

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*).

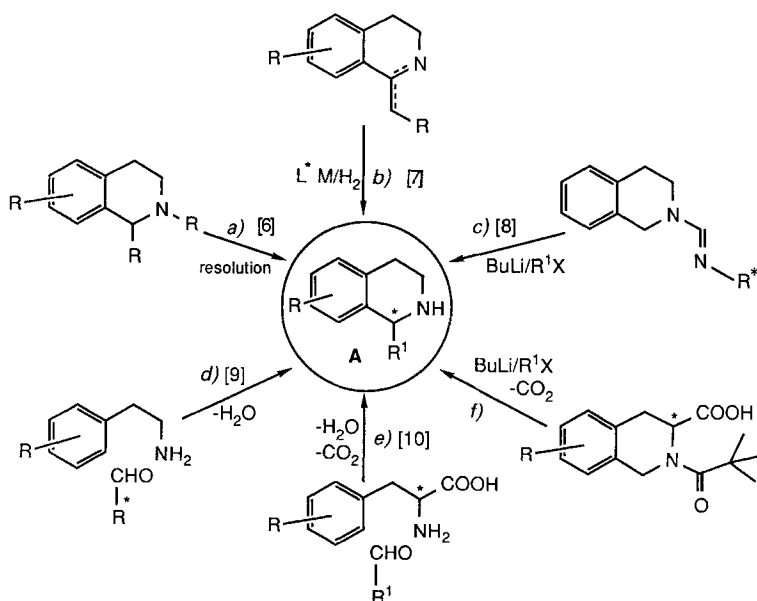
1. Methods of EPC-Synthesis of Tetrahydroisoquinolines. – All possible methods of synthesizing enantiomerically pure compounds (EPC [2–5]) have been applied to obtain tetrahydroisoquinolines **A** (*Scheme 1*): *a*) resolution, *b*) catalytic and *c*) stoichiometric enantioselective reactions as well 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.

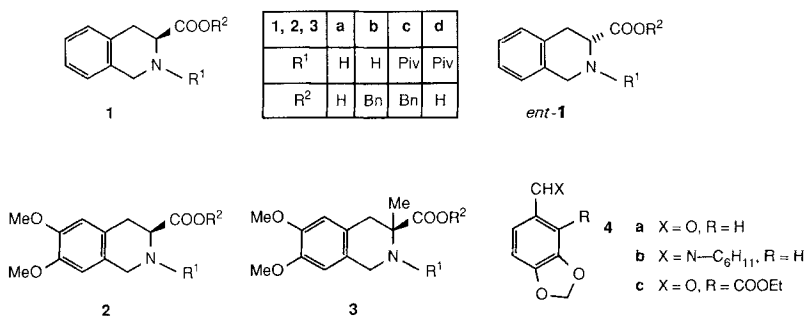
¹⁾ Part II of an investigation on diastereoselective C,C-bond formation in the 1-position of 1,2,3,4-tetrahydroisoquinolines. For part I, see [1].

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

Scheme 1



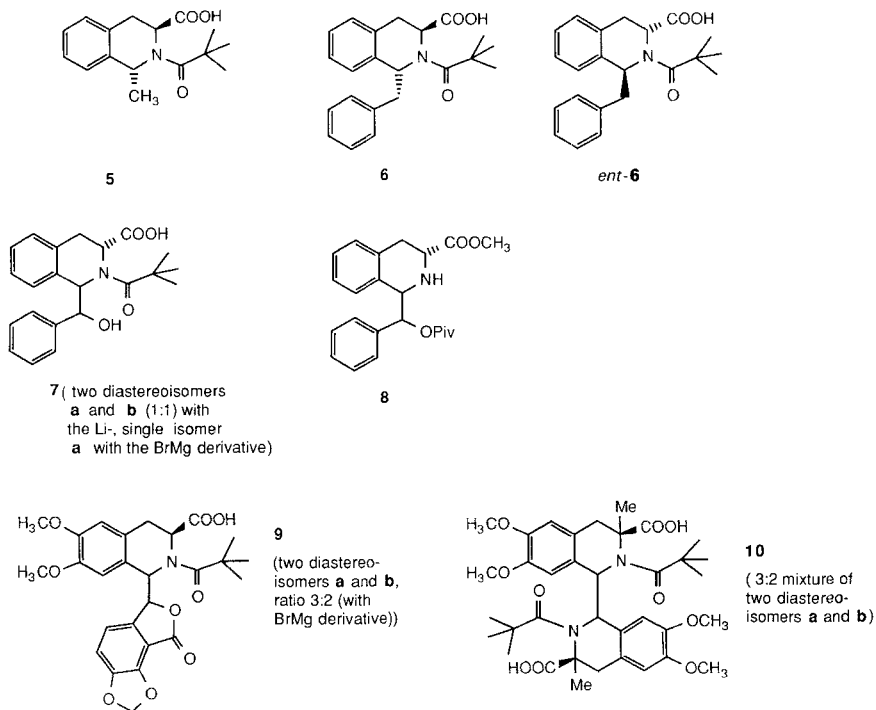
2. Preparation of the Starting Materials. – The *N*-pivaloyltetrahydroisoquinoline-carboxylic acid **1d** was obtained in the following way: (*S*)- or (*R*)-phenylalanine was subjected to a *Pictet-Spengler* cyclization ($\text{CH}_2\text{O}/\text{HCl}$) [15] and the partially racemized product **1a** 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-6,7-dimethoxy 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 = $\text{CH}_2\text{C}_6\text{H}_5$ and Piv. = *t*-BuCO (in all Schemes)

