180. EPC-Synthesis of Tetrahydroisoquinolines by Diastereoselective Alkylation at the 1-Position of Phenylalanine-Derived Precursors. Synthesis of the Alkaloid (+)-Corlumine¹)

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The 1,2,3,4-tetrahydro-*N*-pivaloyl-isoquinoline-3-carboxylic acids 1d, 2d, and 3d, derived from (*R*)- or (*S*)-phenylalanine, (*S*)-dopa, and (*S*)- α -methyldopa, respectively, are doubly deprotonated with (*tert*-butyl)lithium in THF and alkylated at the 1-position (products 5–10). The major diastereoisomers formed are the result of electrophilic attack from the face opposite to the carboxylate group (rel. topicity *ul*-1,3). Even the addition to benzaldehyd (\rightarrow 7, 8) is highly stereoselective (*one* of four diastereoisomers is formed exclusively (300-MHz ¹H-NMR analysis)), if MgBr₂-etherate is added prior to the electrophile. Some of the obtained amino-acid derivatives are decarboxylated by anodic oxidation in MeOH (\rightarrow 11, 12, 17) and NaBH₃CN reduction, and converted to the known 1-methyl- and 1-benzyltetrahydroisoquinolines (15, 16) of >95% ee as well as to the phthalide isoquinoline alkaloid (+)-corlumine of \geq 80% ee. The synthetic approach described here is compared with other methods of synthesizing enantiomerically pure 1-substituted tetrahydroisoquinolines (and thus an important group of alkaloids, *Scheme 1*).

1. Methods of EPC-Synthesis of Tetrahydroisoquinolines. – All possible methods of synthesizing enantiomerically pure compounds (EPC [2–5]) have been applied to obtain tetrahydroisoquinolines A (*Scheme 1*): a) resolution, b) catalytic and c) stoichiometric enantioselective reactions as well as d) e) the incorporation of components from the pool of chiral building blocks [11]. Analogous routes lead to the tetrahydrocarboline skeleton [12]. Both heterocyclic systems are part of numerous alkaloids [13].

After having found [1] [14] that 1-magnesio-2-pivaloyl-tetrahydroquinolines add to aldehydes and unsymmetrical ketones with almost exclusive formation of one diastereoisomer, which can be cleanly epimerized to the other one, and after having applied this reaction to the synthesis of *rac*-ushinsunine and oliveroline (aporphine), ophiocarpine and epi-ophiocarpine (berberine), and β -hydrastine (phthalide alkaloid), we investigated analogous transformations (f) in Scheme 1) with chiral, non-racemic tetrahydroisoquinoline-3-carboxylic acids. These are available from aromatic amino acids such as phenylalanine. Diastereoselective hydroxyalkylation and decarboxylation would lead to the enantiomerically pure alkaloids.

¹) Part II of an investigation on diastereoselective C,C-bond formation in the 1-position of 1,2,3,4-tetrahydroisoquinolines. For part I, see [1].

²) Part of the Ph. D. thesis by I. M. P. H., Dissertation No. 8397, ETH Zürich, 1987.





2. Preparation of the Starting Materials. – The N-pivaloyltetrahydroisoquinolinecarboxylic acid 1d was obtained in the following way: (S)- or (R)-phenylalanine was subjected to a *Pictet-Spengler* cyclization (CH₂O/HCl) [15] and the partially racemized product 1a esterified to the benzyl ester 1b, the tosylate salt of which was recrystallized to high enantiomeric purity [16]. N-Pivaloylation (\rightarrow 1c) and hydrogenolysis gave the desired acid 1d and *ent*-1d, respectively. The analogous 6,7-dimethoxy compound 2d was obtained from the carboxylic acid 2a (which was supplied to us by the *Warner-Lambert Company* (USA) and which had been made from an (S)-dopa derivative as described in a patent [17]) through the benzyl ester 2b and the pivaloyl ester 2c. The 3-methyl-6,7dimethoxy derivative 3d was prepared from the dimethyl ether of (S)- α -methyldopa and formalin; the intermediate 3a was directly converted to the amide 3d in high yield, using a method recommended for peptide synthesis [18] (pivaloyl chloride N,N-di-



 $Bn = CH_2C_6H_5$ and Piv. = t-BuCO(in all Schemes)

ethyl(trimethylsilyl)amine/Et₃N). Finally, the formyl(methylendioxy)benzoate 4c which we required as aldehyde component in the (+)-corlumine synthesis (see Sect. 5) was made from piperonal (4a), as described by Ziegler [19], through the lithiated Schiff base 4b.

3. Dilithiation of the Tetrahydroisoquinolinecarboxylic Acids 1d, 2d, and 3d and Reactions with Electrophiles. – Treatment of the acids with 2 equiv. of (*tert*-butyl)lithium in tetrahydrofuran (THF) gave deep red solutions which were combined with electrophiles such as CH_3I , benzyl bromide, benzaldehyde, and the formyl ester 4c. The 1-methyl and 1-benzyl derivatives 5 and 6, respectively were isolated a single diastereoisomers in yields of *ca.* 80%. The benzaldehyde adduct 7 was formed in 75% yield. It consisted of a 1:1 mixture of diastereoisomers, if the Li derivative was directly combined with the



aldehyde, while a single diastereoisomer **7a** was isolated if a transmetallation was carried out with MgBr₂-etherate prior to aldehyde addition. Treatment with HCl/MeOH converted the hydroxy-amido acid **7** into the amino diester **8** (*cf.* [1]). To our surprise, the product **9** (68% yield) from the highly substituted aldehyde **4c** and the dimethoxy derivative **2d** was not formed stereoselectively, inspite of MgBr₂ addition after lithiation. This is only the second case in which a Mg derivative of this type has failed to produce a single diastereoisomer, the other being a more unfavorable addition to a ketone [1] (see also comment in the *Exper. Part*). Finally, no product of methylation was obtained from the methyl-dopa-derived **3d** and (*tert*-butyl)lithium/CH₃I; instead, two diastereoisomeric dimers **10** were formed (*cf.* [1] [20]).

