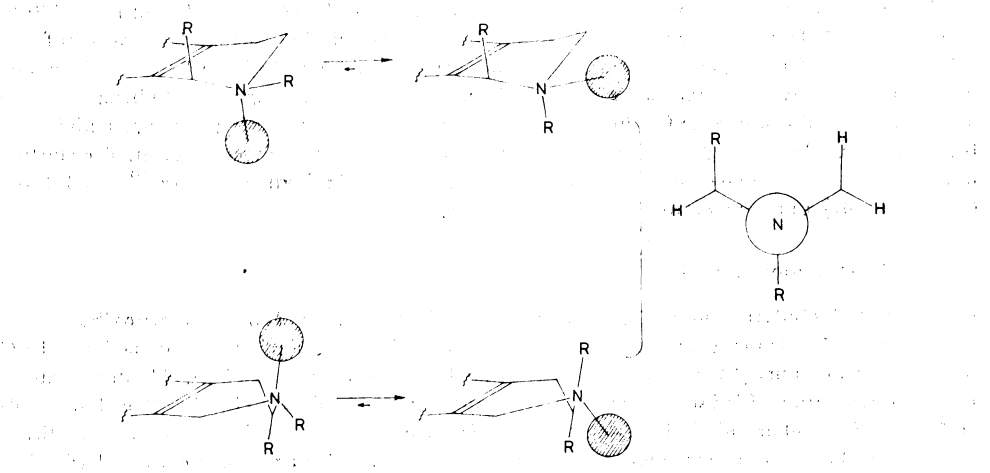
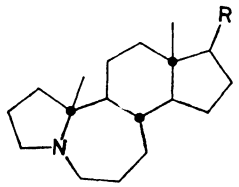


FIG. 3

Conformations of the complexes between $[Rh_2(OAc)_4]$ and amines *IX* and *XVI*. Left: main equilibrium conformations. Right: Projection of preferred conformations from Rh towards N

such method was known before for tertiary amines[19]*. This in situ method has, however, also advantages for the primary amines: we need only to put the compounds together and can measure the CD curves, whereas the other procedures need preparation, isolation, and purification of derivatives before measurement. This in situ method is, therefore, much less time- and amount-of-substance demanding than all others.



XVII

EXPERIMENTAL

NMR spectra were recorded on eiher a Varian T60, an EM360, a Bruker WP80, or an AM400 in $CDCl_3$ if not stated otherwise. Line positions are given as δ in ppm with tetramethylsilane (TMS) as internal standard. IR spectra ($\tilde{\nu}$, cm^{-1}) were recorded on a Perkin–Elmer 221 or 1310 in solution (chloroform) or neat. Optical rotations were determined with a Perkin–Elmer 141 polarimeter at room temperature. Mass spectra were taken with a Varian CH-5 or CH-7-31 spectrometer at 70 eV. The CD was measured on a Jobin–Yvon–ISA-Dichrograph Mark III at room temperature. Values are given as $\Delta\varepsilon'$ (cf. ref.[16]) since concentrations of the optically active complexes are unknown.

Column chromatography was carried out with silica gel MN 60 (0·05—0·1 mm; mesh 140 to 270). For TLC plates Alugram Sil G/UV 254 (Macherey–Nagel Co.) was used. Tetrahydrofuran (THF) was dried in argon atmosphere with lithium aluminium hydride and triphenylmethane as indicator. Diethylether was distilled from sodium wire in argon atmosphere with benzophenone as indicator. Chloroform and methylene chloride were dried by passing through activity III basic alumina (Merck); diglyme and pyridine were used without further purification. The starting material (s)-(−)-2-methyl-1-butanol was commercially available from Fluka $\{[\alpha]_D^{20} -6{\cdot}3 \pm 0{\cdot}3$ (*c* 10, ethanol)} and used without furher purification.

(s)-(+)-2-Aminobutane (*I*)

(s)-(+)-2-Methylbutyric acid (8·67 g, 85 mmol) prepared by oxidation of (s)-(−)-2-methylbutan-1-ol according to Freudenberg und Lwowsky[4], was dissolved in 150 ml of acetone, cooled to −10°C and acetone solutions (40 ml each) of 10 g (99 mmol) triethylamine and 11·9 g (110 mmol) ethylchloroformate were added simultaneously. After stirring for 30 min at −10°C, 8·45 g (130 mmol) sodium azide in 30 ml of distilled water were added dropwise to the mixture, which was stirred for another 30 min and then poured into ice water (400 ml). The azide was extracted with ice-cold toluene (3 × 70 ml) and dried over $MgSO_4$ at −10 to −20°C.

