# 180. EPC-Synthesis of Tetrahydroisoquinolines by Diastereoselective Alkylation at the 1-Position of Phenylalanine-Derived Precursors. Synthesis of the Alkaloid ( + )-Corlumine ${ }^{1}$ ) 

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The 1,2,3,4-tetrahydro- $N$-pivaloyl-isoquinoline-3-carboxylic acids 1d, 2d, and 3d, derived from ( $R$ )- or $(S)$-phenylalaninc, $(S)$-dopa, and $(S)$ - $\alpha$-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 $u l-1,3$ ). Even the addition to benzaldehyd $(\rightarrow \mathbf{7}, \mathbf{8})$ is highly stercoselective (one of four diastereoisomers is formed exclusively ( $\mathbf{3 0 0}-\mathrm{MHz}$ ${ }^{1} \mathrm{H}-\mathrm{NMR}$ analysis)), if $\mathrm{MgBr}_{2} \cdot$ etherate is added prior to the electrophile. Some of the obtained amino-acid derivatives are decarboxylated by anodic oxidation in $\mathrm{MeOH}(\rightarrow \mathbf{1 1}, \mathbf{1 2}, \mathbf{1 7})$ and $\mathrm{NaBH}_{3} \mathrm{CN}$ reduction, and converted to the known 1-methyl- and 1-benzyltetrahydroisoquinolines $(\mathbf{1 5}, \mathbf{1 6})$ of $>95 \%$ ee as well as to the phthalide isoquinoline alkaloid ( + )-corlumine of $\geqslant 80 \%$ ee. The synthetic approach described here is compared with other methods of synthesizing enantiomerically purc 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 $\beta$-hydrastine (phthalide alkaloid), we investigated analogous transformations ( $f$ ) in Scheme 1) with chiral, non-racemic tetrahydroisoqui-noline-3-carboxylic acids. These are available from aromatic amino acids such as phenylalanine. Diastereoselective hydroxyalkylation and decarboxylation would lead to the enantiomerically pure alkaloids.

[^0]Scheme 1

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 $\left(\mathrm{CH}_{2} \mathrm{O} / \mathrm{HCl}\right)$ [15] and the partially racemized product 1a esterified to the benzyl ester $\mathbf{1 b}$, the tosylate salt of which was recrystallized to high enantiomeric purity [16]. $N$-Pivaloylation ( $\rightarrow \mathbf{1 c}$ ) and hydrogenolysis gave the desired acid 1d and ent-1d, respectively. The analogous 6,7-dimethoxy compound $\mathbf{2 d}$ was obtained from the carboxylic acid $\mathbf{2 a}$ (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 ( $S$ )- $\alpha$-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-


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a $X=O, R=H$
b $X=N-C_{6} H_{11}, R=H$
c $\mathrm{X}=\mathrm{O}, \mathrm{R}=\mathrm{COOEt}$
ethyl(trimethylsilyl)amine/ $\mathrm{Et}_{3} \mathrm{~N}$ ). Finally, the formyl(methylendioxy)benzoate $\mathbf{4 c}$ 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 $\mathrm{CH}_{3} \mathrm{I}$, benzyl bromide, benzaldehyde, and the formyl ester $\mathbf{4 c}$. The l-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

5


6

ent-6


7 ( two diastereoisomers $a$ and $b$ (1:1) with the Li -, single isomer a with the BrMg derivative)


8


aldehyde, while a single diastereoisomer $\mathbf{7 a}$ was isolated if a transmetallation was carried out with $\mathrm{MgBr}_{2}$-etherate prior to aldehyde addition. Treatment with $\mathrm{HCl} / \mathrm{MeOH}$ converted the hydroxy-amido acid 7 into the amino diester 8 ( $c f$. [1]). To our surprise, the product 9 ( $68 \%$ yield) from the highly substituted aldehyde $\mathbf{4 c}$ and the dimethoxy derivative $\mathbf{2 d}$ was not formed stereoselectively, inspite of $\mathbf{M g B r}_{2}$ 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/ $\mathrm{CH}_{3} \mathrm{I}$; 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 $\mathrm{C}(1)$ and not at $\mathrm{C}(3)$ ) follows clearly from the ${ }^{1} \mathrm{H}$-NMR spectra measured at $100^{\circ}$ 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 $\mathbf{7 , 8}$, and $\mathbf{1 0}$ 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.

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 $\mathbf{1 2}$ 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 cleaved $^{3}$ ) 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 $\geqslant 96 \%$ 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


[^1]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 $\left(3 R, 1^{\prime} S\right)$ [37]. We are aware of only one synthesis of the alkaloid [38], in its racemic form.

Electrochemical decarboxylation of crude $9(\rightarrow \mathbf{1 7})$ and cyanoborohydride reduction gave a readily separated mixture of the two epimeric $N$-pivaloyl-lactones 18a and $\mathbf{1 8 b}$. The prevailing stereoisomer 18a must have ( $3 R, 1^{\prime} S$ )-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 $N$-methylation ${ }^{4}$ ). The isolated alkaloid had an enantiomeric excess of $c a .80 \%$ as judged by optical comparison ${ }^{5}$ ).
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 available ${ }^{6}$ ) and additional stereogenic centers may be created selectively ${ }^{7}$ ) in the C,C-bondforming process ( $c f . \mathbf{7 , 8}$ ) 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.

[^2]${ }^{4}$ ) Depivaloylation of the $l$-epimer $\mathbf{1 8 b}$ 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 9 a to corlumine. Since the ratios $9 a / 9 b$ and $18 a / 18 b$ 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 $0^{\circ}$ in MeOH , the solvent for recrystallization, and of $77^{\circ}$ in $\mathrm{CHCl}_{3}$ ). See also Footnote 8 in the Exper. Part.
${ }^{6}$ ) 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) ${ }^{2}$ ).

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${ }^{7}$ ) 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!