4. Configuration of the 1-Substituted Tetrahydroisoquinoline-3-carboxylic Acids 5–10. – The constitution of these products (alkylation at C(1) and not at C(3)) follows clearly from the ¹H-NMR spectra measured at 100° in dimethylsulfoxide (rotamers at lower temperature!), see *Exper. Part.* The configuration of the derivatives 5, 6, and 9a was determined by chemical correlation to be *trans*, and we assume that the major stereo-isomers a of 7, 8, and 10 have the same *trans*-disposition of COOH and the newly introduced substituent at C(1).

The correlation of the two alkylation products 5 and 6 with the parent (R)-1-methyland (R)-1-benzyltetrahydroisoquinoline 15 and 16, respectively, is outlined in *Scheme 2*.



In the first step, the COOH group is removed. Of the methods to do this (*e.g.* through the corresponding nitril [21] or acyl chloride [22]), we chose the electrochemical reaction [23] [24] which was successfully applied to non-racemic amino-acid derivatives before [25–27]. The methoxy compounds **11** and **12** resulting from the anodic oxidative decarboxylation were reduced under acidic conditions with sodium cyanoborohydride (review, see [28]) in MeOH, and the pivalamides **13** and **14** cleaved³) to 1-methyl and 1-benzyltetrahydroiso-quinolines **15** and **16**, respectively, by reduction with sodium aluminum hydride [32]. The specific rotations of the two products indicated that they were of \ge 96% enantiomeric excess (ee), and that their chirality sense is (*R*) (comparison with the data in [33]). The configuration of the major diastereoisomer **9a** was determined by conversion to the alkaloid (+)-corlumine (see Sect. 5).

5. Synthesis of the Phthalide Alkaloid (+)-Corlumine (19) from 9. -(+)-Corlumine (19, see Scheme 3) has been isolated from several different plants, belonging to the



a) +2e/CH₃OH; b) NaCNBH₃/H⁺; c) chrom. separation; d) KOH/EtOH, Δ ; e) H₂NNH₂; f) CH₂O/H⁺

³) The reductive cleavage with NaAlH₂(OCH₂CH₂OCH₃)₂ used previously by us [29] was not successful here. Also, Na₂O₂ [30], KOH/H₂NNH₂/glycol [31], and carefully controlled amounts of LiAlH₄ did not cleave satisfactorily. Even in the case of NaAlH₄, the conditions had to be carefully optimized, and they turned out to be somewhat different for optimum yields in the two cases 13 and 14, see *Exper. Part.*

Fumariaceous family [34] found along the North American pacific coast line; it is the main alkaloid in the root of the himalayan medicinal plant *Corydalis govaniana* [35]. The enantiomeric (-)-corlumine was recently isolated by *Shamma* [36] from *Eumeria parviflora*. The configuration of these enantiomeric alkaloids is u, and the chirality sense of the (+)-form **19** was assigned (3R, 1'S) [37]. We are aware of only one synthesis of the alkaloid [38], in its racemic form.

Electrochemical decarboxylation of crude $9 (\rightarrow 17)$ and cyanoborohydride reduction gave a readily separated mixture of the two epimeric *N*-pivaloyl-lactones **18a** and **18b**. The prevailing stereoisomer **18a** must have (3R, 1'S)-configuration because it is converted to the dextrorotatory natural product upon removal of the pivaloyl group by a procedure which we developed for the synthesis of racemic phthalide tetrahydroisoquinoline alkaloids [1] and subsequent *N*-methylation⁴). The isolated alkaloid had an enantiomeric excess of *ca.* 80% as judged by optical comparison⁵).

6. Conclusion. – Although we have done most of the conversions of the products **5–9** with small amounts of material, with the goal of establishing configurations and, thus, the steric course of the reactions, it appears fair to state that, operationally, our method of preparing enantiomerically pure tetrahydroisoquinoline derivatives is not more elaborate than the known convergent ('C,C-connective') routes shown in *Scheme 1*. No chiral auxiliary has to be prepared and recovered. Higher functionalized derivatives are available⁶) and additional stereogenic centers may be created selectively⁷) in the C,C-bond-forming process (*cf.* **7**, **8**) presented here. A catalytic enantioselective hydrogenation (*b*) in *Scheme 1*) is certainly superior on an industrial scale for production of the simple alkyl or benzyl derivatives, granted that the catalyst is not too expensive and the turnover number high.

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⁶) Thus, the carboxylic groups of our intermediates can be converted to other functional groups (see i), and the products of electrolysis can be used for introduction of a double bond to give dihydroisoquinolines (see ii)²).



⁷) In view of the numerous cases of diastereoselective additions to aldehydes and ketones (7, 8, and *ref.* [1]), the non-selective reaction in the above corlumine synthesis (see 9) ought to be considered an accident!

⁴) Depivaloylation of the *l*-epimer **18b** on a small scale did not succeed under the same conditions. This is the more surprizing since in other cases [1], similar phthalide alkaloide precursors of *l*-configuration had been cleaved by this procedure.

⁵) The fact that only two diastereoisomers 9 had been detected would indicate that partial racemization has occurred *en route* from 9a to corlumine. Since the ratios 9a/9b and 18a/18b were the same, and since we do not see a mechanism by which both stereogenic centers should be inverted simultaneously, we are led to believe that the optical comparison is unreliable due to impurities (corlumine is reported to show an optical rotation of 0° in MeOH, the solvent for recrystallization, and of 77° in CHCl₃). See also *Footnote* 8 in the *Exper. Part.*

Experimental Part

1. General. - For the equipment, spectrometers and techniques used, see [1].

Electrolyses. A potentiostat/galvanostat *Amel*, model 552, coupled with a Coulomb meter *Hengstler 794,4* was used. The oxidative decarboxylations were carried out in undivided cells (volumes from 50 to 150 ml) with cooling jackets, with the current kept constant. Anode: $1-4 \text{ cm}^2$ rotating Pt disc, cathode: Pt net. The rotating electrode (2000 rpm) provided sufficient stirring. For further details, see [25] [39].