ethyl(trimethylsilyl)amine/ Et_3N). 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**.

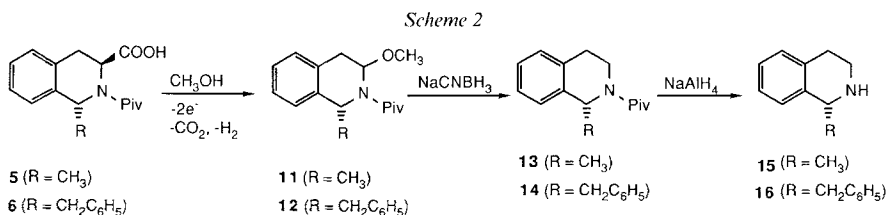
3. Dilithiation of the Tetrahydroisoquinolinecarboxylic Acids 1d, 2d, and 3d and Reactions with Electrophiles. – Treatment of the acids with 2 equiv. of (*tert*-butyl)lithium in tetrahydrofuran (THF) gave deep red solutions which were combined with electrophiles such as CH_3I , benzyl bromide, benzaldehyde, and the formyl ester **4c**. The 1-methyl and 1-benzyl derivatives **5** and **6**, respectively were isolated as 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 MgBr_2 -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, in spite of MgBr_2 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/ CH_3I ; instead, two diastereoisomeric dimers **10** were formed (*cf.* [1] [20]).

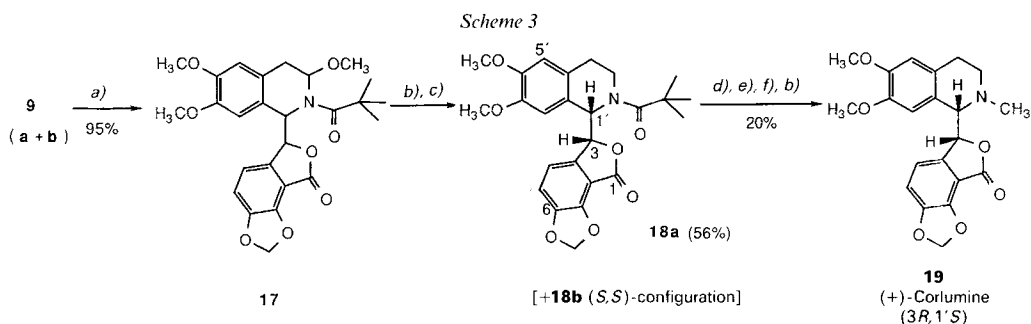
4. Configuration of the 1-Substituted Tetrahydroisoquinoline-3-carboxylic Acids 5–10. – The constitution of these products (alkylation at C(1) and not at C(3)) follows clearly from the $^1\text{H-NMR}$ spectra measured at 100° in dimethylsulfoxide (rotamers at lower temperature!), see *Exper. Part*. The configuration of the derivatives **5**, **6**, and **9a** was determined by chemical correlation to be *trans*, and we assume that the major stereoisomers **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-methyl- and (*R*)-1-benzyltetrahydroisoquinoline **15** and **16**, respectively, is outlined in *Scheme 2*.



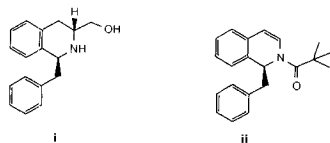
In the first step, the COOH group is removed. Of the methods to do this (e.g. through the corresponding nitril [21] or acyl chloride [22]), we chose the electrochemical reaction [23] [24] which was successfully applied to non-racemic amino-acid derivatives before [25–27]. The methoxy compounds **11** 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-benzyltetrahydroisoquinolines **15** and **16**, respectively, by reduction with sodium aluminum hydride [32]. The specific rotations of the two products indicated that they were of $\geq 96\%$ 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) $+2\text{e}^-/\text{CH}_3\text{OH}$; b) $\text{NaCNBH}_3/\text{H}^+$; c) chrom. separation; d) KOH/EtOH , Δ ; e) H_2NNH_2 ; f) $\text{CH}_2\text{O}/\text{H}^+$

³⁾ The reductive cleavage with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ used previously by us [29] was not successful here. Also, Na_2O_2 [30], $\text{KOH}/\text{H}_2\text{NNH}_2/\text{glycol}$ [31], and carefully controlled amounts of LiAlH_4 did not cleave satisfactorily. Even in the case of NaAlH_4 , 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*.