## 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: $1-4 \mathrm{~cm}^{2}$ 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 $\mathbf{1 b}$, following procedure [1][29]. Yield $70 \%$, oil. $[\alpha]_{\mathrm{D}}=-21.2^{\circ}(c=1.1, \mathrm{MeOH})$. IR $\left(\mathrm{CHCl}_{3}\right): 3080,3040,2690,1745,1635,1415$, $1390,1370,1185,1120,760,705 .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(90 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 7.4-6.9(m, 4$ arom. H$) ; 5.25(t, J=4.5, \mathrm{H}-\mathrm{C}(3))$; $5.05\left(s, \mathrm{PhCH}_{2}\right) ; 4.94,4.59\left(A B, J_{A B}=14.4,2 \mathrm{H}-\mathrm{C}(1)\right) ; 3.2,3.15(2 s$, each $1 \mathrm{H}, 2 \mathrm{H}-\mathrm{C}(4)) ; 1.3(s, t-\mathrm{Bu})$.
(3S)-1,2,3,4-Tetrahydro-2-pivaloylisoquinoline-3-carboxylic Acid (1d). A suspension of 2 g ( 5.6 mmol ) of $\mathbf{1 c}$ and 0.27 g of $10 \% \mathrm{Pd} / \mathrm{C}$ in 30 ml of $\mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O} 3: 1$ was stirred under $\mathrm{H}_{2}$ at r.t. overnight. Evaporation of the solvents and recrystallization from $\mathrm{CH}_{2} \mathrm{Cl}_{2} /$ petroleum ether gave 1.1 g of 1d. M.p. $158-160^{\circ}$. $[\alpha]_{\mathrm{D}}=-26.6^{\circ}$ ( $c=1.2, \mathrm{MeOH}$ ). IR ( K Br ): 3420 (br.), $2960 \mathrm{~m}, 2920 \mathrm{~m}, 1730 \mathrm{~s}, 1595 \mathrm{~s}, 1580 \mathrm{~s}, 1425 \mathrm{~m}, 1370 \mathrm{~m}, 1180 \mathrm{~s}, 975 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}$ ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) : 7.23-7.11 ( $m, 4$ arom. H ); $5.11(t, J=6, \mathrm{H}-\mathrm{C}(3)) ; 4.97,4.57\left(A B, J_{A B}=15.9,2 \mathrm{H}-\mathrm{C}(1)\right.$ ); $3.21-3.17(m, 2 \mathrm{H}-\mathrm{C}(4)) ; 1.33(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(20 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 177.87(\mathrm{~s}) ; 175.87(\mathrm{~s}) ; 133.19(\mathrm{~s}) ; 132.65(\mathrm{~s}) ;$ $128.21(d) ; 127.32(d) ; 126.89(d) ; 125.82(d) ; 54.33(d) ; 46.35(t) ; 38.86(s) ; 30.56(t) ; 28.12(q)$. MS: $262(1.8$, $\left.M^{+\cdot}+1\right), 261\left(7, M^{+}\right), 176(61.5), 158(5.4), 132(37.3), 130(31.9), 57(100)$. Anal. calc. for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{NO}_{3} \cdot 0.25 \mathrm{H}_{2} \mathrm{O}$ (265.83): C 67.96, H 7.39, N 5.26; found: C $67.75, \mathrm{H} 7.30, \mathrm{~N} 5.26$.
(3R)-1,2,3,4-Tetrahydro-2-pivaloylisoquinoline-3-carboxylic Acid (ent-1d). Exactly as 1d, but starting from $(R)$-phenylalanine. M.p. $159-160^{\circ} .[\alpha]_{\mathrm{D}}=+26.5^{\circ}(c=1.0, \mathrm{MeOH})$.