2. Starting Materials. – Benzyl (3S)-1,2,3,4-Tetrahydroisoquinolin-3-carboxylate (1b) was prepared as described in [15] [16].

Benzyl (3S)-1,2,3,4-*Tetrahydro-2-pivaloylisoquinoline-3-carboxylate* (1c). By pivaloylation of 1b, following procedure [1][29]. Yield 70%, oil. $[\alpha]_D = -21.2^{\circ} (c = 1.1, MeOH)$. IR (CHCl₃): 3080, 3040, 2690, 1745, 1635, 1415, 1390, 1370, 1185, 1120, 760, 705. ¹H-NMR (90 MHz, CDCl₃): 7.4–6.9 (*m*, 4 arom. H); 5.25 (*t*, *J* = 4.5, H–C(3)); 5.05 (*s*, PhCH₂); 4.94, 4.59 (*AB*, *J_{AB}* = 14.4, 2 H–C(1)); 3.2, 3.15 (2*s*, each 1 H, 2 H–C(4)); 1.3 (*s*, *t*-Bu).

(3S)-1,2,3,4-Tetrahydro-2-pivaloylisoquinoline-3-carboxylic Acid (1d). A suspension of 2 g (5.6 mmol) of 1c and 0.27 g of 10% Pd/C in 30 ml of EtOH/H₂O 3:1 was stirred under H₂ at r.t. overnight. Evaporation of the solvents and recrystallization from CH₂Cl₂/petroleum ether gave 1.1 g of 1d. M.p. 158–160°. [α]_D = -26.6° (c = 1.2, MeOH). IR (KBr): 3420 (br.), 2960m, 2920m, 1730s, 1595s, 1580s, 1425m, 1370m, 1180s, 975m. ¹H-NMR (300 MHz, CDCl₃): 7.23–7.11 (m, 4 arom. H); 5.11 (t, J = 6, H–C(3)); 4.97, 4.57 (*AB*, $J_{AB} = 15.9$, 2 H–C(1)); 3.21–3.17 (m, 2 H–C(4)); 1.33 (s, t-Bu). ¹³C-NMR (20 MHz, CDCl₃): 177.87 (s); 175.87 (s); 133.19 (s); 132.65 (s); 128.21 (d); 127.32 (d); 126.89 (d); 125.82 (d); 54.33 (d); 46.35 (t); 38.86 (s); 30.56 (t); 28.12 (q). MS: 262 (1.8, $M^{++} + 1$), 261 (7, M^{++}), 176 (61.5), 158 (5.4), 132 (37.3), 130 (31.9), 57 (100). Anal. calc. for C₁₅H₁₉NO₃·0.25 H₂O (265.83): C 67.96, H 7.39, N 5.26; found: C 67.75, H 7.30, N 5.26.

(3R)-1,2,3,4-Tetrahydro-2-pivaloylisoquinoline-3-carboxylic Acid (ent-1d). Exactly as 1d, but starting from (R)-phenylalanine. M.p. 159–160°. [α]_D = +26.5° (c = 1.0, MeOH).

Benzyl (3S)-1,2,3,4-*Tetrahydro-6*,7-*dimethoxy-2-pivaloylisoquinoline-3-carboxylate* (2c). Following the procedure for esterification of 2a in [17] and that for pivaloylation of the parent benzyl ester 2b in [1][29], an 84% yield of 2c was obtained. M.p. 97–98°. [α]_D = +26.59° (*c* = 0.995, MeOH). IR (KBr): 3060w, 3020w, 3000m, 2940m, 2830w, 1745s, 1640s, 1520s, 1465m, 1410m, 1265s, 1175s, 1120s, 1000m. ¹H-NMR (300 MHz, CDCl₃): 7.29–7.03 (*m*, 5 H); 6.59 (*s*, 1 H); 6.55 (*s*, 1 arom. H); 5.36 (br. *s*, H–C(3)); 5.09, 5.05 (*AB*, J_{AB} = 12.3, 2 H–C(1)); 4.87, 4.54 (*AB*, J_{AB} = 16, PhCH₂); 3.84 (*s*, 2 CH₃O); 5.37, 3.17, 3.08 (*ABX*, J_{AB} = 15.7, J_{BX} = 3.7, J_{AX} = 5.7, 2 H–C(4)); 1.32 (*s*, *t*-Bu). ¹³C-NMR (20 MHz, CDCl₃): 177.0 (*s*); 170.77 (*s*); 148.09 (*s*); 135.44 (*s*); 128.14 (*d*); 127.87 (*d*); 127.77 (*d*); 124.21 (*s*); 111.34 (*d*); 109.15 (*d*); 66.50 (*t*); 55.84 (*q*); 55.76 (*q*); 54.02 (*d*); 45.00 (*t*); 38.70 (*s*); 30.35 (*t*); 27.99 (*q*). MS: 412 (2.1, M^{++} + 1), 411 (4.6, M^{++}), 327 (35.6), 326 (98.7), 321 (15.1), 230 (78.4), 237 (16.0), 236 (100.0), 190 (99.7), 91 (83.4), 57 (96.3). Anal. calc. for C₂₄H₂₉NO₅ (411.50): C 70.5, H 7.10, N 3.40; found: C 69.57, H 7.21, N 3.21.

(3S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline-3-carboxylic Acid (2d). Following the procedure given above for 1d, from 6.34 g (15.4 mmol) of 2c, 4.0 g (83%) of 2d were obtained. $[\alpha]_D = +62.6^\circ$ (c = 0.92, MeOH). IR (KBr): 3420 (br.), 3080m, 2970s, 2840m, 1730s, 1630m (sh), 1615m, 1575s, 1520s, 1265s, 1230s, 1120s, 985m. ¹H-NMR (300 MHz, CDCl₃): 6.65 (s, 1 H); 6.59 (s, 1 arom. H); 5.27 (t, J = 5.8, H–C(3)); 4.90, 4.54 (*AB*, $J_{AB} = 15.9$, 2 H–C(1)); 3.853, 3.850 (2s, 2 CH₃O); 3.21–3.04 (m, 2 H–C(4)); 1.33 (s, t-Bu). ¹³C-NMR (20 MHz, CDCl₃): 177.67 (s); 175.14 (s); 148.10 (s); 124.55 (s); 124.24 (s); 111.46 (d); 109.22 (d); 55.91 (q); 55.83 (q); 53.75 (d); 45.73 (t); 38.76 (s); 29.86 (t); 27.99 (q). MS: 322 (3.2, $M^{++} + 1$), 321 (16.9, M^{++}), 303 (5.3), 275 (2.5), 246 (15.8), 236 (33.5), 221 (26.8), 176 (39.3), 164 (11.5), 146 (5.7), 57 (100).

