# Synthesis of the Salutaridine and Aporphine Skeleton via Palladium(0) Catalyzed Cyclization and $\mathrm{S}_{\mathrm{RN}} 1$ Reaction of 2'-Bromoreticulines 

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#### Abstract

Two intramolecular aryl-aryl-coupling reactions of $2^{2}$-bromoreticulines are described. Their regioselectivity depends on the cyclization method. The palladium(0) catalyzed reaction of 22 leads preferentially to the salutaridine derivative 27 , whilst via the photochemically induced $\mathrm{S}_{\mathrm{RN}} 1$ reaction of 22 the aporphine skeleton 24 is obtained.


## Introduction

For decades the synthesis of morphine (3) has presented a continuous challenge in organic synthesis. ${ }^{1}$ Cyclization between C-12 and C-13 has been the key step in a number of approaches. An efficient way to form this bond is the acid catalyzed intramolecular electrophilic aromatic substitution of 1-benzyloctahydroisoquinolines, the Grewe cyclization. ${ }^{2}$ A recent approach uses the Heck reaction to form the quarternary center at $\mathrm{C}-13 .{ }^{3}$ In the biosynthesis ${ }^{4}$ of morphine the $\mathrm{C}-12-\mathrm{C}-13$ bond is formed by an oxidative phenolic coupling that converts reticuline (1) to salutaridine (2) from which morphine is obtained in six steps (scheme 1). With chemical oxidizing agents the regioselectivity of the desired $\mathrm{C}-4 \mathrm{a}-\mathrm{C}-2^{\prime}$ coupling is difficult to control. The best results have been obtained with $I$,I-bistrifluoroacetoxyiodosobenzene ( $21-32 \%$ ) ${ }^{5}$ and thallium tristrifluoroacetate $(23 \%) 6$.


Scheme 1

## Results

We report here on a regioselective $\mathrm{C}-4 \mathrm{a}-\mathrm{C}-2^{\prime}$ coupling of $2^{\prime}$-bromoreticulines by means of a palladium( 0 ) catalyzed reaction and a regioselective C-8-C-2' coupling of the same derivatives by means of a $\mathrm{S}_{\mathrm{RN}} 1$ reaction. The synthetically very powerful palladium( 0 ) catalyzed coupling of aryl halides with metallated arenes ${ }^{7}$ or aryl boronic acids ${ }^{8}$ is not applicable to the $\mathrm{C}-4 \mathrm{a}-\mathrm{C}-2^{\prime}$ coupling in $2^{\prime}$-bromoreticulines since the $\mathrm{C}-4 \mathrm{a}$ position is already substituted. Ames ${ }^{9}$ described a palladium( 0 ) catalyzed biaryl synthesis starting from aryl halides and unactivated arenes. This coupling reaction, however, has not yet been carried out with an aryl residue whose coupling site bears a carbon substituent and thus will lead to a quaternary carbon center as present at C-13 of morphine, nor have phenols been used as nucleophilic aryl residues. In pursuit of such palladium(0) catalyzed reactions the coupling of aryl ether $4^{10}$ under different reaction conditions was investigated (scheme 2).


Scheme 2

The reaction conditions published by Ames $^{9}$ (palladium(II) chloride, potassium carbonate, dimethylformamide, $140^{\circ} \mathrm{C}$ ) were applied to 4 , but an unsatisfactory ratio of $5: 95^{11}$ of the desired cyclized product 7 to the reduced compound 9 was observed. Stabilization of palladium( 0 ) with triphenylphosphine increases this ratio to $69: 31(7: 9)$. With the more soluble sodium acetate instead of potassium carbonate 7 and 9 were obtained in yields of $66 \%(7)$ resp. $5 \%(9)$, this is a satisfactory ratio of $93: 7$. By means of the aryl ethers 5 and 6 the influence of substituents in the aryloxy group which correspond to those in reticuline was studied. With 6 a good selectivity for the cyclized product $8(56 \%, 11: 5 \%)$ was obtained. It was gratifying that the phenolic function in 6 enables a successful cyclization. However, in 5 where the coupling site is substituted by a methyl group reduction to 10 is the only observed reaction.

For the $\mathrm{S}_{\mathrm{RN}} 1$ reaction of aromatic compounds Ar-X with nucleophiles $\mathrm{Nu}^{-}$in which cross coupled products Ar-Nu were obtained the rate constants for the different steps of the radical chain have been determined. ${ }^{12}$ These results give insight both into the mechanism and into the preparative scope of this reaction. Successful couplings between phenolates ( $\mathrm{Nu}^{-}$) and aryl halides (Ar-X) to afford biaryls (Ar-Nu) have been reported. ${ }^{13}$ With 6 in dimethyl sulfoxide and sodium as initiator only the debrominated product 11 was obtained. When the reaction was photoinitiated the desired cyclized product 8 was obtained in a yield of $79 \%$. The generation of the quarternary $\mathrm{C}-13$ center in morphine appears to be possible by a $\mathrm{S}_{\mathrm{RN}} 1$ reaction, since 4 -methylphenol as nucleophile afforded besides $49 \%$ of the ortho coupling product $23 \%$ of the para coupling product with a dienone structure. ${ }^{14}$

The reaction conditions elaborated for $\mathbf{4 , 5} 5$ and $\mathbf{6}$ were now transferred to a $2^{\prime}$-bromoreticuline derivative. For that purpose 23 was synthesized from vanilline (12) and isovanilline (16) via the carbamate 15 and the enolether 21 using the Comins variant ${ }^{15}$ of the Pictet-Spengler cyclization (scheme 3). The overall yield of this nine step procedure is $18 \%$.