Benzyl (3S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline-3-carboxylate (2c). Following the procedure for esterification of $\mathbf{2 a}$ in [17] and that for pivaloylation of the parent benzyl ester $\mathbf{2 b}$ in [1] [29], an 84\% yield of 2 c was obtained. M.p. $97-98^{\circ} .[\alpha]_{\mathrm{D}}=+26.59^{\circ}(c=0.995, \mathrm{MeOH})$. IR (KBr): $3060 w, 3020 w, 3000 \mathrm{~m}, 2940 \mathrm{~m}$, $2830 \mathrm{w}, 1745 \mathrm{~s}, 1640 \mathrm{~s}, 1520 \mathrm{~s}, 1465 \mathrm{~m}, 1410 \mathrm{~m}, 1265 \mathrm{~s}, 1175 \mathrm{~s}, 1120 \mathrm{~s}, 1000 \mathrm{~m} .{ }^{\mathbf{~}} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 7.29-7.03$ $(m, 5 \mathrm{H}) ; 6.59(\mathrm{~s}, 1 \mathrm{H}) ; 6.55(\mathrm{~s}, 1$ arom. H); 5.36 (br. $s, \mathrm{H}-\mathrm{C}(3)) ; 5.09,5.05\left(A B, J_{A B}=12.3,2 \mathrm{H}-\mathrm{C}(1)\right) ; 4.87,4.54$ $\left(A B, J_{A B}=16, \mathrm{PhCH}_{2}\right) ; 3.84\left(s, 2 \mathrm{CH}_{3} \mathrm{O}\right) ; 5.37,3.17,3.08\left(A B X, J_{A B}=15.7, J_{B X}=3.7, J_{A X}=5.7,2 \mathrm{H}-\mathrm{C}(4)\right) ; 1.32$ $(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(20 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 177.0(s) ; 170.77(s) ; 148.09(s) ; 135.44(s) ; 128.14(d) ; 127.87(d) ; 127.67$ $(d) ; 124.70(s) ; 124.21(s) ; 111.34(d) ; 109.15(d) ; 66.50(t) ; 55.84(q) ; 55.76(q) ; 54.02(d) ; 45.0(t) ; 38.70(s) ; 30.35$ $(t) ; 27.99(q)$ MS: $412\left(2.1, M^{+-}+1\right), 411\left(4.6, M^{+\cdot}\right), 327(35.6), 326(98.7), 321(15.1), 230(78.4), 237(16.0), 236$ (100.0), 190 (99.7), 91 (83.4), 57 (96.3). Anal. calc. for $\mathrm{C}_{24} \mathrm{H}_{29} \mathrm{NO}_{5}(411.50)$ : 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 $\mathbf{1 d}$, from $6.34 \mathrm{~g}(15.4 \mathrm{mmol})$ of $\mathbf{2 c}, 4.0 \mathrm{~g}(83 \%)$ of $\mathbf{2 d}$ were obtained. $[\alpha]_{\mathrm{D}}=+62.6^{\circ}(c=0.92$, MeOH ). IR (KBr): 3420 (br.), $3080 \mathrm{~m}, 2970 \mathrm{~s}, 2840 \mathrm{~m}, 1730 \mathrm{~s}, 1630 \mathrm{~m}$ (sh), $1615 \mathrm{~m}, 1575 \mathrm{~s}, 1520 \mathrm{~s}, 1265 \mathrm{~s}, 1230 \mathrm{~s}, 1120 \mathrm{~s}$, $985 m$. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 6.65(s, 1 \mathrm{H}) ; 6.59(s, 1$ arom. H); $5.27(t, J=5.8, \mathrm{H}-\mathrm{C}(3)) ; 4.90,4.54(A B$, $\left.J_{A B}=15.9,2 \mathrm{H}-\mathrm{C}(1)\right) ; 3.853,3.850\left(2 s, 2 \mathrm{CH}_{3} \mathrm{O}\right) ; 3.21-3.04(\mathrm{~m}, 2 \mathrm{H}-\mathrm{C}(4)) ; 1.33(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}(20 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right): 177.67(s) ; 175.14(s) ; 148.21(s) ; 148.10(s) ; 124.55(s) ; 124.24(s) ; 111.46(d) ; 109.22(d) ; 55.91(q) ; 55.83$ $(q) ; 53.75(d) ; 45.73(t) ; 38.76(s) ; 29.86(t) ; 27.99(q) . \mathrm{MS}: 322\left(3.2, M^{+\cdot}+1\right), 321\left(16.9, M^{+\cdot}\right), 303(5.3), 275(2.5)$, 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•HCl). A soln. of 50 g of $(S)$-3-(3,4-dimethoxyphenyl)-2-methylalanine ( $=\mathrm{L}$-methyl-dopa; 220 mmol ) in 155 ml of conc. soln. HCl and 45.5 ml of aq. $\mathrm{CH}_{2} \mathrm{O}$ soln. (ca. $37 \%$ ) was heated at reflux for 20 min . Concentration to 150 ml and cooling in ice led to precipitation of $3 \mathrm{a} \cdot \mathrm{HCl}$. After washing with cold $\mathrm{H}_{2} \mathrm{O}$ and acetone, $59 \mathrm{~g}(98 \%) \cdot[\alpha]_{\mathrm{D}}=-14.9^{\circ}(c=1$, MeOH ). Anal. data, see [22].
(3S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methyl-2-pivaloylisoquinoline-3-carboxylic Acid (3d). Addition of $3.5 \mathrm{ml}(22.2 \mathrm{mmol})$ of $N, N$-dimethyl(trimethylsilyl)amine to a soln. of $5 \mathrm{~g}(17 \mathrm{mmol})$ of $3 \mathrm{a} \cdot \mathrm{HCl}$ in $50 \mathrm{ml} \mathrm{of} \mathrm{CH}_{2} \mathrm{Cl}_{2}$ under Ar was followed by 3 h of heating at reflux. After cooling to $25^{\circ}$, combining with 2.1 ml ( 17 mmol ) of pivaloyl chloride, stirring for 5 min , and cooling to $-5^{\circ}, 2.5 \mathrm{ml}(18 \mathrm{mmol})$ of $\mathrm{Et}_{3} \mathrm{~N}$ was slowly added and stirring continued for 2 h at r.t. The soln. was washed with 2 N aq. HCl and $\mathrm{H}_{2} \mathrm{O}$, dried $\left(\mathrm{MgSO}_{4}\right)$, and evaporated. The residue was dried (high vacuum) and recrystallized from EtOAc to give 5.0 g of $\mathbf{3 d} \cdot \operatorname{EtOAc}$ ( $85 \%$ ). M.p. $110-112^{\circ}$. $[\alpha]_{\mathrm{D}}=-33.1^{\circ}(c=1.0, \mathrm{MeOH})$. $1 \mathrm{R}(\mathrm{KBr}): 3400$ (br.), $2980 \mathrm{~m}, 2840 \mathrm{w}, 1740 \mathrm{~m}, 1710 \mathrm{~m}, 1630 \mathrm{~s}, 1520 \mathrm{~s}, 1410 \mathrm{~m}, 1365 \mathrm{~m}$, $1340 \mathrm{~m}, 1230 \mathrm{~m}, 1170 \mathrm{~s}, 1115 \mathrm{~s}, 1000 \mathrm{w} .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 6.75,6.71(2 \mathrm{~s}, 2$ arom. H); 4.70, $4.59(A B$,
$\left.J_{A B}=14.4,2 \mathrm{H}-\mathrm{C}(1)\right) ; 3.88\left(s, 2 \mathrm{CH}_{3} \mathrm{O}\right) ; 3.21,2.77\left(A B, J_{A B}=14.8,2 \mathrm{H}-\mathrm{C}(4)\right) ; 1.37\left(s, \mathrm{CH}_{3}\right), 1.33(s, t-\mathrm{Bu})$.
${ }^{13} \mathrm{C}-\mathrm{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 178.78(s) ; 176.64(s) ; 148.85(s) ; 147.94(s) ; 127.24(s) ; 126.34(s) ; 111.67(d) ; 109.21$ $(d) ; 62.28(s) ; 56.33(q) ; 56.24(q) ; 47.30(t) ; 39.58(t) ; 38.86(s) ; 28.12(q) ; 21.48(q) . \mathrm{MS}: 336\left(<1, M^{+}+1\right), 335$ (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 $\mathrm{C}_{22} \mathrm{H}_{33} \mathrm{NO}_{7} \cdot 1 / 2 \mathrm{H}_{2} \mathrm{O}$ (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)henzoate (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 $\mathbf{1 d}$, ent- $\mathbf{1 d}$, or $\mathbf{3 d}$ in 60 ml of THF stirred at $-75^{\circ}$ were added $6.7 \mathrm{ml}(10 \mathrm{mmol})$ of $t$-BuLi ( 1.5 m 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 $-75^{\circ}$ overnight. The resulting yellow soln, was poured into 100 ml of $\mathrm{H}_{2} \mathrm{O}$, extracted 2 times with 20 ml of $\mathrm{Et}_{2} \mathrm{O}$, and the aq. phase acidified with 2 N HCl . Extraction ( 3 times with 40 ml of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ), drying $\left(\mathrm{MgSO}_{4}\right)$, 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 $\mathbf{1 d}$ and $0.62 \mathrm{ml}(10 \mathrm{mmol})$ of Mel following $G P 1,1.36 \mathrm{~g}(98 \%)$ of $\mathbf{5}$. M.p. $163-164^{\circ}\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} /\right.$ petroleum ether $)$. IR (KBr): 3400 (br.), 2960s, $2690 \mathrm{~m}, 2570 \mathrm{~m}, 1740 \mathrm{~s}, 1590 \mathrm{~s}, 1580 \mathrm{~s}, 1410 \mathrm{~m}, 1370 \mathrm{~m}, 1120 \mathrm{~m}, 940 \mathrm{~m}, 760 \mathrm{~m}, 755 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}$ ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}, 25^{\circ}$ ): $8.6-8.0$ (br., COOH ); $7.20-7.06(m, 4$ arom. H$) ; 5.34(q, J=6.5, \mathrm{H}-\mathrm{C}(1)$ ); $5.30-3.25$ (br., $\mathrm{H}-\mathrm{C}(3)$ ); 3.25-3.19 ( $m, 2 \mathrm{H}-\mathrm{C}(4)$ ); 1.61-1.45 (br., $\mathrm{CH}_{3}$ ); $1.27(s, t-\mathrm{Bu}) . \mathrm{MS}: 275$ (1.9, $\left.\mathrm{M}^{+\prime}\right), 260$ (5.0), 242 (2.5), 190 (11.6), 176 (12.7), 149 (30.7), 130 (15.9), 57 (100). Anal. calc. for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{3}$ (275.35): C 69.79, H 7.69, N 5.09; found: C 69.49, H 7.72, N 5.10.