(3S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methylisoquinoline-3-carboxylic Acid Hydrochloride (3a \cdot HCl). A soln. of 50 g of (S)-3-(3,4-dimethoxyphenyl)-2-methylalanine (\equiv L-methyl-dopa; 220 mmol) in 155 ml of conc. soln. HCl and 45.5 ml of aq. CH₂O soln. (*ca.* 37%) was heated at reflux for 20 min. Concentration to 150 ml and cooling in ice led to precipitation of 3a \cdot HCl. After washing with cold H₂O and acetone, 59 g (98%). [α]_D = -14.9° (*c* = 1, MeOH). Anal. data, see [22].

(3S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methyl-2-pivaloylisoquinoline-3-carboxylic Acid (3d). Addition of 3.5 ml (22.2 mmol) of N,N-dimethyl(trimethylsilyl)amine to a soln. of 5 g (17 mmol) of 3a ·HCl in 50 ml of CH₂Cl₂ under Ar was followed by 3 h of heating at reflux. After cooling to 25°, combining with 2.1 ml (17 mmol) of pivaloyl chloride, stirring for 5 min, and cooling to -5°, 2.5 ml (18 mmol) of Et₃N was slowly added and stirring continued for 2 h at r.t. The soln. was washed with 2N aq. HCl and H₂O, dried (MgSO₄), and evaporated. The residue was dried (high vacuum) and recrystallized from EtOAc to give 5.0 g of 3d ·EtOAc (85%). M.p. 110–112°. [α]_D = -33.1° (c = 1.0, MeOH). IR (KBr): 3400 (br.), 2980m, 2840w, 1740m, 1710m, 1630s, 1520s, 1410m, 1365m, 1340m, 1230m, 1170s, 1115s, 1000w. ¹H-NMR (300 MHz, CDCl₃): 6.75, 6.71 (2 s, 2 arom. H); 4.70, 4.59 (*AB*,

 $J_{AB} = 14.4, 2 \text{ H}-\text{C}(1)$; 3.88 (*s*, 2 CH₃O); 3.21, 2.77 (*AB*, $J_{AB} = 14.8, 2 \text{ H}-\text{C}(4)$); 1.37 (*s*, CH₃), 1.33 (*s*, *t*-Bu). ¹³C-NMR (75 MHz, CDCl₃): 178.78 (*s*); 176.64 (*s*); 148.85 (*s*); 147.94 (*s*); 127.24 (*s*); 126.34 (*s*); 111.67 (*d*); 109.21 (*d*); 62.28 (*s*); 56.33 (*q*); 56.24 (*q*); 47.30 (*t*); 39.58 (*t*); 38.86 (*s*); 28.12 (*q*); 21.48 (*q*). MS: 336 (< 1, M^{++} + 1), 335 (3.5, M^{++}), 290 (2.2), 250 (5.3), 234 (7.0), 206 (20.2), 203 (30.1), 190 (10.7), 160 (13), 57 (100). Anal. calc. for C₂₂H₃₃NO₇· $\frac{1}{2}$ H₂O (432.52, including 1 equiv. of EtOAc): C 61.11, H 7.87, N 3.24; found: C 61.23, H 7.87, N 2.99.

Ethyl 6-Formyl-2,3-(methylenedioxy)benzoate (4c). Following exactly the procedure given in [19].

3. Products from the Dilithiated Tetrahydroisoquinolines and Alkyl Halides. – General Procedure (GP 1). To a soln. of 5 mmol of 1d, ent-1d, or 3d in 60 ml of THF stirred at -75° were added 6.7 ml (10 mmol) of t-BuLi (1.5m in hexane). The deep red soln. formed after 1.5 h stirring was quenched with 5.5 mmol of alkyl halide and stirring continued at -75° overnight. The resulting yellow soln. was poured into 100 ml of H₂O, extracted 2 times with 20 ml of Et₂O, and the aq. phase acidified with 2N HCl. Extraction (3 times with 40 ml of CH₂Cl₂), drying (MgSO₄), and evaporation gave the crude product which was purified by FC and recrystallization.

(1R,3S)-1,2,3,4-Tetrahydro-1-methyl-2-pivaloylisoquinoline-3-carboxylic Acid (5). From 1.3 g (5.0 mmol) of 1d and 0.62 ml (10 mmol) of Mel following *GP* 1, 1.36 g (98%) of 5. M.p. 163–164° (CH₂Cl₂/petroleum ether). IR (KBr): 3400 (br.), 2960s, 2690m, 2570m, 1740s, 1590s, 1580s, 1410m, 1370m, 1120m, 940m, 760m, 755m. ¹H-NMR (300 MHz, CDCl₃, 25°): 8.6–8.0 (br., COOH); 7.20–7.06 (m, 4 arom. H); 5.34 (q, J = 6.5, H–C(1)); 5.30–3.25 (br., H–C(3)); 3.25–3.19 (m, 2 H–C(4)); 1.61–1.45 (br., CH₃); 1.27 (s, t-Bu). MS: 275 (1.9, M^+), 260 (5.0), 242 (2.5), 190 (11.6), 176 (12.7), 149 (30.7), 130 (15.9), 57 (100). Anal. calc. for C₁₆H₂₁NO₃ (275.35): C 69.79, H 7.69, N 5.09; found: C 69.49, H 7.72, N 5.10.