However, a conversion of $\mathbf{2 3}$ could neither be observed under the most favorable conditions for the palladium( 0 ) catalyzed cyclization nor under those for the $\mathrm{S}_{\mathrm{RN}} 1$ reaction. 23 differs from $\mathbf{4 , 5} 5$ and $\mathbf{6}$ since both aromatic rings are negatively charged owing to the phenolate formation. Thus in both reactions two anions have to couple, which should be unfavorable due to electrostatic repulsion and could explain the failure of the reaction.




a: $\mathrm{PhCH}_{2} \mathrm{Cl}, \mathrm{KOH}, \Delta(90 \%) ;$ b: $\mathrm{CH}_{3} \mathrm{NO}_{2}, \mathrm{HOAc}, \Delta(86 \%) ;$ c: $\mathrm{LiAlH}_{4}$, tetrahydrofuran ( $81 \%$ ); d: $\mathrm{ClCOOCH}_{3}$, $\mathrm{NEt}_{3}\left(75 \%\right.$ ); e: $\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{charcoal}, \mathrm{CH}_{3} \mathrm{OH}(97 \%)$; f: Br $2, \mathrm{Fe}, \mathrm{HOAc}, \mathrm{NaOAc}(56 \%)$; $\mathrm{g}: \mathrm{CH}_{3} \mathrm{I}, \mathrm{KOH}$, dmso ( $96 \%$ ); h: TBDMSCI, $\mathrm{NE}_{3}$, 4,4-dimethylaminopyridine ( $94 \%$ ); i: $\mathrm{Ph}_{3} \mathrm{PCH}_{2} \mathrm{OCH}_{3}{ }^{+} \mathrm{Cl}$, $\mathrm{KO}{ }^{+} \mathrm{Bu}$, dioxane, $\Delta(79 \%)$; j: $\mathrm{Ph}_{3} \mathrm{PCH}_{2} \mathrm{OCH}_{3}{ }^{+} \mathrm{Cl}$, KOtBu, dioxane, $\Delta\left(86 \%\right.$; $\mathrm{k}: 20, \mathrm{POCl}_{3}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, \Delta(87 \%)$; l: 21, $\mathrm{POCl}_{3}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, \Delta(89 \%)$.

## Scheme 3

Therefore the reticuline derivative 22 , in which the 3 -hydroxy substituent of 23 is replaced by a $3^{\prime}$-methoxy group, was synthesized in the same sequence as 23 in nine steps and $17 \%$ overall yield. The photoinitiated $\mathrm{S}_{\mathrm{RN}} 1$ reaction of 22 in liquid ammonia afforded at complete conversion the $\mathbf{C - 8}-\mathrm{C}-2^{1}$ coupling product 24 in $19 \%$ yield together with the noncyclized compounds 25 ( $8 \%$ ) and 26 ( $8 \%$ ) (scheme 4). ${ }^{16}$ In the comparable tributyltinhydride induced radical cyclization of 2'-bromo-7-O-benzyl- N -ethoxycarbonyl-3- O methylnorreticuline only $3.5 \%$ of the cyclized and $48 \%$ of the reduced product were obtained. ${ }^{17}$ The formation of the reduced product 25 can be explained by way of a hydrogen abstraction from the solvent by the intermediate $\sigma$-aryl radical, 26 is possibly formed via an intramolecular $1,5-\mathrm{H}$-abstraction by this aryl radical followed by loss of a hydrogen atom.


Scheme 4

The desired C-4a - C-2' coupling was finally achieved by palladium(0) catalysis. Using the optimized conditions for 6 the bromoreticuline 22 yielded the salutaridine derivative $27(17 \%)$, the aporphine derivative $28^{18}(8 \%)$ and the non cyclized compounds $29(3 \%)$ and $30(4 \%)$ (scheme 5$) .{ }^{16}$


Scheme 5

The C-2' selectivity in the cyclization was expected due to the exclusive insertion of palladium(0) into the carbon bromine bond. The remarkably high C-4a selectivity could be due to a coordination of the palladium(II) intermediate by the carbamate group. It is known that the oxygen atom of carbonyl groups are able to coordinate to palladium(II). ${ }^{19}$

The described palladium(0) catalyzed coupling of 22 compares quite well with the best biomimetic approaches 5,6 to salutaridine derivatives. Furthermore, with this conversion palladium(0) catalyzed couplings of aryl halides with phenolates were realized for the first time. Even more interesting is the formation of a quaternary sp $^{3}$ carbon center at the connection site. This reaction may possibly be used for the total synthesis of other alkaloids with a corresponding skeleton e.g. amaryllidaceae alkaloids ${ }^{20}$ like narwedine or proaporphine alkaloids ${ }^{21}$ like orientalinone.

## EXPERIMENTAL SECTION

## General

IR spectra were recorded as a neat film or in solid KBr on a Nicolet 5DXC FT-IR. NMR spectra were taken on a Bruker WM 300, the mass spectra on a Finnigan-MAT MAT 8230 with data system SS 300 or on a Varian Saturn II (ion trap spectra). High resolution mass spectra were recorded on a Finnigan-MAT MAT 312. Meltings points were determined with a Kofler melting point apparatus (Reichert) and are uncorrected. Flash column chromatography was performed with Merck silica gel ( $0.040-0.063 \mu \mathrm{~m}$ ) under argon overpressure. For HPLC a Knauer system (pump 64.00, refractometer 98.00) was used together with steel columns ( 250 mm , 8 mm inside diameter) filled with Nucleosil 100-3. For photochemical reactions a Hanau TQ 150 mercury highpressure vapor lamp was employed.

## Palladium(0) catalyzed cyclizations of the aryl halides $\mathbf{4 , 5} 5$ and 6

0.500 mmol of the aryl halide, $0.125 \mathrm{mmol} \mathrm{PdCl}_{2}, 0.375 \mathrm{mmol}_{\mathrm{PPh}}^{3}$ and 1.800 mmol of the required base were suspended in 2 ml of freshly distilled dimethylformamide. Under an atmosphere of argon the mixture was stirred at $140^{\circ} \mathrm{C}$. After complete conversion of the aryl halide ( $20-48 \mathrm{~h}$ ) the mixture was poured into 20 ml 2 N HCl and the reaction products were extracted with diethyl ether ( $3 \times 10 \mathrm{ml}$ ), dried and separated by flash column chromatography (petroleum ether / diethyl ether $=2: 1$ )

5,6-Dimethoxy-benzo[3,4-c]2H-chromene (7):
145.6 mg 4 , base: NaOAc , Yield: 69.1 mg 7 ( $0.328 \mathrm{mmol}, 66 \%$ ); $\mathbb{R}(\mathrm{KBr}): \tilde{v} 1493,1265,1242,1103 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 3.76,3.91\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 4.94\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{ArCH}_{2} \mathrm{OR}\right), 6.85,6.89\left(\mathrm{~d}, J_{3,4}=8.3 \mathrm{~Hz}, 2 \mathrm{H}\right.$, $3-\mathrm{H}$ and $4-\mathrm{H}$ ), $7.01\left(\mathrm{dd}, J_{9,10}=8.3 \mathrm{~Hz}, J_{8,10}=1.5 \mathrm{~Hz}, 1 \mathrm{H}, 10-\mathrm{H}\right), 7.07\left(\mathrm{ddd}, J_{7,8}=7.9 \mathrm{~Hz}, J_{8,9}=7.5 \mathrm{~Hz}\right.$, $J_{8,10}=1.5 \mathrm{~Hz}, 1 \mathrm{H}, 8-\mathrm{H}$ ), 7.23 (ddd, $\left.J_{9,10}=8.3 \mathrm{~Hz}, J_{8,9}=7.5 \mathrm{~Hz}, J_{7,9}=1.5 \mathrm{~Hz}, 1 \mathrm{H}, 9-\mathrm{H}\right), 8.45$ (dd, $J_{7,8}=$ $7.9 \mathrm{~Hz}, J_{7,9}=1.5 \mathrm{~Hz}, 1 \mathrm{H}, 7-\mathrm{H}$ ); MS ( 70 eV ): m/z (\%) $242(100)\left[\mathrm{M}^{+}\right], 241(87)\left[\mathrm{M}^{+}-\mathrm{H}\right] ;$ HRMS ( $\mathrm{M}^{+}$) calcd 242.0943, found 242.0937 ; mp $83-85^{\circ} \mathrm{C}$.