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 cm² rotating Pt disc, cathode: Pt net. The rotating electrode (2000 rpm) provided sufficient stirring. For further details, see [25] [39].

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

Benzyl (3*S*)-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).

(3*S*)-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°. $[\alpha]_D = -26.6^\circ$ ($c = 1.2$, MeOH). IR (KBr): 3420 (br.), 2960*m*, 2920*m*, 1730*s*, 1595*s*, 1580*s*, 1425*m*, 1370*m*, 1180*s*, 975*m*. 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.

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

Benzyl (3*S*)-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°. $[\alpha]_D = +26.59^\circ$ ($c = 0.995$, MeOH). IR (KBr): 3060*w*, 3020*w*, 3000*m*, 2940*m*, 2830*w*, 1745*s*, 1640*s*, 1520*s*, 1465*m*, 1410*m*, 1265*s*, 1175*s*, 1120*s*, 1000*m*. 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*); 127.67 (*d*); 124.70 (*s*); 124.21 (*s*); 111.34 (*d*); 109.15 (*d*); 66.50 (*t*); 55.84 (*q*); 55.76 (*q*); 54.02 (*d*); 45.0 (*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.

(3*S*)-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.), 3080*m*, 2970*s*, 2840*m*, 1730*s*, 1630*m* (sh), 1615*m*, 1575*s*, 1520*s*, 1265*s*, 1230*s*, 1120*s*, 985*m*. 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 (2*s*, 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*); 148.21 (*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).

(3*S*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methylisoquinoline-3-carboxylic Acid Hydrochloride (**3a**·HCl). A soln. of 50 g of (*S*)-3-(3,4-dimethoxyphenyl)-2-methylalanine (≡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**·HCl. After washing with cold H₂O and acetone, 59 g (98%). $[\alpha]_D = -14.9^\circ$ ($c = 1$, MeOH). Anal. data, see [22].

(3*S*)-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 2*N* 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°. $[\alpha]_D = -33.1^\circ$ ($c = 1.0$, MeOH). IR (KBr): 3400 (br.), 2980*m*, 2840*w*, 1740*m*, 1710*m*, 1630*s*, 1520*s*, 1410*m*, 1365*m*, 1340*m*, 1230*m*, 1170*s*, 1115*s*, 1000*w*. ¹H-NMR (300 MHz, CDCl₃): 6.75, 6.71 (2 *s*, 2 arom. H); 4.70, 4.59 (*AB*,

$J_{AB} = 14.4$, 2 H-C(1)); 3.88 (s, 2 CH₃O); 3.21, 2.77 (AB, $J_{AB} = 14.8$, 2 H-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 · ½ 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.

(1*R*,3*S*)-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 MeI 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). [α]_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.

(1*S*,3*R*)-Enantiomer *ent*-**6**. Exactly like **6**, from *ent*-**1**. M.p. 192–193°, opposite sense for [α]_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*, α *S*) configuration, i.e. coupling of the trigonal centers with rel. topology *ul* (as with the achiral tetrahydroisoquinoline analogues [1]), and approach of the aldehyde from the face opposite to the COOLi group (rel. topology *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): 181.34, 175.25 (2s); 176.82, 173.07 (2s); 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

(2*r*); 28.58, 26.98 (2*q*). 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-[α -(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). IR (CHCl₃): 3020*w*, 2980*w*, 2870*w*, 1730*s* (br.), 1480*m*, 1150*s*, 1030*w*. 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*); 137.54 (*s*); 133.62 (*s*); 133.30 (*s*); 128.90 (*d*); 128.44 (*d*); 128.20 (*d*); 128.09 (*d*); 127.09 (*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).