(1 R,3 S)-1-Benzyl-1,2,3,4-tetrahydro-2-pivaloylisoquinoline-3-carboxylic Acid (6). From 1.3 g (5 mmol) of 1d and 0.65 ml (5.5 mmol) of benzyl bromide following *GP* 1, 1.43 g (81%) of 6 after FC (Et₂O/CHCl₃/AcOH 7:3:0.1). M.p. 193–194° (CH₂Cl₂/petroleum ether). $[\alpha]_D = -12.43°$ (c = 0.96, MeOH). IR (KBr): 3420 (br.), 3020m, 2960m, 1740s, 1610m, 1575s, 1480w, 1450w, 1410m, 1365m, 1190s, 925w, 765m. ¹H-NMR (300 MHz, (D₆)DMSO, 98.5°); 12.2–11.0 (br., COOH); 7.12–7.02 (m, 6 H); 6.78–6.73 (m, 3 arom. H); 5.35 (t, J = 6, H–C(1)); 4.85 (t, J = 4.2, H–C(3)); 3.04–2.98 (m, PhCH₂, H_{ax}–C(4)); 2.76–2.60 (m, H_{eq}–C(4)); 1.21 (s, t-Bu). MS: 352 (< 1, M^{++} + 1), 260 (42.4), 216 (7.3), 176 (55.5), 149 (13.6), 130 (50.3), 57 (100). Anal. calc. for C₂₂H₂₅NO₃ (351.45): C 75.19, H 7.17, N 3.99; found: C 75.19, H 7.20, N 3.89.

(1S,3R)-Enantiomer ent-6. Exactly like 6, from ent-1. M.p. 192–193°, opposite sense for $[\alpha]_D$.

1,1',2,2',3,3',4,4'-Octahydro-6,6',7,7'-tetramethoxy-3,3'-dimethyl-2,2'-pivaloyl-[1,1'-biisoquinoline]-3,3'-dicarboxylic Acid (10). From 1.7 g (5 mmol) of 3d and 0.65 ml (10 mmol) of MeI following *GP 1* (FC with Et₂O/MeOH/ AcOH 3:2:0.1), 1.6 g (90%) of 10a/10b (cf. Footnote 14 in [1]). IR (KBr): 3430 (br.), 2970m, 2870w, 2840w, 2740-2340, 1705s, 1645s, 1620s, 1595 (sh), 1520s, 1390m, 1360s, 1290s, 1230s, 1110m, 1010w, 880w, 845w. ¹H-NMR (300 MHz, (D₆)DMSO, 98.5°; 10a/10b): 6.76/6.70 (s, 1 arom. H); 6.42/6.38 (s, 1 arom. H); 5.14/5.05 (s, H-C(1)); 3.76/3.75 (s, CH₃O); 3.69/3.67 (s, CH₃O); 3.11-3.04 (m, 1 H); 2.73-2.62 (m, H-C(4)); 1.37/1.27 (s, CH₃); 1.23/1.18 (s, t-Bu). MS: 335 (1.2), 279 (10.1), 250 (94.6), 235 (45.3), 206 (46.8), 204 (100), 188 (10.3), 174 (4.1), 131 (3.5), 57 (9.5). Mol. wt. calc. for 10: 668.76.

4. Adducts of the Tetrahydroisoquinolinecarboxylic Acids to Benzaldehydes. – General Procedure (GP 2). The soln. of 5 mmol of 1d or 2d in 60 ml of THF was combined with 6.7 ml (10 mmol) of 1.50m t-BuLi (in hexane) at -75° . After 1.5 h at -75° , 3.9 ml (10 mmol) of MgBr₂·OEt₂[1] [40] was added all at once to the stirred deep red mixture. The cooling bath was removed, and after 15 min at 0°, the mixture was recooled to -75° . The aldehyde (5.5 mmol; neat C₆H₅CHO or THF soln. of 4c, ca. 10 ml/g) was added and stirring continued at -80° overnight, before pouring into 100 ml H₂O and working up.

(3 R)-1,2,3,4-Tetrahydro-1-(α -hydroxybenzyl)-2-pivaloylisoquinoline-3-carboxylic Acid (7a). Following GP 2, 1.3 g (5 mmol) of ent-1d and 0.55 ml (5.5 mmol) of benzaldehyde gave 1.08 g (58%) of 7a, single diastereoisomer [probably (1 $R, \alpha S$) configuration, *i.e.* coupling of the trigonal centers with rcl. topicity *ul* (as with the achiral tetrahydroisoquinoline analogues [1]), and approach of the aldehyde from the face opposite to the COOLi group (rel. topicity *ul*-1,3 as with the alkyl halides above)]. FC with EtOAc/hexane/AcOH 10:15:0.2 gave a colorless powder which was not further purified. [α]_D = +18.9° (c = 0.79, CHCl₃). IR (KBr): 3600m, 3400 (br.), 3030m, 2970s, 1740s, 1720m (sh), 1600s, 1580s, 1480m, 1450m, 1410m, 1365m, 1180s, 1050m, 760m, 700m. ¹H-NMR (300 MHz, (D₆)DMSO, 98.5°): 7.24–7.02 (m, 7 H); 6.83–6.78 (m, 1 arom. H); 6.12 (d, J = 7.3, 1 arom. H); 5.36 (d, J = 1.9, H–C(1)); 5.10 (d, J = 1.9, H–C(α)); 5.04 (ABX, $J_{AX} + J_{BX} = 8$, H–C(3)); 4.90–4.70 (m, OH); 3.50, 3.05 (ABX, $J_{AX} = 5$, $J_{BX} = 3$, $J_{AB} = 14.8$, 2 H–C(4)); 1.24 (s, t-Bu). ¹³C-NMR (75 MHz, CDCl₃, r.t.; both rotamers): 18.1.34, 175.25 (2s); 176.82, 173.07 (s); 140.74; 136.31; 133.42; 133.07; 129.75; 128.96; 128.74; 128.11; 127.95; 127.54; 127.24; 126.62; 126.19; 79.99, 76.38 (2d); 64.39, 56.97 (2d); 58.42, 52.82 (2d); 40.14, 38.82 (2s); 32.34, 29.46

(2t); 28.58, 26.98 (2q). MS: 368 (< 1, M^{++} + 1), 322 (< 1), 266 (1.8), 243 (3.0), 220 (4.7), 176 (100), 130 (32), 57 (14.6).