O-Phenyl-3,4-dimethoxybenzyl alcohol (9):
145.6 mg 4 , base: NaOAc, Yield: 5.3 mg 9 ( $0.025 \mathrm{mmol}, 5 \%$ ); $\mathbb{R}$ (film): $\tilde{v} 1498,1240 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 3.89,3.89\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArOCH} \mathrm{H}_{3}\right), 4.99\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{ArCH}_{2} \mathrm{OR}\right), 6.87\left(\mathrm{~d}, J_{5,6}=8.7 \mathrm{~Hz}, 1 \mathrm{H}, 5-\mathrm{H}\right), 6.95-$ 6.99 (m, $5 \mathrm{H}, 2-\mathrm{H}, 6-\mathrm{H}, 2^{\prime}-\mathrm{H}, 4^{\prime}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ ), $7.27-7.31$ (m, $2 \mathrm{H}, 3^{\prime}-\mathrm{H}$ and $5^{\prime}-\mathrm{H}$ ); MS ( 70 eV ): m/z (\%) $244(11)\left[\mathrm{M}^{+}\right], 151(100)\left[\left(\mathrm{H}_{3} \mathrm{CO}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3} \mathrm{CH}_{2}^{+}\right]$; HRMS $\left(\mathrm{M}^{+}\right)$calcd 244.1099, found 244.1093.

O-(2,6-Dimethylphenyl)-3,4-dimethoxybenzyl alcohol (10):
175.7 mg 5 , base: $\mathrm{K}_{2} \mathrm{CO}_{3}$, Yield: 56.2 mg 10 ( $0.206 \mathrm{mmol}, 41 \%$ ); IR (film): $\tilde{\mathrm{v}} 1516,1262,1197 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.30\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArCH}_{3}\right), \mathbf{3 . 8 8}, 3.91\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 4.76\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{ArCH}_{2} \mathrm{OR}\right), 6.88(\mathrm{~d}$, $\left.J_{5,6}=7.9 \mathrm{~Hz}, 1 \mathrm{H}, 5-\mathrm{H}\right), 6.91-7.05\left(\mathrm{~m}, 5 \mathrm{H}, 2-\mathrm{H}, 6-\mathrm{H}, 3^{\prime}-\mathrm{H}, 4^{\prime}-\mathrm{H}\right.$ and $\left.5^{\prime}-\mathrm{H}\right)$; MS ( 70 eV ): m/z (\%) 151 (100) $\left[\left(\mathrm{H}_{3} \mathrm{CO}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3} \mathrm{CH}_{2}{ }^{+}\right]$; microanalysis calcd C 74.97, H 7.40, found C 75.01, H 7.45.

9-Hydroxy-5,6-dimethoxy-10-methyl-benzo[3,4-c]2H-chromene (8):
176.5 mg 6 , base: $\mathrm{K}_{2} \mathrm{CO}_{3}$, Yield: $76.5 \mathrm{mg} 8(0.281 \mathrm{mmol}, 56 \%)$; $\mathbb{R}(\mathrm{KBr}): \tilde{\mathrm{v}} 3378,2936,1489,1406,1261$, $1071 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.17\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArCH}_{3}\right), 3.72,3.88\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 4.93$ ( $\left.\mathrm{s}, 2 \mathrm{H}, 2-\mathrm{H}\right)$, $5.07(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 6.53\left(\mathrm{~d}, J_{7.8}=8.6 \mathrm{~Hz}, 1 \mathrm{H}, 8-\mathrm{H}\right), 6.79,6.86\left(\mathrm{~d}, J_{3,4}=8.2 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}\right.$ and $\left.4-\mathrm{H}\right)$, $8.18\left(\mathrm{~d}, J_{7,8}=8.6 \mathrm{~Hz}, 1 \mathrm{H}, 7-\mathrm{H}\right) ; \mathrm{MS}(70 \mathrm{eV}): m / z(\%) 272(100)\left[\mathrm{M}^{+}\right]$; microanalysis calcd C $70.57, \mathrm{H} 5.92$, found C 70.40, H 6.06; $\mathrm{mp}=167-173{ }^{\circ} \mathrm{C}$.

O-(2-Hydroxy-3-methylphenyl)-3,4-dimethoxybenzyl alcohol (11):
176.5 mg 6, base: $\mathrm{K}_{2} \mathrm{CO}_{3}$, Yield: $6.4 \mathrm{mg} 11(0.023 \mathrm{mmol}, 5 \%$; $\mathrm{IR}(\mathrm{KBr}): ~ \tilde{v} 3458,1517,1463,1091,1078$ $\mathrm{cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ([ $\left.\mathrm{D}_{6}\right]$ Aceton): $\delta 2.13\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArCH}_{3}\right), 3.81,3.83\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 5.00\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{ArCH} \underline{H}_{2} \mathrm{OR}\right)$, $6.50,6.54\left(\mathrm{~d},{ }^{3} J=8.2 \mathrm{~Hz}, 2 \mathrm{H}, 4^{\prime}-\mathrm{H}\right.$ and $\left.6^{\prime}-\mathrm{H}\right), 6.91-6.97\left(\mathrm{~m}, 2 \mathrm{H}, 5-\mathrm{H}\right.$ and $\left.5^{\prime}-\mathrm{H}\right), 7.00\left(\mathrm{dd}, J_{5,6}=8.1 \mathrm{~Hz}\right.$, $\left.J_{2,6}=1.9 \mathrm{~Hz}, 1 \mathrm{H}, 6-\mathrm{H}\right), 7.10\left(\mathrm{~d}, J_{2,6}=1.9 \mathrm{~Hz}, 1 \mathrm{H}, 2-\mathrm{H}\right) ; \mathrm{MS}\left(70 \mathrm{eV}, \mathrm{NH}_{3}-\mathrm{DCI}\right): m / z(\%) 151$ (100) $\left[\left(\mathrm{H}_{3} \mathrm{CO}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3} \mathrm{CH}_{2}{ }^{+}\right.$]; microanalysis calcd $\mathrm{C} 70.06, \mathrm{H} 6.61$, found $\mathrm{C} 69.92, \mathrm{H} 6.65$; $\mathrm{mp}=144-146{ }^{\circ} \mathrm{C}$.