( $/ \mathrm{R}, 3 \mathrm{~S}$ )-1-Benzyl-1,2,3,4-tetrahydro-2-pivaloylisoquinoline-3-carboxylic Acid (6). From $1.3 \mathrm{~g}(5 \mathrm{mmol})$ of 1d and $0.65 \mathrm{ml}(5.5 \mathrm{mmol})$ of benzyl bromide following $G P I, 1.43 \mathrm{~g}(81 \%)$ of 6 after $\mathrm{FC}\left(\mathrm{Et}_{2} \mathrm{O} / \mathrm{CHCl}_{3} / \mathrm{AcOH}\right.$ 7:3:0.1). M.p. $193-194^{\circ}\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} /\right.$ petroleum ether). $[\alpha]_{\mathrm{D}}=-12.43^{\circ}(c=0.96, \mathrm{MeOH})$. IR ( K Br ): 3420 (br.), $3020 \mathrm{~m}, 2960 \mathrm{~m}, 1740 \mathrm{~s}, 1610 \mathrm{~m}, 1575 \mathrm{~s}, 1480 \mathrm{w}, 1450 \mathrm{w}, 1410 \mathrm{~m}, 1365 \mathrm{~m}, 1190 \mathrm{~s}, 925 \mathrm{w}, 765 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}(300 \mathrm{MHz}$, $\left(\mathrm{D}_{6}\right)$ DMSO, $\left.98.5^{\circ}\right) ; 12.2-11.0($ br., COOH$) ; 7.12-7.02(\mathrm{~m}, 6 \mathrm{H}) ; 6.78-6.73(\mathrm{~m}, 3$ arom. H$) ; 5.35(t, J=6, \mathrm{H}-\mathrm{C}(1))$; $4.85(t, J=4.2, \mathrm{H}-\mathrm{C}(3)) ; 3.04-2.98\left(m, \mathrm{PhCH}_{2}, \mathrm{H}_{\mathrm{ax}}-\mathrm{C}(4)\right) ; 2.762 .60\left(m, \mathrm{H}_{\mathrm{eq}}-\mathrm{C}(4)\right) ; 1.21(s, t-\mathrm{Bu}) . \mathrm{MS}: 352$ $\left(<1, M^{+\cdot}+1\right), 260(42.4), 216(7.3), 176(55.5), 149(13.6), 130(50.3), 57(100)$. Anal. calc. for $\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{NO}_{3}$ (351.45): C 75.19, H 7.17, N 3.99; found: C 75.19, H 7.20, N 3.89.
(IS,3R)-Enantiomer ent-6. Exactly like 6, from ent-1. M.p. 192-193 ${ }^{\circ}$, opposite sense for $[\alpha]_{\mathrm{D}}$.
$1,1^{\prime}, 2,2^{\prime}, 3,3^{\prime}, 4,4^{\prime}$-Octahydro- $6,6^{\prime}, 7,7^{\prime}$-tetramethoxy-3, $3^{\prime}$-dimethyl-2, $2^{\prime}$-pivaloyl-[1, $1^{\prime}$-biisoquinoline $]-3,3^{\prime}$-dicarboxylic Acid (10). From $1.7 \mathrm{~g}(5 \mathrm{mmol})$ of 3 d and $0.65 \mathrm{ml}(10 \mathrm{mmol})$ of MeI following GP 1 ( FC with $\mathrm{Et}_{2} \mathrm{O} / \mathrm{MeOH} /$ $\mathrm{AcOH} 3: 2: 0.1), 1.6 \mathrm{~g}(90 \%$ ) of $\mathbf{1 0 a} / 10 \mathrm{~b}$ (cf. Footnote 14 in [1]). IR ( KBr ): 3430 (br) $, 2970 \mathrm{~m}, 2870 \mathrm{w}, 2840 \mathrm{w}$, $2740-2340,1705 s, 1645 s, 1620 s, 1595(\mathrm{sh}), 1520 \mathrm{~s}, 1390 \mathrm{~m}, 1360 \mathrm{~s}, 1290 \mathrm{~s}, 1230 \mathrm{~s}, 1110 \mathrm{~m}, 1010 \mathrm{w}, 880 \mathrm{w}, 845 \mathrm{w}$. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz},\left(\mathrm{D}_{6}\right) \mathrm{DMSO}, 98.5^{\circ} ; \mathbf{1 0 a} / \mathbf{1 0 b}\right): 6.76 / 6.70(s, 1$ arom. H); 6.42/6.38 ( $s, 1$ arom. H); 5.14/5.05 ( $s$, $\mathrm{H}-\mathrm{C}(1)) ; 3.76 / 3.75\left(s, \mathrm{CH}_{3} \mathrm{O}\right) ; 3.69 / 3.67\left(s, \mathrm{CH}_{3} \mathrm{O}\right) ; 3.11-3.04(\mathrm{~m}, 1 \mathrm{H}) ; 2.73-2.62(\mathrm{~m}, \mathrm{H}-\mathrm{C}(4)) ; 1.37 / 1.27\left(s, \mathrm{CH}_{3}\right)$; $1.23 / 1.18(s, t$-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 $\mathbf{1 d}$ or $\mathbf{2 d}$ in 60 ml of THF was combined with $6.7 \mathrm{ml}(10 \mathrm{mmol})$ of $1.50 \mathrm{~m} t-\mathrm{BuLi}$ (in hexane) at $-75^{\circ}$. After 1.5 h at $-75^{\circ}, 3.9 \mathrm{ml}(10 \mathrm{mmol})$ of $\mathrm{MgBr}_{2} \cdot \mathrm{OEt}_{2}$ [1] [40] was added all at once to the stirred deep red mixture. The cooling bath was removed, and after 15 min at $0^{\circ}$, the mixture was recooled to $-75^{\circ}$. The aldehyde ( 5.5 mmol; neat $\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{CHO}$ or THF soln. of $4 \mathrm{c}, c a .10 \mathrm{ml} / \mathrm{g}$ ) was added and stirring continued at $-80^{\circ}$ overnight, before pouring into $100 \mathrm{ml} \mathrm{H}_{2} \mathrm{O}$ and working up.
(3R)-1,2,3,4-Tetrahydro-3-( $\alpha$-hydroxybenzyl)-2-pivaloylisoquinoline-3-carboxylic Acid (7a). Following GP 2, $1.3 \mathrm{~g}(5 \mathrm{mmol})$ of ent $\mathbf{1 d}$ and $0.55 \mathrm{ml}(5.5 \mathrm{mmol})$ of benzaldehyde gave $1.08 \mathrm{~g}(58 \%)$ of $7 \mathbf{a}$, single diastereoisomer [probably $(1 R, \alpha S)$ configuration, i.e. coupling of the trigonal centers with rel. topicity $u l$ (as with the achiral tetrahydroisoquinoline analogues [1]), and approach of the aldehyde from the face opposite to the COOLi group (rel. topicity $u l-1,3$ as with the alkyl halides above)]. FC with EtOAc/hexane/AcOH 10:15:0.2 gave a colorless powder which was not further purified. $[\alpha]_{\mathrm{D}}=+18.9^{\circ}\left(c=0.79, \mathrm{CHCl}_{3}\right.$ ). IR ( KBr ): $3600 \mathrm{~m}, 3400$ (br.), 3030 m , $2970 \mathrm{~s}, 1740 \mathrm{~s}, 1720 \mathrm{~m}$ (sh), $1600 \mathrm{~s}, 1580 \mathrm{~s}, 1480 \mathrm{~m}, 1450 \mathrm{~m}, 1410 \mathrm{~m}, 1365 \mathrm{~m}, 1180 \mathrm{~s}, 1050 \mathrm{~m}, 760 \mathrm{~m}, 700 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}$ ( 300 $\left.\mathrm{MHz},\left(\mathrm{D}_{6}\right) \mathrm{DMSO}, 98.5^{\circ}\right): 7.247 .02(m, 7 \mathrm{H}) ; 6.83-6.78(m, 1$ arom. H$) ; 6.12(d, J=7.3,1$ arom. H); $5.36(d$, $J=1.9, \mathrm{H}-\mathrm{C}(1)) ; 5.10(d, J=1.9, \mathrm{H}-\mathrm{C}(\alpha)) ; 5.04\left(A B X, J_{A X}+J_{B X}=8, \mathrm{H}-\mathrm{C}(3)\right) ; 4.90-4.70(m, \mathrm{OH}) ; 3.50,3.05$ $\left(A B X, J_{A X}=5, J_{B X}=3, J_{A B}=14.8,2 \mathrm{H}-\mathrm{C}(4)\right) ; 1.24(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$, r.t.; both rotamers): $181.34,175.25(2 s) ; 176.82,173.07(2 s) ; 140.74 ; 136.31 ; 133.42 ; 133.07 ; 129.75 ; 128.96 ; 128.74 ; 128.11 ; 127.95 ;$ $127.54 ; 127.24 ; 126.62 ; 126.19 ; 79.99,76.38(2 d) ; 64.39,56.97(2 d) ; 58.42,52.82(2 d) ; 40.14,38.82(2 s) ; 32.34,29.46$
(2t); $28.58,26.98(2 q)$. MS: $368\left(<1, M^{+*}+1\right), 322(<1), 266(1.8), 243(3.0), 220(4.7), 176(100), 130(32), 57$ (14.6).