*(1*S*,3*S*)-1-[1'-(3',4'-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 3:2^b); 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 (2*s*, each 2 H, 2 $\times$ OCH₂O); 5.84–5.81 (*m*, 2 $\times$ 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 (4*s*, 4 $\times$ CH₃O); 3.38–3.03 (*m*, 2 $\times$ 2 H–C(4)); 1.30, 1.26 (2*s*, 2 $\times$ *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. 2*M* acid in MeOH was neutralized to the extent of 10–15% with Et₃N and electrolyzed with a current density of ca. *i* = 300 mA/cm². The temp. of the mixture was kept between –2 and +5°. 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 ((1*R*)-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.), 3040*w*, 2980*m*, 2920*m*, 2820*w*, 1640*s*, 1460*m*, 1400*m*, 1380*m*, 1340*m*, 1290*m*, 1060*s*, 760*m*. 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 mA/cm², 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(3*H*)-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 (4*s*, 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*, $J = 7.5$, PhCH_2); 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 NaCNBH_3 reduction conditions used in the previous two cases, 1.04 g (2.16 mmol) of **17** (mixture of diastereoisomers) gave 0.82 g (83%) of crude product containing two and only two diastereoisomers **18a/18b** which were separated by FC with $\text{Et}_2\text{O}/\text{CHCl}_3$ 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 (+)-corlumine, it is the (3*R*,1'*S*)-stereoisomer.

Major Epimer 18a (colorless powder). $[\alpha]_D = -128.14^\circ$ ($c = 0.97$, CHCl_3). 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*. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.27–7.18 (*AB*, $J_{AB} = 7.5$, 2 arom. H); 6.58 (*s*, 1 arom. H); 6.14 (*m*, OCH_2O); 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*, CH_3O); 3.34 (*s*, CH_3O); 2.96–2.85 (*m*, 2 H–C(4')); 1.38 (*s*, *t*-Bu). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 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°. $[\alpha]_D = -82.3^\circ$ ($c = 0.82$, CHCl_3). 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*. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 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*, OCH_2O); 5.96 (*d*, $J = 3$, H–C(3)); 4.11–4.05 (*m*, 1 H–C(3')); 3.90, 3.86 (2*s*, 2 CH_3O); 3.69–3.59 (*m*, 1 H–C(3')); 2.77–2.70 (*m*, 2 H–C(4')); 1.01 (*s*, *t*-Bu). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 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 $\text{C}_{25}\text{H}_{27}\text{NO}_7$ (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 NaAlH_4 . – (*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 NaAlH_4 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 NaAlH_4 [32] in 5 ml of THF. The mixture was allowed to warm slowly to r.t. and was stirred overnight. H_2O (1 ml) was added. Et_2O was added and the amine first extracted into the H_2O layer with 2*N* HCl , and then set free with 10% KOH soln. and extracted into CH_2Cl_2 . After drying (MgSO_4), 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]: $+62.6^\circ$ ($c = 0.92$, 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. $^1\text{H-NMR}$ (90 MHz, CDCl_3): 7.55–6.93 (*m*, 9 arom. H); 4.23 (*dd*, $J = 10$, 4 H–C(1)); 3.53–2.56 (*m*, PhCH_2 , 2 H–C(3), 2 H–C(4)); 1.73 (*s*, NH).

8. Conversion of 18a to (+)-Corlumine (19). – Norcorlumine (NH instead of NCH_3 ; obtained by hydrolytic cleavage of the pivalamide following the procedure given for this type of reaction in [1], yield 31% (FC with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 15:1)) was methylated (63%) as indicated in Scheme 3 to give (3*R*,1'*S*)-6,7-(methylenedioxy)-3-(1',2',3',4'-tetrahydro-6',7'-dimethoxy-2'-methylisoquinolin-1'-yl)isobenzofuran-1(3H)-one (**19**) (FC with $\text{Et}_2\text{O}/\text{MeOH}$ 15:1). M.p. 156–157° (from MeOH ; [35]: 162°). $[\alpha]_D = +61^\circ$ ($c = 1.9$, CHCl_3 ; [35]: $[\alpha]_D = +77.0^\circ$ ($c = 1.0$, CHCl_3), cf. Footnote 5). IR (KBr): 3340 (br.), 2940*m*, 2910*m*, 2840*w*, 2800*w*, 1760*s*, 1650*w*, 1610*m*, 1520*s*, 1480*s*, 1200*s*, 1140*m*, 1100*m*, 1040*m*, 1025*m*, 970*m*, 780*w*. $^1\text{H-NMR}$ (90 MHz, CDCl_3): 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*, OCH_2O); 5.63 (*d*, $J = 7.5$, 1 arom. H); 4.06 (*d*, $J = 4.5$, H–C(3)); 3.83, 3.65 (2*s*, 2 CH_3O); 3.13–2.06 (*m*, 2 H–C(3), 2 H–C(4)); 2.56 (*s*, CH_3N) (see [35]). $^{13}\text{C-NMR}$ (20 MHz, CDCl_3): 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 $\text{C}_{21}\text{H}_{21}\text{NO}_6 \cdot 0.4\text{H}_2\text{O}$ (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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