## Photochemically induced $S_{\text {RN }} 1$ reaction of 5

The aryl halide $5(10.3 \mathrm{mg}, 0.029 \mathrm{mmol})$ and $\mathrm{KO}^{\mathrm{t}} \mathrm{Bu}(11.7 \mathrm{mg}, 0.104 \mathrm{mmol})$ were dissolved in 2 ml distilled dimethyl sulfoxide. Under an atmosphere of argon the solution was irradiated with a mercury high-pressure vapor lamp ( 150 W ). After 60 min the mixture was poured into 10 ml 2 N HCl . The product was extracted with diethyl ether ( $3 \times 20 \mathrm{ml}$ ), dried and after evaporation of the solvent purified by flash column chromatography (petroleum ether / diethyl ether $=1: 1$ ). $6.2 \mathrm{mg}(0.023 \mathrm{mmol}, 79 \%)$ of 8 could be isolated.

## Synthesis of the reticuline derivatives 22 and 23

2-(4-Benzyloxy-3-methoxyphenyl)-ethyl-N-methoxycarbonylamine (14):
A solution of $13^{22}(3.00 \mathrm{~g}, 11.7 \mathrm{mmol})$, chloroformic acid methyl ester ( $0.87 \mathrm{ml}, 12.8 \mathrm{mmol}$ ) and triethylamine ( $1.85 \mathrm{ml}, 14.0 \mathrm{mmol}$ ) in 30 ml dichloromethane was stirred at $0^{\circ} \mathrm{C}$ for 30 min . Concentration and flash column chromatography (petroleum ether / diethyl ether $=10: 1)$ gave $14(2.76 \mathrm{~g}, 8.8 \mathrm{mmol}, 75 \%)$ as a white solid. IR (KBr): $\left.\tilde{v} 3380,3347,1686,1521,1274,1237 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H} \mathrm{NMR}^{(~} \mathrm{CDCl}_{3}\right): \delta 2.74\left(\mathrm{t}, J_{1,2}=7.0 \mathrm{~Hz}, 2 \mathrm{H}, 2-\mathrm{H}\right)$, $3.41(\mathrm{~m}, 2 \mathrm{H}, 1-\mathrm{H}), 3.66\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{COOCH}_{3}\right), 3.88\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 4.64(\mathrm{~s}, \mathrm{br}, 1 \mathrm{H}, \mathrm{NH}), 5.13(\mathrm{~s}, 2 \mathrm{H}$, $\mathrm{OCH}_{2} \mathrm{Ph}$ ), $6.65\left(\mathrm{dd}, J_{5^{\prime}, 6^{\prime}}=8.3 \mathrm{~Hz}, J_{2^{\prime}, 6^{\prime}}=1.9 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 6.72\left(\mathrm{~d}, J_{2^{\prime}, 6^{\prime}}=1.9 \mathrm{~Hz}, 1 \mathrm{H}, 2^{\prime}-\mathrm{H}\right), 6.82(\mathrm{~d}$, $\left.J_{5^{\prime}, 6^{\prime}}=8.3 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 7.29-7.45\left(\mathrm{~m}, 5 \mathrm{H}, 2^{\prime \prime}-\mathrm{H}-6^{\prime \prime}-\mathrm{H}\right) ; \mathrm{MS}(70 \mathrm{eV}): m / z(\%) 315$ (19) [M$\left.{ }^{+}\right], 91$ (100) $\left[\mathrm{C}_{7} \mathrm{H}_{7}{ }^{+}\right]$; microanalysis calcd C 68.55, H 6.71, N 4.44, found C 68.55, H 6.72, N 4.35; $\mathrm{mp}=74{ }^{\circ} \mathrm{C}$.

## 2-(4-Hydroxy-3-methoxyphenyl)-ethyl-N-methoxycarbonylamine (15):

To a solution of $14(1.00 \mathrm{~g}, 3.2 \mathrm{mmol})$ in 40 ml methanol was added palladium on charcoal ( $10 \% \mathrm{Pd}, 0.12 \mathrm{~g}$ ). Unter an atmosphere of hydrogen the resulting suspension was stirred for 2 h . After filtration through silica gel and evaporation of methanol a white solid was obtained $(0.70 \mathrm{~g} \mathrm{15}, 3.1 \mathrm{mmol}, 97 \%)$. IR (KBr): $\tilde{\mathrm{v}} 3356,1700$, $1516,1270,1237,1202,1033 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.73\left(\mathrm{t}, J_{1,2}=6.8 \mathrm{~Hz}, 2 \mathrm{H}, 2-\mathrm{H}\right), 3.35-3.42(\mathrm{~m}, 2 \mathrm{H}$, $1-\mathrm{H}), 3.48(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 3.67\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{COOCH}_{3}\right), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 4.73(\mathrm{~s}, \mathrm{br} ., 1 \mathrm{H}, \mathrm{NH}), 6.65-6.72(\mathrm{~m}$, $2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 6.84\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=7.9 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right)$; $\mathrm{MS}(70 \mathrm{eV}): m / z(\%) 225(24)\left[\mathrm{M}^{+}\right], 150(100)\left[\mathrm{M}^{+}\right.$$\left.\mathrm{NH}_{2} \mathrm{COOCH}_{3}(\mathrm{McL})\right], 137(98)\left[\mathrm{CH}_{2} \mathrm{C}_{6} \mathrm{H}_{3}(\mathrm{OH})\left(\mathrm{OCH}_{3}\right)^{+}\right]$; microanalysis calcd C 58.66, H 6.71, N 6.22, found C 58.53, H 6.89, N 6.11; mp $=66-69^{\circ} \mathrm{C}$.