Methyl (3R)-1,2,3,4-Tetrahydro-1-1 $\alpha$-(pivaloyloxy)benzy/jisoquinoline-3-carboxylate (8). Following the procedure given in [1], 0.4 g ( 1.06 mmol ) of 7a were heated at reflux with $\mathrm{MeOH} / \mathrm{HCl}$ (causing both esterification, and pivaloyl migration with retention of configuration [1] from N to O$)$ for 5 h to give, after $\mathrm{FC}\left(\mathrm{Et}_{2} \mathrm{O} /\right.$ pentane $\left.1: 1\right)$, $0.27 \mathrm{~g}(66 \%)$ of 8 (single diastereoisomer, probably of ( $1 R, \alpha S$ ) configuration, see above 7a). $[\alpha]_{\mathrm{D}}=+6.1^{\circ}(c=1$, $\mathrm{MeOH}),[\alpha]_{\mathrm{D}}=+3.46^{\circ}\left(c=0.98, \mathrm{CHCl}_{3}\right)$. IR $\left(\mathrm{CHCl}_{3}\right): 3020 w, 2980 w, 2870 w, 1730 s$ (br.), $1480 \mathrm{~m}, 1150 \mathrm{~s}, 1030 w$. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 7.40-7.02(\mathrm{~m}, 9 \mathrm{arom} . \mathrm{H}) ; 5.95(d, J=6, \mathrm{H}-\mathrm{C}(\alpha)) ; 4.57(d, J=6, \mathrm{H}-\mathrm{C}(1)) ; 3.63(s$, $\left.\mathrm{CH}_{3} \mathrm{O}\right) ; 3.63-3.60(\mathrm{~m}, \mathrm{H}-\mathrm{C}(3)) ; 2.85-2.80(\mathrm{~m}, 2 \mathrm{H}-\mathrm{C}(4)) ; 1.22(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 177.19(s)$; $173.45(s) ; 137.54(s) ; 133.62(s) ; 133.30(s) ; 128.90(d) ; 128.44(d) ; 128.20(d) ; 128.09(d) ; 127.09(d) ; 125.87(d)$; $78.43(d) ; 58.14(d) ; 52.11(d) ; 51.82(q) ; 38.87(t) ; 31.48(s) ; 27.15(q)$. MS: $322(3.8), 220(18.4), 190(95.5), 130$ (100), 57 (51.3).
( $1 \mathrm{~S}, 3 \mathrm{~S}$ )-1-[ $I^{\prime}, 3^{\prime}$-Dihydro-4',5'-(methylenedioxy)-3'-oxoisobenzofuryl]-1,2,3,4-tetrahydro-6,7-dimethoxyiso-quinoline-3-carboxylic Acid $(\mathbf{9 a} / \mathbf{9 b})$. Following GP 2, we obtained from $1.6 \mathrm{~g}(5.5 \mathrm{mmol})$ of $\mathbf{2 d}$ and $1.2 \mathrm{~g}(5.5 \mathrm{mmol})$ of $4 \mathrm{c} 1.89 \mathrm{~g}(68 \%)$ of unseparated $9 \mathrm{a} / 9 \mathrm{~b}$ (ratio $\left.3: 2^{8}\right) ; 0.5 \mathrm{~g}$ of unreacted 2 d was recovered), after FC with $\mathrm{Et}_{2} \mathrm{O} / \mathrm{CHCl}_{3} / \mathrm{AcOH} 7: 3: 0.1$. ${ }^{l} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz},\left(\mathrm{D}_{6}\right) \mathrm{DMSO}, 98.6^{\circ} ; 2\right.$ diastereoisomers): 7.24 7.11 ( $\mathrm{m}, 4$ arom. $\mathrm{H}) ; 6.88-6.61(\mathrm{~m}, 3$ arom. H$) ; 6.14,6.10\left(2 s\right.$, each $\left.2 \mathrm{H}, 2 \times \mathrm{OCH}_{2} \mathrm{O}\right) ; 5.84-5.81(m, 2 \times \mathrm{H}-\mathrm{C}(1), 1$ arom. H$) ; 5.69$ $\left(d, J=4, \mathrm{H}-\mathrm{C}\left(1^{\prime}\right)\right) ; 5.64\left(d, J=1.3, \mathrm{H}-\mathrm{C}\left(1^{\prime}\right)\right) ; 5.13(m, \mathrm{H}-\mathrm{C}(3)) ; 5.08(m, \mathrm{H}-\mathrm{C}(3)) ; 3.74,3.70,3.68,3.31$ (4s, $4 \times \mathrm{CH}_{3} \mathrm{O}$ ); 3.38-3.03 ( $m, 2 \times 2 \mathrm{H}-\mathrm{C}(4)$ ); 1.30, $1.26(2 s, 2 \times t-\mathrm{Bu})$. 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 $\mathrm{Et}_{3} \mathrm{~N}$ and electrolized with a current density of $c a . i=300 \mathrm{~mA} / \mathrm{cm}^{2}$. The temp. of the mixture was kept between -2 and $+5^{\circ}$. The solvent was evaporated, the residue dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, the resulting soln. washed with aq. $\mathrm{Na}_{2} \mathrm{CO}_{3}$ and sat. NaCl soln., dried $\left(\mathrm{MgSO}_{4}\right)$, and evaporated.
tert-Butyl (( 1 R )-1,2,3,4-Tetrahydro-3-methoxy-1-methylisoquinolin-2-yl) Ketone (11). A soln. of $1.67 \mathrm{~g}(6$ $\mathrm{mmol})$ of 5 and 0.282 ml of $\mathrm{Et}_{3} \mathrm{~N}$ in 15 ml of MeOH was electrolyzed following $G P 3\left(i=300 \mathrm{~mA} / \mathrm{cm}^{2}, 2.6 \mathrm{~F} / \mathrm{mol}\right)$. Removal of the MeOH gave $1.26 \mathrm{~g}(80 \%)$ of a single diastereoisomer 11 of undetermined configuration. M.p. $117.5-118.5^{\circ}$ (from $\mathrm{Et}_{2} \mathrm{O}$ ). IR (KBr): 3420 (br.), $3040 \mathrm{w}, 2980 \mathrm{~m}, 2920 \mathrm{~m}, 2820 \mathrm{w}, 1640 \mathrm{~s}, 1460 \mathrm{~m}, 1400 \mathrm{~m}, 1380 \mathrm{~m}$, $1340 \mathrm{~m}, 1290 \mathrm{~m}, 1060 \mathrm{~s}, 760 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) ; 7.23-7.13(\mathrm{~m}, 4$ arom. H$) ; 5.51\left(A B X, J_{A X}=5\right.$, $\mathrm{H}-\mathrm{C}(3)) ; 5.28(q, J=6.4, \mathrm{H}-\mathrm{C}(1)) ; 3.19,3.00\left(A B X, J_{A B}=15.6, J_{A X}=15.6, J_{B X}=1.7,2 \mathrm{H}-\mathrm{C}(4)\right) ; 3.06(s$, $\left.\mathrm{CH}_{3} \mathrm{O}\right) ; 1.34(s, t-\mathrm{Bu}) ; 1.29\left(d, J=6.4, \mathrm{CH}_{3}\right) . \mathrm{MS}: 246(1.6), 230(10.5), 214.5$ (19.0), $130(53.2), 118$ (10.2), 57 (100). Anal. calc. for $\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{NO}_{2}$ (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$)$-I-Benzyl-l,2,3,4-tetrahydro-3-methoxyisoquinolin-2-yl) Ketone (12). From $0.7 \mathrm{~g}(2 \mathrm{mmol})$ of $6,0.055 \mathrm{ml}(0.4 \mathrm{mmol})$ of $\mathrm{Et}_{3} \mathrm{~N}$, and 3 ml of MeOH following $G P 3\left(i=250 \mathrm{~mA} / \mathrm{cm}^{2}, 2.2 \mathrm{~F} / \mathrm{mol}\right), 0.53 \mathrm{~g}(78 \%)$ of 12 were obtained as a yellow oil. ${ }^{1} \mathrm{H}-\mathrm{NMR}(90 \mathrm{MHz})$ : $7.28-6.53(\mathrm{~m}, 9$ arom. H$) ; 5.50-5.23(m, \mathrm{H}-\mathrm{C}(1), \mathrm{H}-\mathrm{C}(3))$; 3.16-2.76 ( $m, \mathrm{CH}_{3} \mathrm{O}, \mathrm{PhCH}_{2}$ ); $1.48(s, t-\mathrm{Bu})$.