* For a few cases a Cotton effect (or its onset) has been detected for tertiary amines, cf. ref.[19].

This solution (slow decomposition at room temperature) was added dropwise into a heated (100°C) flask fitted with a reflux condenser and a dropping funnel. The reaction mixture was refluxed until evolution of nitrogen ceased, 6M-HCl was added (100 ml), and the mixture was further refluxed until no more carbon dioxide was formed. The aqueous layer was made strongly alkaline (sodium hydroxide) and the amine steam distilled into 6M hydrochloric acid. The free base was obained by evaporation of the distillate and treating the solid residue with concentrated aqueous sodium hydroxide.

Extraction with ether, drying over anhydrous Na_2CO_3 and distillation (normal pressure) at 63–64°C yielded 4·2 g (67%) (*S*)-(+)-*III*, $[\alpha]_D^{20}$ +3·9 (*c* 4·7, water). ^{1}H NMR (60 MHz): 1·00 (3 H, t); 1·03 (3 H, d); 1·16 (2 H, s); 1·3 (2 H, m); 2·80 (1 H, m). IR (neat): 3 300, 1 600.

(*S*)-N-(2-Methylbutyl)-1-phthalimide

The compound was prepared following Mitsunobu et al.[5]. Diethyl azo-dicarboxylate (29·6 g, 170 mmol) was added dropwise to a stirred solution of 10 g (113 mmol) (s)-2-methylbutan-1-ol, 44·6 g (170 mmol) triphenylphosphine, and 16·2 g (110 mmol) phthalimide in 250 ml of dry tetrahydrofuran. After stirring for 24 h the solution was evaporated and the residue purified chromatographically (silica gel, methylene chloride) to yield 22 g (91%) product as colourless oil. ^{1}H NMR (60 MHz): 0·9 (6 H, d and t); 2·0 (3 H, m); 3·55 (2 H, d); 7·7 (4 H, m). IR (neat): 1 775, 1 710. MS (*m*/*z* (%)): 217 ($M^{+\cdot}$, 29), 160 (100).

(*S*)-(−)-2-Methyl-1-aminobutane (*II*)

(*S*)-N-(2-Methylbutyl)-1-phthalimide (20 g, 92 mmol) was refluxed for 2 h with 4 ml of hydrazine hydrate (100%) in 100 ml of methanol. After cooling to room temperature the mixture was acidified with concentrated hydrochloric acid and heated for 1 h. The voluminous precipitate was filtered off, washed well with hot water, and the combined aqueous layers were evaporated to yield a residue which on treatment with concentrated aqueous potassium hydroxide solution afforded crude (*S*)-(−)-*II*. This product was distilled directly from the reaction mixture into 6M hydrochloric acid and worked up as described for (*S*)-(+)-*I*.

Kugelrohr-distillation under reduced pressure (1·6 kPa) at 40–41°C afforded 1·6 g (20%) (*S*)-(−)-2-methyl-1-aminobutane, $[\alpha]_D^{20}$ −5·4 (neat). ^{1}H NMR (60 MHz): 0·9 (6 H, d and t); 1·16 (2 H, s); 1·23 (3 H, m); 2·5 (2 H, AB-q). IR (neat): 3 300, 1 600. MS (*m*/*z* (%)): 87 ($M^{+\cdot}$, 3), 30 (100).

(*S*)-(−)-2-Methyl-1-butyl tosylate

(*S*)-(−)-2-Methyl-1-butanol (24·6 g, 279 mmol) and 55 g (289 mmol) *p*-toluenesulfonyl chloride in 100 ml of dry chloroform were cooled in an ice-bath from 0 to +3°C, then 40 g of dry pyridine were added under stirring. The solution was stirred for 24 h at room temperature and poured into a mixture of 200 g ice and 70 ml concentrated HCl. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to yield 64·8 g of a colourless oil (96%). Further drying was achieved by azeotropic distillation with benzene. ^{1}H NMR (60 MHz): 0·87 (6 H, d and t); 1·5 (3 H, m); 2·50 (3 H, s); 3·80 (2 H, d); 7·5 (4 H, AB-q).