## 2-Bromo-3,4-dimethoxybenzaldehyde (18):

Powdered sodium hydroxide ( $4.63 \mathrm{~g}, 82.5 \mathrm{mmol}$ ) was stirred in 35 ml dimethyl sulfoxide for exactly 5 min . To this suspension a solution of $17^{23}$ ( $7.63 \mathrm{~g}, 33.0 \mathrm{mmol}$ ) in 5 ml dimethyl sulfoxide and methyl iodide ( 2.40 ml , 36.9 mmol ) were added simultaneously. After 10 min the reaction mixture was poured into 400 ml 2 N HCl , extracted with dichloromethane ( $3 \times 100 \mathrm{ml}$ ) and dried. Flash column chromatography (petroleum ether / diethyl ether $=1: 1$ ) afforded 18 as a white solid ( $7.78 \mathrm{~g}, 31.8 \mathrm{mmol}, 96 \%$ ). IR ( KBr ): $\tilde{\mathrm{v}} 1679,1583,1490,1282$, $1258,1023 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H} \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 3.88,3.97\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{ArOCH}_{3}\right), 6.97\left(\mathrm{~d}, J_{5,6}=8.7 \mathrm{~Hz}, 1 \mathrm{H}, 5-\mathrm{H}\right), 7.70(\mathrm{~d}$, $\left.J_{5,6}=8.7 \mathrm{~Hz}, 1 \mathrm{H}, 6-\mathrm{H}\right), 10.23(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CHO})$; MS ( 70 eV ): $m / z(\%) 244 / 246$ (100/93) [ $\left.\mathrm{M}^{+}\right], 243 / 245$ (67/94) $\left[\mathrm{M}^{+}-\mathrm{H}\right]$; microanalysis calcd $\mathrm{C} 44.11, \mathrm{H} 3.70, \mathrm{Br} 32.60$, found $\mathrm{C} 44.05, \mathrm{H} 3.67, \mathrm{Br} 32.64 ; \mathrm{mp}=83-84^{\circ} \mathrm{C}$.
(E)- and (Z)-1-(2-Bromo-3,4-dimethoxyphenyl)-2-methoxyethene (20):

Methoxymethyltriphenylphosphonium chloride ( $4.20 \mathrm{~g}, 12.2 \mathrm{mmol}$ ) and $\mathrm{KO}^{\mathrm{H} B u}(1.44 \mathrm{~g}, 12.8 \mathrm{mmol})$ were suspended in 35 ml freshly distilled dioxane. After $60 \mathrm{~min} 18(2.00 \mathrm{~g}, 8.2 \mathrm{mmol})$ was added and the mixture was refluxed for 5 h . The cold solution was poured into 100 ml water and 100 ml diethyl ether, the phases were separated and the aqueous phase was extracted with diethyl ether ( $3 \times 50 \mathrm{ml}$ ). The solvent was completely removed and the residue was redissolved in 5 ml dichloromethane. $\mathrm{PPh}_{3} \mathrm{O}$ as a side product was precipitated by quickly adding of 200 ml petroleum ether to this solution. Evaporation of the filtered solution and chromatography (petroleum ether / diethyl ether $=5: 1$ ) gave 20 as a colourless oil ( $1.76 \mathrm{~g}, 6.4 \mathrm{mmol}, 79 \%$ ). IR (film): $\tilde{\mathrm{v}} 1486,1277,1256,1218,1030 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 3.69\left(\mathrm{~s}, 3 \mathrm{H},(\mathrm{Z})=\mathrm{CH}-\mathrm{OCH}_{3}\right), 3.74$ (s, $\left.3 \mathrm{H},(E)=\mathrm{CH}-\mathrm{OCH}_{3}\right), 3.83,3.84,3.84,3.85\left(\mathrm{~s}, 3 \mathrm{H},(E)\right.$ - and $\left.(Z)-\mathrm{ArOCH}_{3}\right), 5.55\left(\mathrm{~d}, J_{1,2}=7.2 \mathrm{~Hz}, 1 \mathrm{H}\right.$, (Z) $-1-\mathrm{H}), 6.03\left(\mathrm{~d}, J_{1,2}=12.9 \mathrm{~Hz}, 1 \mathrm{H},(E)-1-\mathrm{H}\right), 6.17\left(\mathrm{~d}, J_{1,2}=7.2 \mathrm{~Hz}, 1 \mathrm{H},(\mathrm{Z})-2-\mathrm{H}\right), 6.77-6.86(\mathrm{~m}, 3 \mathrm{H}$, (E)-2-H, (E)- and (Z)-5'-H), $7.03\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=8.6 \mathrm{~Hz}, 1 \mathrm{H},(E)-6^{\prime}-\mathrm{H}\right), 7.77\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=8.8 \mathrm{~Hz}, 1 \mathrm{H},(Z)-6^{\prime}-\mathrm{H}\right)$; MS ( 70 eV ): $m / 2(\%) 272 / 274$ ( $91 / 91$ ) [ $\left.\mathrm{M}^{+}\right]$, 178 (100) [ $\left.\mathrm{M}^{+}-\mathrm{Br}-\mathrm{CH}_{3}\right]$; microanalysis calcd $\mathrm{C} 48.37, \mathrm{H} 4.80$, found C 48.19, H 4.86.