Mixture of Diastereoisomers of 6,7-( Methylenedioxy)-3-( $1^{\prime}, 2^{\prime}, 3^{\prime}, 4^{\prime}$-tetrahydro-3', $6^{\prime}, 7^{\prime}$-trimethoxy-2'-pivaloyl-isoquinolin- $\left.I^{\prime}-y l\right)$ isobenzofuran- $1(3 \mathrm{H})$-one ( $\mathbf{1 7}$ ). A soln. of $1.3 \mathrm{~g}(2.6 \mathrm{mmol})$ of $9 \mathrm{a} / 9 \mathrm{~b}, 0.07 \mathrm{ml}^{2} \mathrm{of} \mathrm{Et}_{3} \mathrm{~N}$, and 10 ml of MeOH was electrolyzed according to $G P 3\left(i=300 \mathrm{~mA} / \mathrm{cm}^{2}, 2.6 \mathrm{~F} \cdot \mathrm{~mol}\right)$. Evaporation of the MeOH gave 1.2 g ( $95 \%$ ) of a mixture of diastereoisomers 17 ( FC with $\mathrm{Et}_{2} \mathrm{O} / \mathrm{CHCl}_{3} 4: 1$ ). ${ }^{1} \mathrm{H}-\mathrm{NMR}$ ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$; mixture of diastereoisomers): $7.13(s, 1 \mathrm{H}) ; 7.05-6.57(\mathrm{~m}, 3$ arom. H$) ; 6.11\left(\mathrm{~m}, \mathrm{OCH}_{2} \mathrm{O}\right) ; 6.08-5.29\left(\mathrm{~m}, \mathrm{H}-\mathrm{C}\left(\mathrm{l}^{\prime}\right), \mathrm{H}-\mathrm{C}(3)\right.$, $\mathrm{H}-\mathrm{C}\left(3^{\prime}\right)$ ); 3.86, $3.85,3.83,3.45\left(4 s, 2 \mathrm{CH}_{3} \mathrm{O}\right) ; 3.48\left(s, \mathrm{CH}_{3} \mathrm{O}-\mathrm{C}\left(3^{\prime}\right)\right.$ ); 1.40, $1.30(s, t-\mathrm{Bu}) . \mathrm{MS}: 452(<0.1), 368$ (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 $\mathbf{N a C N B H}_{3}$. - tert-Butyl (( R$)-1,2,3,4$-Tetrahydro-I-methyl-isoquinolin-2-yl) Ketone (13). A soln. of $1.0 \mathrm{~g}(3.8 \mathrm{mmol})$ of 11 and 0.250 g of $\mathrm{NaCNBH}_{3}(3.9 \mathrm{mmol})$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The soln. was washed with $\mathrm{H}_{2} \mathrm{O}$ and dried $\left(\mathrm{MgSO}_{4}\right)$. Removal of the solvent gave $0.85 \mathrm{~g}(96 \%)$ 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 $\mathrm{NaCNBH}_{3}$ reduction of 12 as described for 13. Yield $>90 \%$. ${ }^{\prime} \mathrm{H}-\mathrm{NMR}\left(90 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $7.28-6.73$ ( $\mathrm{m}, 9$ arom. H ); $5.8(t, J=7.5$ );