Methyl (3 R)-1,2,3,4-Tetrahydro-1- $\{\alpha$ -(pivaloyloxy)benzyl]isoquinoline-3-carboxylate (8). Following the procedure given in [1], 0.4 g (1.06 mmol) of **7a** were heated at reflux with MeOH/HCl (causing both esterification, and pivaloyl migration with retention of configuration [1] from N to O) for 5 h to give, after FC (Et₂O/pentane 1:1), 0.27 g (66%) of **8** (single diastereoisomer, probably of (1*R*, α S) configuration, see above **7a**). [α]_D = +6.1° (*c* = 1, MeOH), [α]_D = +3.46° (*c* = 0.98, CHCl₃). 1R (CHCl₃): 3020w, 2980w, 2870w, 1730s (br.), 1480m, 1150s, 1030w. ¹H-NMR (300 MHz, CDCl₃): 7.40-7.02 (*m*, 9 arom. H); 5.95 (*d*, *J* = 6, H–C(α)); 4.57 (*d*, *J* = 6, H–C(1)); 3.63 (*s*, CH₃O); 3.63-3.60 (*m*, H–C(3)); 2.85-2.80 (*m*, 2 H–C(4)); 1.22 (*s*, *t*-Bu). ¹³C-NMR (75 MHz, CDCl₃): 177.19 (*s*); 173.45 (*s*); 133.62 (*s*); 133.30 (*s*); 128.90 (*d*); 128.44 (*d*); 128.20 (*d*); 128.09 (*d*); 127.69 (*d*); 125.87 (*d*); 78.43 (*d*); 58.14 (*d*); 52.11 (*d*); 51.82 (*q*); 38.87 (*t*); 31.48 (*s*); 27.15 (*q*). MS: 322 (3.8), 220 (18.4), 190 (95.5), 130 (100), 57 (51.3).

(15,35)-1-[1',3'-Dihydro-4',5'-(methylenedioxy)-3'-oxoisobenzofuryl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-3-carboxylic Acid (9a/9b). Following GP 2, we obtained from 1.6 g (5.5 mmol) of 2d and 1.2 g (5.5 mmol) of 4c 1.89 g (68%) of unseparated 9a/9b (ratio 3:2⁸); 0.5 g of unreacted 2d was recovered), after FC with Et₂O/CHCl₃/AcOH 7:3:0.1. ¹H-NMR (300 MHz, (D₆)DMSO, 98.6°; 2 diastereoisomers): 7.24–7.11 (*m*, 4 arom. H); 6.88–6.61 (*m*, 3 arom. H); 6.14, 6.10 (2s, each 2 H, 2 × OCH₂O); 5.84–5.81 (*m*, 2 × H–C(1), 1 arom. H); 5.69 (d, J = 4, H–C(1')); 5.64 (d, J = 1.3, H–C(1')); 5.13 (*m*, H–C(3)); 5.08 (*m*, H–C(3)); 3.74, 3.70, 3.68, 3.31 (4s, 4 × CH₃O); 3.38–3.03 (*m*, 2 × 2 H–C(4)); 1.30, 1.26 (2s, 2 × t-Bu). MS: 464 (< 1), 365 (< 1), 302 (17.5), 246 (13.7), 216 (38.2), 188 (29.3), 57 (100).

5. Anodic Electrochemical Decarboxylations of the Tetrahydroisoquinoline-3-carboxylic Acids in MeOH. – General Procedure (GP 3). Ca. 2M acid in MeOH was neutralized to the extent of 10–15% with Et_3N and electrolized with a current density of ca. $i = 300 \text{ mA/cm}^2$. The temp. of the mixture was kept between -2 and $+5^\circ$. The solvent was evaporated, the residue dissolved in CH₂Cl₂, the resulting soln. washed with aq. Na₂CO₃ and sat. NaCl soln., dried (MgSO₄), and evaporated.

tert-Butyl ((1R)-1,2,3,4-Tetrahydro-3-methoxy-1-methylisoquinolin-2-yl) Ketone (11). A soln. of 1.67 g (6 mmol) of **5** and 0.282 ml of Et₃N in 15 ml of MeOH was electrolyzed following *GP* 3 (*i* = 300 mA/cm², 2.6 F/mol). Removal of the MeOH gave 1.26 g (80%) of a single diastereoisomer **11** of undetermined configuration. M.p. 117.5–118.5° (from Et₂O). IR (KBr): 3420 (br.), 3040w, 2980m, 2920m, 2820w, 1640s, 1460m, 1400m, 1380m, 1340m, 1290m, 1060s, 760m. ¹H-NMR (300 MHz, CDCl₃); 7.23–7.13 (*m*, 4 arom. H); 5.51 (*ABX*, J_{AX} = 5, H–C(3)); 5.28 (*q*, *J* = 6.4, H–C(1)); 3.19, 3.00 (*ABX*, J_{AB} = 15.6, J_{AX} = 15.6, J_{BX} = 1.7, 2 H–C(4)); 3.06 (*s*, CH₃O); 1.34 (*s*, *t*-Bu); 1.29 (*d*, *J* = 6.4, CH₃). MS: 246 (1.6), 230 (10.5), 214.5 (19.0), 130 (53.2), 118 (10.2), 57 (100). Anal. calc. for C₁₆H₂₃NO₂ (261.37): C 73.53, H 8.87, N 5.36; found: C 73.59, H 8.94, N 5.33.

tert-Butyl ((1 R)-1-Benzyl-1,2,3,4-tetrahydro-3-methoxyisoquinolin-2-yl) Ketone (12). From 0.7 g (2 mmol) of 6, 0.055 ml (0.4 mmol) of Et₃N, and 3 ml of MeOH following GP 3 ($i = 250 \text{ mA/cm}^2$, 2.2 F/mol), 0.53 g (78%) of 12 were obtained as a yellow oil. ¹H-NMR (90 MHz): 7.28–6.53 (m, 9 arom. H); 5.50–5.23 (m, H–C(1), H–C(3)); 3.16–2.76 (m, CH₃O, PhCH₂); 1.48 (s, t-Bu).