2-Bromo-3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (19):
$17^{23}(2.02 \mathrm{~g}, 8.7 \mathrm{mmol})$, tert-butyldimethylsilyl chloride ( $1.32 \mathrm{~g}, 8.7 \mathrm{mmol}$ ), triethylamine ( $2.31 \mathrm{ml}, 17.5 \mathrm{mmol}$ ) and a catalytic amount of $4-N^{\prime}, N^{\prime}$-dimethylaminopyridine were dissolved in 50 ml dichloromethane. After stirring the mixture for 19 h 100 ml dichloromethane were added, the organic phase was washed with 25 ml saturated sodium bicarbonate and 20 ml water, dried and evaporated. Flash column chromatography afforded 19 as a yellow oil ( $2.82 \mathrm{~g}, 8.2 \mathrm{mmol}, 94 \%$ ). IR (film): $\tilde{\mathrm{v}} 1685,1577,1489,1310,1279,1033 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right)$ : $\delta 0.21\left(\mathrm{~s}, 6 \mathrm{H}, \mathrm{OSi}\left(\mathrm{CH}_{3}\right)_{2}\right), 1.04\left(\mathrm{~s}, 9 \mathrm{H}, \operatorname{OSiC}\left(\mathrm{CH}_{3}\right)_{3}\right), 3.86\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{ArOCH} \mathrm{H}_{3}\right), 6.86\left(\mathrm{~d}, \mathrm{~J}_{5,6}=8.8 \mathrm{~Hz}, 1 \mathrm{H}\right.$, $5-\mathrm{H}), 7.55\left(\mathrm{~d}, J_{5,6}=8.8 \mathrm{~Hz}, 1 \mathrm{H}, 6-\mathrm{H}\right), 10.23(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CHO})$; MS ( 70 eV ): m/z (\%) 287/289 (89/89) [ $\mathrm{M}^{+}$. $\left.\mathrm{C}_{4} \mathrm{H}_{9}\right], 272 / 274(98 / 100)\left[\mathrm{M}^{+}-\mathrm{CH}_{3}-\mathrm{C}_{4} \mathrm{H}_{9}\right]$, microanalysis calcd C $48.70, \mathrm{H} 6.13$, found $\mathrm{C} 48.40, \mathrm{H} 6.27$.
(E)- and (Z)-1-(2-Bromo-3-(tert-butyldimethylsilyloxy)-4-methoxyphenyl)-2-methoxyethene (21):
$19(2.50 \mathrm{~g}, 7.2 \mathrm{mmol})$, methoxymethyltriphenylphosphonium chloride $(4.19 \mathrm{~g}, 12.2 \mathrm{mmol})$ and $\mathrm{KO}{ }^{\mathrm{B}} \mathrm{Bu}(1.37 \mathrm{~g}$, 12.2 mmol ) in 30 ml dioxane were by analogy to the preparation of $\mathbf{2 0}$ converted into $\mathbf{2 1}$. The flash column chromatography was carried out with petroleum ether / diethyl ether $=40: 1$ as eluent and yielded 21 as a
 $\left(\mathrm{CDCl}_{3}\right): \delta 0.26\left(\mathrm{~s}, 6 \mathrm{H},(\mathrm{Z})-\mathrm{OSi}\left(\mathrm{CH}_{3}\right)_{2}\right), 0.26\left(\mathrm{~s}, 6 \mathrm{H},(E)-\mathrm{OSi}\left(\mathrm{CH}_{3}\right)_{2}\right), 1.09\left(\mathrm{~s}, 9 \mathrm{H},(\mathrm{Z})-\mathrm{OSiC}\left(\mathrm{CH}_{3}\right)_{3}\right), 1.09(\mathrm{~s}$, $\left.9 \mathrm{H},(\mathrm{E})-\mathrm{OSiC}\left(\mathrm{CH}_{3}\right)_{3}\right), 3.72\left(\mathrm{~s}, 3 \mathrm{H},(\mathrm{E})=\mathrm{CH}-\mathrm{OCH}_{3}\right), 3.75\left(\mathrm{~s}, 3 \mathrm{H},(\mathrm{Z})=\mathrm{CH}-\mathrm{OCH}_{3}\right), 3.79,3.80(\mathrm{~s}, 6 \mathrm{H}$, $(E)$ - and (Z)-ArOCH3 3$), 5.63\left(\mathrm{~d}, J_{1,2}=7.2 \mathrm{~Hz}, 1 \mathrm{H},(\mathrm{Z})-1-\mathrm{H}\right), 6.11\left(\mathrm{~d}, J_{1,2}=12.7 \mathrm{~Hz}, 1 \mathrm{H},(E)-1-\mathrm{H}\right), 6.17(\mathrm{~d}$, $\left.J_{1,2}=7.2 \mathrm{~Hz}, 1 \mathrm{H},(\mathrm{Z})-2-\mathrm{H}\right), 6.74\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=8.5 \mathrm{~Hz}, 1 \mathrm{H},\left(\right.\right.$ (E) $\left.5^{\prime}-\mathrm{H}\right), 6.79\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=8.7 \mathrm{~Hz}, 1 \mathrm{H},(\mathrm{Z})-5^{\prime}-\mathrm{H}\right), 6.86$ (d, $\left.J_{1,2}=12.7 \mathrm{~Hz}, 1 \mathrm{H},(E)-2-\mathrm{H}\right), 6.92\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=8.5 \mathrm{~Hz}, 1 \mathrm{H},(E)-6^{\prime}-\mathrm{H}\right), 7.67\left(\mathrm{~d}, J_{5^{\prime}, 6^{\prime}}=8.7 \mathrm{~Hz}, 1 \mathrm{H},(Z)-6^{\prime}-\mathrm{H}\right)$; MS ( 70 eV ): $m / z(\%) 315 / 317(97 / 100)\left[\mathrm{M}^{+}-\mathrm{C}_{4} \mathrm{H}_{9}\right], 300 / 302(80 / 88)\left[\mathrm{M}^{+}-\mathrm{C}_{4} \mathrm{H}_{9}-\mathrm{CH}_{3}\right]$; microanalysis calcd C 51.47, H 6.75, found C 51.59, H 6.57.