(*S*)-(+)-2-Methyl-butyronitrile

The aforementioned tosylate was converted to the nitrile following the procedure of Pawson et al.[20]. The crude tosylate (126 g, 520 mmol) was dissolved in 600 ml of dry dimethyl sulfoxide. Sodium cyanide (38·2 g, 780 mmol) was added and the mixture stirred at 90°C for 12 h in an

atmosphere of nitrogen. It was then poured into 1·5 l of water saturated with ammonium chloride. The separating oil was collected, the aqueous layer extracted with methylene chloride (4 × 500 ml) and the organic layers were washed with water and dried ($MgSO_4$). Evaporation at room temperature and distillation (152—153°C) afforded 33 g (65%) (s)-(+)-2-methyl-butyronitrile, $[\alpha]_D^{25}$ +6·1 (neat). ^{1}H NMR (60 MHz): 1·06 (3 H, t); 1·13 (3 H, d); 1·6 (3 H, m); 2·3 (2 H, d). IR (neat): 2 230 (CN).

(*S*)-(+)-1-Amino-3-methylpentane (*III*)

Reduction of the nitrile was performed according to Brown et al.[7]. Diborane, generated by addition of a solution of 6 g (154 mmol) sodium borohydride in 120 ml of dry diglyme to 30 g (211 mmol) boron trifluoride etherate in 120 ml of dry diglyme, was passed into a solution of the nitrile (10 g, 103 mmol) in 80 ml of dry tetrahydrofuran under an atmosphere of nitrogen. After stirring overnight excess diborane was destroyed carefully with methanol and the solution acidified with gaseous HCl. Evaporation yielded an oil which was made strongly alkaline by addition of concentrated aqueous potassium hydroxide solution. Distillation (b.p. 125—126°C) and subsequent purification was carried out as described for *I* to afford 8·1 g (78%) (*S*)-(+)-1--amino-3-methylpentane, $[\alpha]_D^{25}$ +7·8 (neat). ^{1}H NMR (60 MHz): 0·9 (6 H, d + t); 1·16 (2 H, s); 1·3 (5 H, m); 2·7 (2 H, t). IR (neat): 3 300, 1 600. MS (*m/z* (%)): 101 ($M^{+\cdot}$, 1), 30 (100).

(*S*)-(—)-N-Methyl-1-phenylethylamine (*V*)

Ethylchloroformate (4·6 g, 42 mmol), was dropped at 0°C to a well stirred solution of 5 g of (*S*)-(—)-1-phenylethylamine (*IV*) (71 mmol) and 4·4 g (44 mmol) triethylamine in 100 ml of dry ether. After stirring at room temperature for 30 min the mixture was filtered, the residue was washed twice with ether (50 ml), and the combined organic layers were dried ($MgSO_4$) after extraction with dilute HCl and saturated $NaHCO_3$ solution. Evaporation yielded a crystalline solid, which was dissolved in dry tetrahydrofuran (100 ml) and added dropwise to a well stirred suspension of excess lithium aluminium hydride (8 g, 211 mmol) in 200 ml of dry tetrahydrofuran. After refluxing for 2 h excess reagent was destroyed by careful addition of concentrated aqueous potassium hydroxide, the resulting precipitate washed twice with hot tetrahydrofuran, and the combined organic layers were dried over anhydrous Na_2CO_3. Evaporation and subsequent vacuum distillation (57°C, 650 Pa) yielded 4·8 g (*S*)-(—)-N-methyl-1-phenylethylamine (87%), $[\alpha]_D^{23}$ −64·1 (*c* 4, ethanol). ^{1}H NMR (60 MHz): 1·3 (4 H, d); 2·3 (3 H, s); 3·6 (1 H, q); 7·2 (5 H, s).

Ethyl (*S*)-(—)-N-Methyl-N-(1-phenylethyl)glycinate (*VI*)

Compound *V* (2·1 g, 15·6 mmol), $NaHCO_3$ (4 g), and ethyl bromoacetate (2·5 ml, 22·6 mmol) were stirred in 100 ml of aqueous ethanol (90%) at room temperature for 15 h. The mixture was refluxed for 2 h. filtered and evaporated. The oily residue was dissolved in ethyl acetate, filtered and evaporated to give 3·3 g of crude compound *VI* (96%), which was not further purified. $[\alpha]_D^{23}$ −67·2 (*c* 0·32, ethanol). ^{1}H NMR (60 MHz): 1·20 (3 H, t); 1·40 (3 H, d); 2·40 (3 H, s); 3·2 (2 H, AB-q); 3·80 (1 H, q); 4·10 (2 H, q); 7·30 (5 H, s). IR (neat): 2 800, 1 740, 1 605, 1 495, 1 455, 700. MS (*m/z* (%)): 221 ($M^{+\cdot}$, 4), 148 (43), 105 (100), 44 (60).