Mixture of Diastereoisomers of 6,7-(Methylenedioxy)-3-(1',2',3',4'-tetrahydro-3',6',7'-trimethoxy-2'-pivaloylisoquinolin-1'-yl)isobenzofuran-1(3H)-one (17). A soln. of 1.3 g (2.6 mmol) of 9a/9b, 0.07 ml of Et₃N, and 10 ml of MeOH was electrolyzed according to GP 3 (i = 300 mA/cm², 2.6 F·mol). Evaporation of the MeOH gave 1.2 g (95%) of a mixture of diastereoisomers 17 (FC with Et₂O/CHCl₃ 4:1). ¹H-NMR (300 MHz, CDCl₃; mixture of diastereoisomers): 7.13 (s, 1 H); 7.05–6.57 (m, 3 arom. H); 6.11 (m, OCH₂O); 6.08–5.29 (m, H–C(1'), H–C(3), H–C(3')); 3.86, 3.85, 3.83, 3.45 (4s, 2 CH₃O); 3.48 (s, CH₃O–C(3')); 1.40, 1.30 (s, t-Bu). MS: 452 (< 0.1), 368 (2.3), 306 (99.7), 274 (39.8), 222.0 (14.2), 190 (99.9), 57 (100).

6. Demethoxylation of 11, 12, and 17 with NaCNBH₃. – tert-*Butyl* ((R)-1,2,3,4-Tetrahydro-1-methylisoquinolin-2-yl) Ketone (13). A soln. of 1.0 g (3.8 mmol) of 11 and 0.250 g of NaCNBH₃ (3.9 mmol) in 10 ml of MeOH was combined dropwise with a sat. HCl soln. in MeOH until a constant pH of 3 was reached. After stirring for 1 h at r.t., the solvent was evaporated and the residue dissolved in CH₂Cl₂. The soln. was washed with H₂O and dried (MgSO₄). Removal of the solvent gave 0.85 g (96%) of 13, the NMR of which was identical with that of the racemic compound described earlier [29]. Removal of the pivaloyl group was carried out with this crude product.

((R)-Benzyl-1,2,3,4-tetrahydroisoquinolin-2-yl) tert-Butyl Ketone (14). Prepared by NaCNBH₃ reduction of 12 as described for 13. Yield > 90%. ¹H-NMR (90 MHz, CDCl₃): 7.28–6.73 (m, 9 arom. H); 5.8 (t, J = 7.5);

⁸) The long reaction time used (14 h, -80° ; see *GP* 2) may have been responsible for the loss of diastereoselectivity, due to epimerization at C(1')!

4.26-3.95 (1 H); 3.56-2.63 (m, 3 H, together 2 H–C(3), 2 H–C(4)); 3.13 (d, J = 7.5, PhCH₂); 1.16 (s, t-Bu); identical with the previously reported spectrum of rac-14 [29].

6.7 - (Methylenedioxy) - 3 - (1', 2', 3', 4' - tetrahydro - 6', 7' - dimethoxy - 2' - pivaloylisoquinolin - 1' - yl) isobenzofuran-1(3H)-one (18). Under the NaCNBH₃ reduction conditions used in the previous two cases, 1.04 g (2.16 mmol) of17 (mixture of diastereoisomers) gave 0.82 g (83%) of crude product containing two and only two diastereoisomers18a/18b which were separated by FC with Et₂O/CHCl₃ 4:1 and recrystallized from EtOAc: 0.55 g (56%) of 18a(u-configuration) and 0.23 g (23%) of 18b (l-configuration). Since 18a gave (+)-corlumin, it is the (3R,1'S)-stereoisomer.

Major Epimer **18a** (colorless powder). $[\alpha]_D = -128.14^\circ$ (c = 0.97, CHCl₃). IR (KBr): 3420 (br.), 2970*m*, 2930*m*, 2840*w*, 1770*s*, 1640*s*, 1540*s*, 1480*s*, 1410*m*, 1245*s*, 1180*m*, 1120*m*, 970*m*, 760*m*. ¹H-NMR (300 MHz, CDCl₃): 7.27–7.18 (*AB*, $J_{AB} = 7.5$, 2 arom. H); 6.58 (*s*, 1 arom. H); 6.14 (*m*, OCH₂O); 5.87 (*s*, 1 arom. H); 5.78 (*m*, H–C(1')); 5.65 (br. *s*, H–C(3)); 4.11–4.03 (*m*, 2 H–C(3')); 3.80 (*s*, CH₃O); 3.34 (*s*, CH₃O); 2.96–2.85 (*m*, 2 H–C(4')); 1.38 (*s*, *t*-Bu). ¹³C-NMR (75 MHz, CDCl₃): 177.71 (*s*); 149.35 (*s*); 148.39 (*s*); 146.51 (*s*); 144.86 (*s*); 141.07 (*s*); 127.96 (*s*); 120.93 (*s*); 115.37 (*d*); 113.82 (*d*); 111.09 (*d*); 109.83 (*d*); 103.39 (*t*); 85.49 (*d*); 57.72 (*d*); 55.74 (*q*); 55.35 (*q*); 42.60 (*t*); 39.16 (*s*); 28.65 (*t*); 28.19 (*q*). MS: 452 (< 1, M^{++} – 1), 276 (100), 192 (31.6), 177 (5.9), 85 (7.9), 57 (91.9).