1-(2-Bromo-3,4-dimethoxybenzyl)-7-hydroxy-6-methoxy-N-methoxycarboryl-1,2,3,4-tetrahydroisoquinoline (22):
To a solution of $15(1.41 \mathrm{~g}, 6.3 \mathrm{mmol})$ and $20(1.67 \mathrm{~g}, 6.1 \mathrm{mmol})$ in 50 ml dichloromethane was added $\mathrm{POCl}_{3}$ ( $1.70 \mathrm{ml}, 18.2 \mathrm{mmol}$ ). After refluxing the mixture for 6 h it was quenched with 150 ml water and the product was extracted with dichloromethane ( $3 \times 50 \mathrm{ml}$ ). Flash column chromatography (dichloromethane / ethyl acetate $=5: 1$ ) afforded 22 as a white solid ( $2.51 \mathrm{~g}, 5.4 \mathrm{mmol}, 89 \%$ ). $\mathbb{R}(\mathrm{KBr})$ : $\tilde{\mathbf{v}} 1685,1487,1452,1241,1202,1039$ $\mathrm{cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.62-2.96,3.21-3.35(\mathrm{~m}$, integration of all signals in the range of $2.62-3.60 \mathrm{ppm}$ : $17 \mathrm{H}, 1 \times 3-\mathrm{H}$ ( a and b ), $1 \times 3-\mathrm{H}$ ( a or b ), $2 \times 4-\mathrm{H}$ ( a and b ) and $2 \times \alpha-\mathrm{H}$ ( a and b ), , $3.21\left(\mathrm{~s}, \mathrm{COOCH}_{3}\right.$ (a)), $3.60\left(\mathrm{~s}, \mathrm{COOCH}_{3}(\mathrm{~b})\right.$ ), $3.84,3.86,3.87\left(\mathrm{~s}, 18 \mathrm{H}, 3 \times \mathrm{ArOCH}_{3}\right.$ (a and b)), $4.30\left(\mathrm{ddd},{ }^{2} J=13.3 \mathrm{~Hz},{ }^{3} \mathrm{~J}=6.2 \mathrm{~Hz}\right.$,
${ }^{3} J=1.9 \mathrm{~Hz}, 1 \mathrm{H}, 1 \times 3-\mathrm{H}(\mathrm{a}$ or b$)$ ), 5.33 (dd, $J_{1, \alpha_{1}}=10.7 \mathrm{~Hz}, J_{1, \alpha_{2}}=3.3 \mathrm{~Hz}, 2 \mathrm{H}, 1-\mathrm{H}$ (a and b)), 5.68 (s, br., $2 \mathrm{H}, \mathrm{OH}(\mathrm{a}$ and b$)$ ), $6.54-6.60(\mathrm{~m}), 6.77(\mathrm{~s}), 6.88$ (s, integration of all signals in the range of $6.54-6.88 \mathrm{ppm}$ : $8 \mathrm{H}, 5-\mathrm{H}, 8-\mathrm{H}, 5{ }^{\prime}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ (a and b)) (most signals are doubled because of the hindered rotation around the amide linkage, the main rotamer is marked with an a); MS ( $70 \mathrm{eV}, \mathrm{NH}_{3}-\mathrm{DCI}$ ): $m / \mathrm{z}(\%)$ 483/485 (96/100) $\left[\mathrm{M}^{+}+\right.$ $\mathrm{NH}_{3}+\mathrm{H}$ ]; microanalysis calcd C $54.09, \mathrm{H} 5.19, \mathrm{~N} 3.00$, found C $54.16, \mathrm{H} 5.17$, N 3.15 ; $\mathrm{mp}=199-200^{\circ} \mathrm{C}$.

## 1-(2-Bromo-3-hydroxy-4-methoxybenzyl)-7-hydroxy-6-methoxy-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (23):

To a solution of 15 ( $200.0 \mathrm{mg}, 0.888 \mathrm{mmol}$ ) and $21(371.5 \mathrm{mg}, 0.995 \mathrm{mmol})$ in 10 ml dichloromethane $\mathrm{POCl}_{3}$ ( $0.33 \mathrm{ml}, 3.5 \mathrm{mmol}$ ) was added. After refluxing the mixture for 7 h it was quenched with 10 ml water and the product was extracted with dichloromethane ( $3 \times 10 \mathrm{ml}$ ). Purification by chromatography (diethyl ether / methanol $=20: 1$ ) afforded 23 as a white solid ( $350.0 \mathrm{mg}, 0.774 \mathrm{mmol}, 87 \%$ ). $\mathrm{IR}(\mathrm{KBr}): \tilde{v} \mathbf{1 6 8 5}, 1489,1286$, 1264, $1033 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.58-2.96,3.02-3.12,3.21-3.44$ ( m , integration of all signals in the range of $2.58-3.60 \mathrm{ppm}: 17 \mathrm{H}, 1 \times 3-\mathrm{H}(\mathrm{a}$ and b$), 1 \times 3-\mathrm{H}(\mathrm{a}$ or b$), 2 \times 4-\mathrm{H}(\mathrm{a}$ and b$)$ and $2 \times \alpha-\mathrm{H}(\mathrm{a}$ and b$)$ ), $3.12\left(\mathrm{~s}, \mathrm{COOCH}_{3}(\mathrm{a})\right.$ ), $3.60\left(\mathrm{~s}, \mathrm{COOCH}_{3}\right.$ (b)), $3.86\left(\mathrm{~s}, 12 \mathrm{H}, 2 \times \mathrm{ArOCH}_{3}\right.$ (a and b)), $4.30\left(\mathrm{ddd},{ }^{2} J=13.1 \mathrm{~Hz}\right.$, $3^{3} J=6.0 \mathrm{~Hz}, 3 J=2.4 \mathrm{~Hz}, 1 \mathrm{H}, 1 \times 3-\mathrm{H}\left(\mathrm{a}\right.$ or b)), $5.35\left(\mathrm{dd}, J_{1, \alpha_{1}}=10.7 \mathrm{~Hz}, J_{1, \alpha_{2}}=3.6 \mathrm{~Hz}, 2 \mathrm{H}, 1-\mathrm{H}(\mathrm{a}\right.$ and b) ), $6.55-6.73(\mathrm{~m}), 6.87$ (s, integration of all signals in the range of $6.55-6.87 \mathrm{ppm}: 8 \mathrm{H}, 5-\mathrm{H}, 8-\mathrm{H}, 5^{\circ}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ ( $a$ and $b$ )) (most signals are doubled because of the hindered rotation around the amide linkage, the main rotamer is marked with an a); MS ( $70 \mathrm{eV}, \mathrm{NH}_{3}-\mathrm{DCI}$ ): $m / z(\%) 452 / 454(35 / 100)\left[\mathrm{M}^{+}+\mathrm{H}\right]$; microanalysis calcd C 53.11 , H4.90, found C $53.37, \mathrm{H} 5.27 ; \mathrm{mp}=74-76^{\circ} \mathrm{C}$.

## Photochemically induced $\mathrm{S}_{\mathrm{RN}} 1$ reaction of 22

$22(124.0 \mathrm{mg}, 0.266 \mathrm{mmol})$ was dissolved in 20 ml of refluxing $\mathrm{NH}_{3}$ (acetone / dry ice reflux condenser). KOtBu ( $131.7 \mathrm{mg}, 1.078 \mathrm{mmol}$ ) was added and the resulting suspension was irradiated for 75 min . To allow an intensive irradiation the frozen water on the outside of the flask had to be removed by dropping ethanol on the flask. The ammonia was evaporated and the residue was redissolved in 10 ml sat. $\mathrm{NaHCO}_{3}$, extracted with dichloromethane ( $4 \times 15 \mathrm{ml}$ ), dried and evaporated. The products 24,25 and 26 were separated by flash column chromatography (silica gel was deactivated by adding $10 \%$ water; eluent: diethyl ether) and purified by HPLC (petroleum ether $/$ ethyl acetate $/$ methanol $=10: 2: 1$ ).