(*S*)-(+)-1,2-Dimethyl-1,2,3,4-tetrahydroisoquinolin-4-one (*VIII*)

Derivative *VI* (1 g, 4·5 mmol) was stirred overnight in 50 ml of conc. HCl at 100°C. Then charcoal was added and the filtered solution evaporated to yield a colourless oil. Treatment with methylene chloride (4 × 50 ml) and subsequent azeotropic distillation gave after evaporation the amino

acid hydrochloride *VII*. HCl as a white solid, which was further dried for 1 h at 50°C in vacuum. It was dissolved in 20 ml of dry methylene chloride, cooled in an ice-bath and stirred for 1 h with 0·4 ml (4·7 mmol) of oxalylchloride. An amount of 1·20 g (9 mmol) of anhydrous aluminium chloride were added, and after stirring the reaction mixture for 3 h it was quenched with ice cold aqueous NaOH (20%). The aminoketone was extracted with methylene chloride (4 × 50 ml), the organic layers were dried ($MgSO_4$) and evaporated at room temperature to yield 0·6 g of crude *VIII* (76%). Since it decomposes quickly it was used without further purification. $[\alpha]_D^{23}$ +11·4 (*c* 0·14, ethanol). ^{1}H NMR (60 MHz, C_6D_6): 1·00 (3 H, d): 2·10 (3 H, s): 3·30 (2 H, AB-q); 3·60 (1 H, q); 6·70—7·30 (3 H, m); 8·10 (1 H, m). IR (neat): 2 800, 1 690, 1 605, 1 455, 770. MS (*m/z* (%)): 175 ($M^{+\cdot}$, 10), 160 (100), 132 (24).

(*S*)-(−)-1-Methyl-1,2,3,4-tetrahydroisoquinoline

It was prepared according to Meyers et al.[11]. The already reported low yield and poor optical purity reported by the authors could even not be realized (61% ee). Therefore recrystallization of its salt with L-(+)-tartaric acid from distilled water was necessary.

Cleavage of the hydrogentartrate with concentrated aqueous NaOH yielded then the product of high optical purity after chromatography (silica gel, ether/triethylamine 100 : 1) and distillation in the Kugelrohr. $[\alpha]_D^{23}$ −88·2 (neat). ^{1}H NMR (400 MHz): 1·45 (3 H, d); 1·60 (1 H, s); 2·73 (1 H, m); 2·85 (1 H, m); 3·02 (1 H, m); 3·25 (1 H, m); 4·10 (1 H, q); 7·12 (4 H, m). IR (neat): 3 280, 1 490, 750. MS (*m/z* (%)): 147 ($M^{+\cdot}$, 2), 146 (18), 132 (100).

(*S*)-(−)-1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline (*IX*)

a) Crude *VIII* (0·6 g, 3·4 mmol) was hydrogenated in acidified (HCl) aqueous ethanol over Pd charcoal under normal pressure. After evaporation the residue was treated with aqueous KOH and the free base extracted with ether (4 × 50 ml) and distilled under reduced pressure (1·95 kPa, 1·18°, Kugelrohr) to yield 463 mg (84%) of (*S*)-(−)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline.

b) It was also prepared from (*S*)-(−)-1-methyltetrahydroisoquinoline via its urethane derivative. This compound (1 g, 6·80 mmol) was stirred with 1 ml (10·5 mmol) of ethylchloroformate and 50 ml of dry methylene chloride for ten minutes. Saturated $NaHCO_3$ solution (50 ml) was added, followed by a catalytical amount of triethylbenzylammonium chloride; then the mixture was stirred intensely for 20 min. The organic layer was separated, the aqueous one was extracted with methylene chloride (2 × 50 ml), and the combined organic layers were evaporated after drying ($MgSO_4$). The oily residue was dissolved in 50 ml of dry tetrahydrofuran and dropped to a suspension of 1 g (26 mmol) lithium aluminium hydride in 50 ml of dry tetrahydrofuran and refluxed for 2 h. The mixture was quenched with aqueous 40% KOH, the precipitate extracted twice with hot tetrahydrofuran, and the combined organic solutions were evaporated at room temperature after drying over anhydrous Na_2CO_3. The residue was chromatographed (silica gel, ether-triethylamine 100 : 1) and distilled under reduced pressure (118°C, 1·95 kPa, Kugelrohr) to yield 814 mg *IX* (74%), $[\alpha]_D^{23}$ −45·2 (*c* 0·4, ethanol). ^{1}H NMR (60 MHz): 1·40 (3 H, d); 2·40 (3 H, s); 2·8 (4 H, m); 3·60 (1 H, q); 7·00 (4 H, s). IR (neat): 2 790, 1 610, 1 585, 1 500, 760, 735 .MS (*m/z* (%)): 161 ($M^{+\cdot}$, 4), 147 (100).