Minor Epimer **18b.** M.p. 237–238°. $[\alpha]_D = -82.3°$ (c = 0.82, CHCl₃). IR (KBr): 3440 (br.), 2980*m*, 2940*m*, 2840*w*, 1760*s*, 1620*s*, 1520*s*, 1480*s*, 1410*m*, 1255*s*, 1170*m*, 1120*m*, 1040*s*, 980*m*, 960*m*. ¹H-NMR (300 MHz, CDCl₃): 7.14–7.05 (*m*, 2 arom. H); 6.83, 6.60 (2*s*, 2 arom. H); 6.37 (*d*, J = 2.2, H–C(1')); 6.15 (*s*, OCH₂O); 5.96 (*d*, J = 3, H–C(3)); 4.11–4.05 (*m*, 1 H–C(3')); 3.90, 3.86 (2*s*, 2 CH₃O); 3.69–3.59 (*m*, 1 H–C(3')); 2.77–2.70 (*m*, 2 H–C(4')); 1.01 (*s*, *t*-Bu). ¹³C-NMR (75 MHz, CDCl₃): 177.27 (*s*); 166.89 (*s*); 149.16 (*s*); 148.52 (*s*); 148.07 (*s*); 144.19 (*s*); 139.30 (*s*); 126.78 (*s*); 124.25 (*s*); 117.01 (*d*); 113.10 (*d*); 111.79 (*d*); 109.89 (*d*); 103.23 (*t*); 86.84 (*d*); 56.25 (*q*); 56.00 (*q*); 52.99 (*d*); 42.73 (*t*); 38.87 (*s*); 29.02 (*t*); 28.07 (*q*). MS: 452 (1, M^{++} – 1), 176 (100), 192 (34.1), 177 (6.1), 57 (74.8). Anal. calc. for C₂₅H₂₇NO₇ (453.497): C 66.21, H 6.00, N 3.09; found: C 65.82, H 6.05, N 2.89.

7. Depivaloylation of 13 and 14 with NaAlH₄. – (R)-1,2,3,4-Tetrahydro-1-methylisoquinoline (15). Following the procedure given below for 16, a soln. of 0.3 g (1.3 mmol) of 13 in 3 ml of THF was combined with a soln. of 58 mg (0.8 mmol) of NaAlH₄ in 5 ml of THF to give 0.11 g (60%) of oily free amine. Hydrochloride: $[\alpha]_D = +42^{\circ}$ (c = 1.13, EtOH; [33]: -44° (c = 1.24, EtOH) for ent-15).

(R)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline (16). To a soln. of 0.41 g (1.33 mmol) of 14 in 3 ml of dry THF stirred at 0° was added dropwise a pale soln. of 84 mg (1.2 mmol) of NaAlH₄ [32] in 5 ml of THF. The mixture was allowed to warm slowly to r.t. and was stirred overnight. H₂O (1 ml) was added. Et₂O was added and the amine first extracted into the H₂O layer with 2N HCl, and then set free with 10% KOH soln. and extracted into CH₂Cl₂. After drying (MgSO₄), evaporation, and freeing the product of last traces of volatile impurities under high vacuum, 0.24 g (80%) of a slightly yellow oil was isolated. $[\alpha]_D = +60.1^\circ$ (c = 1.11, THF; [8]: +62.6° (c = 0.92, THF). $[\alpha]_D = +43.3^\circ$ (c = 1.05, MeOH; [33]: -44° (c = 16, MeOH) for *ent*-16). IR (film): 3400-3200, 3020, 2920, 2830, 2800, 1600, 1490, 1450, 1425, 1315, 1125, 1080, 1030, 960. ¹H-NMR (90 MHz, CDCl₃): 7.55-6.93 (m, 9 arom. H); 4.23 (dd, J = 10, 4 H–C(1)); 3.53-2.56 (m, PhCH₂, 2 H–C(3), 2 H–C(4)); 1.73 (s, NH).

8. Conversion of 18a to (+)-Corlumine (19). – Norcorlumine (NH instead of NCH₃; obtained by hydrolytic cleavage of the pivalamide following the procedure given for this type of reaction in [1], yield 31% (FC with Cl1₂Cl₂/MeOH 15:1)) was methylated (63%) as indicated in *Scheme 3* to give (*3* R, *I*'S)-6,7-(*methylenedioxy*)-3-(*I'*,2',3',4'-tetrahydro-6',7'-dimethoxy-2'-methylisoquinolin-1'-yl)isobenzofuran-1(*3*H)-one (19) (FC with Et₂O/MeOH 15:1). M.p. 156–157° (from MeOH; [35]: 162°). $[\alpha]_D = +61°$ (c = 1.9, CHCl₃; [35]: $[\alpha]_D = +77.0°$ (c = 1.0, CHCl₃), *cf. Footnote 5*). IR (KBr): 3340 (br.), 2940m, 2910m, 2840w, 2800w, 1760s, 1650w, 1610m, 1520s, 1480s, 1200s, 1140m, 1100m, 1040m, 1025m, 970m, 780w. ¹H-NMR (90 MHz, CDCl₃): 6.91 (*d*, *J* = 7.5, 1 arom. H); 6.6 (*s*, 1 arom. H); 6.39 (*s*, 1 arom. H); 6.23 (*d*, *J* = 7.5, 1 arom. H); 6.13 (*s*, OCH₂O); 5.63 (*d*, *J* = 7.5, 1 arom. H); 6.6 (*s*, 1 = 4.5, H-C(3)); 3.83, 3.65 (2*s*, 2 CH₃O); 3.13–2.06 (*m*, 2 H-C(3), 2 H-C(4)); 2.56 (*s*, CH₃N) (see [35]). ¹³C-NMR (20 MHz, CDCl₃): 166.60; 148.94; 148.35; 147.26; 140.72; 129.41; 123.42; 115.35; 112.79; 111.54; 111.03; 110.32; 102.99; 84.69; 65.77; 55.92; 55.80; 49.29; 44.89; 27.31 (see [41]). MS: 384 (< 1, $M^+ + 1$), 383 (< 1, M^+), 206 (100), 190 (12.3), 177 (3.2), 162 (4.7), 145 (2.9), 132 (2.7). Anal. calc. for C₂₁H₂₁NO₆·0.4H₂O (390.6): C 64.50, H 5.58, N 3.58; found: C 64.61, H 5.59, N 3.28.

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