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

6,7-( Methylenedioxy)-3-( $I^{\prime}, 2^{\prime}, 3^{\prime}, 4^{\prime}$-tetrahydro- $6^{\prime}, 7^{\prime}$-dimethoxy- $2^{\prime}$-pivaloylisoquinolin- $\left.I^{\prime}-y l\right)$ isobenzofuran$I(3 \mathrm{H})$-one (18). Under the $\mathrm{NaCNBH}_{3}$ reduction conditions used in the previous two cases, $1.04 \mathrm{~g}(2.16 \mathrm{mmol})$ of 17 (mixture of diastereoisomers) gave $0.82 \mathrm{~g}(83 \%)$ of crude product containing two and only two diastereoisomers $\mathbf{1 8 a} / \mathbf{1 8 b}$ which were separated by FC with $\mathrm{Et}_{2} \mathrm{O} / \mathrm{CHCl}_{3} 4: 1$ and recrystallized from EtOAc: $0.55 \mathrm{~g}(56 \%)$ of $\mathbf{1 8 a}$ ( $u$-configuration) and $0.23 \mathrm{~g}\left(23 \%\right.$ ) of $\mathbf{1 8 b}$ ( $l$-configuration). Since 18 a gave $(+)$-corlumin, it is the ( $3 R, 1^{\prime} S$ )-stereoisomer.

Major Epimer 18a (colorless powder). $[\alpha]_{\mathrm{D}}=-128.14^{\circ}\left(c=0.97, \mathrm{CHCl}_{3}\right)$. IR (KBr): 3420 (br.), 2970m, $2930 \mathrm{~m}, 2840 \mathrm{w}, 1770 \mathrm{~s}, 1640 \mathrm{~s}, 1540 \mathrm{~s}, 1480 \mathrm{~s}, 1410 \mathrm{~m}, 1245 \mathrm{~s}, 1180 \mathrm{~m}, 1120 \mathrm{~m}, 970 \mathrm{~m}, 760 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}(300 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right): 7.27-7.18\left(A B, J_{A B}=7.5,2\right.$ arom. H$) ; 6.58(\mathrm{~s}, 1$ arom. H$) ; 6.14\left(\mathrm{~m}, \mathrm{OCH}_{2} \mathrm{O}\right) ; 5.87(\mathrm{~s}, 1$ arom. H$) ; 5.78(\mathrm{~m}$, $\mathrm{H}-\mathrm{C}\left(1^{\prime}\right)$ ) ; 5.65 (br. $s, \mathrm{H}-\mathrm{C}(3)$ ); 4.11-4.03 ( $\mathrm{m}, 2 \mathrm{H}-\mathrm{C}\left(3^{\prime}\right)$ ); $3.80\left(\mathrm{~s}, \mathrm{CH}_{3} \mathrm{O}\right) ; 3.34\left(\mathrm{~s}, \mathrm{CH}_{3} \mathrm{O}\right) ; 2.96-2.85(\mathrm{~m}, 2$ $\left.\mathrm{H}-\mathrm{C}\left(4^{*}\right)\right) ; 1.38(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 177.71(\mathrm{~s}) ; 149.35(\mathrm{~s}) ; 148.39(s) ; 146.51(\mathrm{~s}) ; 144.86(s)$; $141.07(s) ; 127.96(s) ; 120.93(s) ; 115.37(d) ; 113.82(d) ; 111.09(d) ; 109.83(d) ; 103.39(t) ; 85.49(d) ; 57.72(d) ;$ $55.74(q) ; 55.35(q) ; 42.60(t) ; 39.16(s) ; 28.65(t) ; 28.19(q)$. MS: $452\left(<1, M^{+\cdot}-1\right), 276(100), 192(31.6), 177$ (5.9): 85 (7.9), 57 (91.9).