(*S*)-(+)-3-Methyl-1,2,3,4-tetrahydroisoquinolin-1-one (*XIII*)

(*S*)-(−)-2-Ethoxycarbonylamino-1-phenylpropane (*XII*) (5 g, 24 mmol) prepared from L-alanine via *X* and *XI* according to Buckley III et al. [12] were added to 100 g of mechanically stirred polyphosphoric acid and heated in an oil bath to 120 to 140°C until the evolution of gas ceased.

The hot reaction mixture was poured onto water/ice. The yellow precipitate was filtered off, the aqueous layer extracted with chloroform (8 × 100 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The combined solids were purified by chromatography (silicagel, ethyl acetate) and recrystallized from cyclohexane to afford 3·60 g *XIII* (93%, m.p. 143—145°C). $[\alpha]_D^{20}$ +93·4 (*c* 0·45, methanol). ^{1}H NMR (80 MHz): 1·30 (3 H, d); 2·6—3·2 (2 H, ABX, J_{AB} = 16·2 Hz); 3·6—4·2 (1 H, ABX, J_{AX} = 1·8 Hz, J_{BX} = 13 Hz); 5·9 (1 H, m); 7·2—7·7 (3 H, m); 82—8·8 (1 H, m). IR ($CHCl_3$): 3 400, 1 665, 1 605, 1 575, 1 465, 700. MS (*m/z* (%)): 161 ($M^{+\cdot}$, 22), 146 (100), 128 (32), 118 (90), 90 (58).

(*S*)-(+)-3-Methyl-1,2,3,4-tetrahydroisoquinoline (*XIV*)

Compound *XIII* (5 g, 31 mmol) was reduced with 1·6 g lithium aluminium hydride (42 mmol) in 100 ml of boiling dry tetrahydrofuran. After completion of the reaction (TLC) excess of reagent was hydrolyzed by careful addition of conc. aqueous KOH, the precipitate was filtered off, washed with hot tetrahydrofuran, and the combined organic layers were dried over anhydrous K_2CO_3. Evaporation and distillation in a Kugelrohr-apparatus (118°C, 2·26 kPa) yielded 3·4 g *XIV* (74·5%). $[\alpha]_D^{23}$ +118·9 (*c* 0·2, ethanol). ^{1}H NMR (80 MHz): 1·23 (3 H, d); 1·55 (1 H, s); 2·3—3·2 (3 H, m); 4·05 (2 H, AB-q); 7·05 (4 H, m). IR (neat): 3 300, 1 580, 1 490, 740. MS (*m/z* (%)): 147 ($M^{+\cdot}$, 16), 146 (22), 131 (87), 104 (100).

(*S*)-(+)-2,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline (*XVI*)

Compound *XIV* (300 mg, 2 mmol) was reacted with 0·7 g (6·5 mmol) of ethyl chloroformate in 50 ml of methylene chloride. After stirring for 10 min, a saturated aqueous solution of 50 ml $NaHCO_3$ solution and a catalytic amount of triethylbenzylammonium chloride were added and the mixture stirred extensively for 10 min. The aqueous layer was separated, extracted with methylene chloride (2 × 50 ml), and the organic layers were dried ($MgSO_4$) and evaporated. The solid residue (*XV*) was dissolved in dry tetrahydrofuran (50 ml) and dropped to a boiling, well stirred suspension of 2 g lithium aluminium hydride in 50 ml of dry tetrahydrofuran. Boiling was continued for 2 h, then the reaction was quenched by careful addition of concentrated aqueous KOH, and the resulting precipitate was filtered off and washed with hot tetrahydrofuran. Evaporation of the combined organic layers after drying (anhydr. K_2CO_3) left an oil, which was purified by chromatography (silica gel, ether/triethylamine 100 : 1) and distilled (Kugelrohr 120°C, 2·26 kPa) to yield 279 mg *XVI* (87%). $[\alpha]_D^{23}$ +86·3 (*c* 2·1, ethanol). ^{1}H NMR (400 MHz): 1·14 (3 H, d); 2·38 (3 H, s); 2·63 (2 H, m); 2·83 (1 H, m); 3·65 (2 H, AB-q); 7·06 (4 H, m). IR (neat): 2 790, 1 660, 1 590, 1 500, 745, 735. MS (*m/z* (%)): 161 ($M^{+\cdot}$, 10), 160 (14), 146 (100), 104 (48).

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