Minor Epimer 18b. M.p. $237-238^{\circ} .[\alpha]_{\mathrm{D}}=-82.3^{\circ}\left(c=0.82, \mathrm{CHCl}_{3}\right)$. IR ( KBr ): 3440 (br), $2980 \mathrm{~m}, 2940 \mathrm{~m}$, $2840 w, 1760 s, 1620 s, 1520 s, 1480 s, 1410 \mathrm{~m}, 1255 s, 1170 \mathrm{~m}, 1120 \mathrm{~m}, 1040 \mathrm{~s}, 980 \mathrm{~m}, 960 \mathrm{~m} .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $7.14-7.05(m, 2$ arom. H$) ; 6.83,6.60(2 s, 2$ arom. H$) ; 6.37\left(d, J=2.2, \mathrm{H}-\mathrm{C}\left(1^{\prime}\right)\right) ; 6.15\left(s, \mathrm{OCH}_{2} \mathrm{O}\right) ; 5.96(d, J=3$, $\mathrm{H}-\mathrm{C}(3)) ; 4.11-4.05\left(\mathrm{~m}, 1 \mathrm{H}-\mathrm{C}\left(3^{\prime}\right)\right) ; 3.90,3.86\left(2 \mathrm{~s}, 2 \mathrm{CH}_{3} \mathrm{O}\right) ; 3.69-3.59\left(\mathrm{~m}, 1 \mathrm{H}-\mathrm{C}\left(3^{\prime}\right)\right) ; 2.77-2.70\left(\mathrm{~m}, 2 \mathrm{H}-\mathrm{C}\left(4^{\prime}\right)\right)$; $1.01(s, t-\mathrm{Bu}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 177.27(\mathrm{~s}) ; 166.89(\mathrm{~s}) ; 149.16(\mathrm{~s}) ; 148.52(\mathrm{~s}) ; 148.07(\mathrm{~s}) ; 144.19(\mathrm{~s})$; $139.30(s) ; 126.78(s) ; 124.25(s) ; 117.01(d) ; 113.10(d) ; 111.79(d) ; 109.89(d) ; 103.23(t) ; 86.84(d) ; 56.25(q)$; $56.00(q) ; 52.99(d) ; 42.73(t) ; 38.87(s) ; 29.02(t) ; 28.07(q)$. MS: $452\left(1, M^{+\cdot}-1\right), 176(100), 192(34.1), 177(6.1)$, 57 (74.8). Anal. calc. for $\mathrm{C}_{25} \mathrm{H}_{27} \mathrm{NO}_{7}$ (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 $\mathbf{N a A l H}_{4}-$ ( R )-I,2,3,4-Tetrahydro-I-methylisoquinoline ( $\mathbf{1 5}$ ). Following the procedure given below for 16, a soln. of $0.3 \mathrm{~g}(1.3 \mathrm{mmol})$ of 13 in 3 ml of THF was combined with a soln. of 58 $\mathrm{mg}(0.8 \mathrm{mmol})$ of $\mathrm{NaAlH}_{4}$ in 5 ml of THF to give $0.11 \mathrm{~g}(60 \%)$ of oily frce amine. Hydrochloride: $[\alpha]_{\mathrm{D}}=+42^{\circ}$ $\left(c=1.13, \mathrm{EtOH} ;[33]:-44^{\circ}(c=1.24, \mathrm{EtOH})\right.$ for ent-15).
(R)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline (16). To a soln. of $0.41 \mathrm{~g}(1.33 \mathrm{mmol})$ of $\mathbf{1 4} \mathrm{in} 3 \mathrm{ml}$ of dry THF stirred at $0^{\circ}$ was added dropwise a pale soln. of $84 \mathrm{mg}(1.2 \mathrm{mmol})$ of $\mathrm{NaAlH}_{4}[32]$ in 5 ml of THF. The mixture was allowed to warm slowly to r.t. and was stirred overnight. $\mathrm{H}_{2} \mathrm{O}(\mathrm{I} \mathrm{ml})$ was added. $\mathrm{Et}_{2} \mathrm{O}$ was added and the amine first extracted into the $\mathrm{H}_{2} \mathrm{O}$ layer with 2 N HCl , and then set free with $10 \% \mathrm{KOH}$ soln. and extracted into $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. After drying $\left(\mathrm{MgSO}_{4}\right)$, evaporation, and freeing the product of last traces of volatile impurities under high vacuum, 0.24 $\mathrm{g}(80 \%)$ of a slightly yellow oil was isolatcd. $[\alpha]_{\mathrm{D}}=+60.1^{\circ}\left(c=1.11\right.$, THF; $[8]:+62.6^{\circ}(c=0.92$, THF $)$. $[\alpha]_{\mathrm{D}}=+43.3^{\circ}\left(c=1.05, \mathrm{MeOH} ;[33]:-44^{\circ}(c=16, \mathrm{MeOH})\right.$ for ent-16). IR (film$): 3400-3200,3020,2920,2830$, $2800,1600,1490,1450,1425,1315,1125,1080,1030,960 .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(90 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 7.55-6.93(\mathrm{~m}, 9$ arom. H$)$; $4.23(d d, J=10,4 \mathrm{H}-\mathrm{C}(1)) ; 3.53-2.56\left(\mathrm{~m}, \mathrm{PhCH}_{2}, 2 \mathrm{H}-\mathrm{C}(3), 2 \mathrm{H}-\mathrm{C}(4)\right) ; 1.73(\mathrm{~s}, \mathrm{NH})$.
8. Conversion of 18 a to (+)-Corlumine (19). - Norcorlumine ( NH instead of $\mathrm{NCH}_{3}$; obtained by hydrolytic cleavage of the pivalamide following the procedure given for this type of reaction in [1], yield $31 \%$ (FC with $\mathrm{Cl}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 15: 1$ ) ) was methylated ( $63 \%$ ) as indicated in Scheme 3 to give ( $3 \mathrm{R}, 1^{\prime} \mathrm{S}$ )-6,7-(methylenedioxy)-3( $I^{\prime}, 2^{\prime}, 3^{\prime}, 4^{\prime}$-tetrahydro- $6^{\prime}, 7^{\prime}$-dimethoxy-2'-methylisoquinolin- $I^{\prime}-y l$ ) isobenzofuran- $1\left(3 \mathrm{H}\right.$ )-one (19) ( FC with $\mathrm{Et}_{2} \mathrm{O}$ / MeOH 15:1). M.p. $156-157^{\circ}$ (from MeOH; [35]: $162^{\circ}$ ). $[\alpha]_{\mathrm{D}}=+61^{\circ}\left(c=1.9, \mathrm{CHCl}_{3} ;[35]:[\alpha]_{\mathrm{D}}=+77.0^{\circ}(c=1.0\right.$, $\mathrm{CHCl}_{3}$ ), cf. Footnote 5). IR (KBr): 3340 (br.), 2940m, 2910m, 2840w, 2800w, 1760s, $1650 \mathrm{w}, 1610 \mathrm{~m}, 1520 \mathrm{~s}, 1480 \mathrm{~s}$, $1200 \mathrm{~s}, 1140 \mathrm{~m}, 1100 \mathrm{~m}, 1040 \mathrm{~m}, 1025 \mathrm{~m}, 970 \mathrm{~m}, 780 \mathrm{w} .{ }^{.} \mathrm{H}-\mathrm{NMR}\left(90 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 6.91(d, J=7.5,1$ arom. H$) ; 6.6(s$, 1 arom. H); $6.39\left(s, 1\right.$ arom. H); $6.23\left(d, J=7.5,1\right.$ arom. H); $6.13\left(s, \mathrm{OCH}_{2} \mathrm{O}\right) ; 5.63(d, J=7.5,1$ arom. H); $4.06(d$, $J=4.5, \mathrm{H}-\mathrm{C}(3)) ; 3.83,3.65\left(2 s, 2 \mathrm{CH}_{3} \mathrm{O}\right) ; 3.13-2.06(m, 2 \mathrm{H}-\mathrm{C}(3), 2 \mathrm{H}-\mathrm{C}(4)) ; 2.56\left(s, \mathrm{CH}_{3} \mathrm{~N}\right)$ (see [35]). ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(20 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): 166.60 ; 148.94 ; 148.35 ; 147.26 ; 140.72 ; 129.41 ; 123.42 ; 115.35 ; 112.79 ; 111.54$; $111.03 ; 110.32 ; 102.99 ; 84.69 ; 65.77 ; 55.92 ; 55.80 ; 49.29 ; 44.89 ; 27.31$ (see [41]). MS: $384\left(<1, M^{+\cdot}+1\right), 383(<1$, $M^{+}$), $206(100), 190(12.3), 177(3.2), 162(4.7), 145(2.9), 132(2.7)$. Anal. calc. for $\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{NO}_{6} \cdot 0.4 \mathrm{H}_{2} \mathrm{O}(390.6): \mathrm{C}$ 64.50, H 5.58, N 3.58 ; found: C 64.61, H 5.59, N 3.28.

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[^0]:    ${ }^{1}$ ) Part II of an investigation on diastereoselective C,C-bond formation in the 1-position of 1,2,3,4-tetrahydroisoquinolines. For part I, sce [1].
    ${ }^{2}$ ) Part of the Ph. D. thesis by I.M.P.H., Dissertation No.8397, ETH Zürich, 1987.

[^1]:    ${ }^{3}$ ) The reductive cleavage with $\mathrm{NaAlH}_{2}\left(\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OCH}_{3}\right)_{2}$ used previously by us [29] was not successful here. Also, $\mathrm{Na}_{2} \mathrm{O}_{2}$ [30], $\mathrm{KOH} / \mathrm{H}_{2} \mathrm{NNH}_{2} / \mathrm{glycol}$ [31], and carefully controlled amounts of $\mathrm{LiAlH}_{4}$ did not cleave satisfactorily. Even in the case of $\mathrm{NaAlH}_{4}$, 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.

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[^3]:    ${ }^{8}$ ) The long reaction time used ( $14 \mathrm{~h},-80^{\circ}$; see $G P 2$ ) may have been responsible for the loss of diastereoselectivity, due to epimerization at $C\left(1^{\prime}\right)$ !