## 11-O-Methyl-N-methoxycarbonylnorcorytuberine (24):

Yield of 24: $19.3 \mathrm{mg}, 0.050 \mathrm{mmol}, 19 \%$. $\mathrm{R}(\mathrm{KBr}): \tilde{v} 1695,1466,1449,1286,1234 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right)$ : $\delta 2.61-3.04(\mathrm{~m}, 5 \mathrm{H}, 2 \times 4-\mathrm{H}, 1 \times 5-\mathrm{H}, 2 \times 8-\mathrm{H}), 3.76,3.76,3.91,3.92\left(\mathrm{~s}, 12 \mathrm{H}, \mathrm{ArOCH}_{3}\right.$ and $\left.\mathrm{COOCH}_{3}\right)$, $4.40-4.44(\mathrm{~m}, 1 \mathrm{H}, 1 \times 5-\mathrm{H}), 4.67\left(\mathrm{dd}, J_{8 \mathrm{a}, 7}=13.0 \mathrm{~Hz}, J_{8 \mathrm{~b}, 7}=3.1 \mathrm{~Hz}, 1 \mathrm{H}, 7-\mathrm{H}\right), 6.71(\mathrm{~s}, 1 \mathrm{H}, 3-\mathrm{H}), 6.89$, $7.09\left(\mathrm{~d}, J_{9,10}=8.2 \mathrm{~Hz}, 2 \mathrm{H}, 9-\mathrm{H}\right.$ and $\left.10-\mathrm{H}\right), 8.88(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}) ; \mathrm{MS}\left(70 \mathrm{eV}, \mathrm{NH}_{3}-\mathrm{DCI}\right): m / z(\%) 403(100)\left[\mathrm{M}^{+}\right.$ $+\mathrm{H}+\mathrm{NH}_{3}$ ]; HRMS $\left(\mathrm{M}^{+}\right)$calcd 385.1525 , found $385.1516 ; \mathrm{mp}=200-202{ }^{\circ} \mathrm{C}$.

I-(2-Bromo-3,4-dimethoxybenzyl)-7-hydroxy-6-methoxy-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (25):
Yield of 25: $8.0 \mathrm{mg}, 0.021 \mathrm{mmol}, 8 \%$. IR ( KBr ): $\tilde{\mathrm{v}} 1685,1515,1263 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 2.35-2.86$, 2.96-3.21 (m, $11 \mathrm{H}, 1 \times 3-\mathrm{H}$ (a and b), $1 \times 3-\mathrm{H}(\mathrm{a}$ or b$), 2 \times 4-\mathrm{H}(\mathrm{a}$ and b$), 2 \times \alpha-\mathrm{H}(\mathrm{a}$ and b$)$ ), $3.47(\mathrm{~s}$, integration of all signals in the range of $3.47-3.86 \mathrm{ppm}: 24 \mathrm{H}, \mathrm{COOCH}_{3}$ (a)), $3.69\left(\mathrm{~s}, \mathrm{COOCH}_{3}(\mathrm{~b})\right.$ ), 3.74, $3.80,3.84,3.86\left(\mathrm{~s}, 3 \times \mathrm{ArOCH}_{3}(\mathrm{a}\right.$ and b$\left.)\right), 4.08-4.17(\mathrm{~m}, 1 \mathrm{H}, 1 \times 3-\mathrm{H}(\mathrm{a}$ or b)$)$, $5.10-5.14(\mathrm{~m}, 1 \mathrm{H}, 1-\mathrm{H}$ (a)), $5.24-5.31$ (m, 1H, 1-H (b)), $5.53,5.55$ ( s , br., $2 \mathrm{H}, \mathrm{OH}$ (a and b), $6.54-6.77$ (m, $8 \mathrm{H}, 5-\mathrm{H}, 8-\mathrm{H}, 5 \mathrm{H}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ ( a and b )) (most signals are doubled because of the hindered rotation around the amide linkage, the main rotamer is marked with an a); MS (70 eV): $m / z(\%) 387(11)\left[\mathrm{M}^{+}\right], 236(100)\left[\mathrm{M}^{+}-\left(\mathrm{H}_{3} \mathrm{CO}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3} \mathrm{CH}_{2}\right]$; microanalysis calcd C $65.10, \mathrm{H} 6.50$, found $\mathrm{C} 65.18, \mathrm{H} 6.65$; $\mathrm{mp}=57-58{ }^{\circ} \mathrm{C}$.

## 1-(3,4-Dimethoxybenzyl)-7-hydroxy-6-methoxy-N-methoxycarbonyl-1,2-dihydroisoquinoline (26):

Yield of 26: $8.2 \mathrm{mg}, 0.021 \mathrm{mmol}, 8 \%$. IR (film): $\tilde{\mathrm{v}} 1700,1518,1269 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 2.65-2.88$ (m, $4 \mathrm{H}, 2 \times \alpha-\mathrm{H}(\mathrm{a}$ and b$)$ ), $3.50,3.66,3.76,3.78,3.80,3.85,3.87,3.89\left(\mathrm{~s}, 24 \mathrm{H}, \mathrm{ArOCH}_{3}\right.$ and $\mathrm{COOCH}_{3}(\mathrm{a}$ and b)), $5.21-5.25(\mathrm{~m}, 1 \mathrm{H}, 1-\mathrm{H}(\mathrm{a}$ or b)), $5.36-5.40(\mathrm{~m}, 1 \mathrm{H}, 1-\mathrm{H}(\mathrm{a}$ or b)), $5.46-5.82(\mathrm{~m}, 2 \mathrm{H}, 4-\mathrm{H}(\mathrm{a}$ and b)), $6.26(\mathrm{~s}), 6.45-6.91\left(\mathrm{~m}, 12 \mathrm{H}, 3-\mathrm{H}, 5-\mathrm{H}, 8-\mathrm{H}, 2^{\prime}-\mathrm{H}, 5^{\prime}-\mathrm{H}\right.$ and $6^{\prime}-\mathrm{H}(\mathrm{a}$ and b$)$ ) (most signals are doubled because of the hindered rotation around the amide linkage, the main rotamer is marked with an a); MS (70 eV): $m / 2(\%)$ 234 (100) $\left[\mathrm{M}^{+}-\left(\mathrm{H}_{3} \mathrm{CO}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3} \mathrm{CH}_{2}\right]$; HRMS $\left(\mathrm{M}^{+}\right)$calcd 403.1869, found 403.1886 .

## Palladium(0) catalyzed reaction of 22

In 15 ml of freshly distilled dimethylformamide were dissolved 22 ( $162.7 \mathrm{mg}, 0.349 \mathrm{mmol}$ ), palladium(II) chloride ( $5.9 \mathrm{mg}, 0.033 \mathrm{mmol}$ ), triphenylphosphine ( $26.2 \mathrm{mg}, 0.100 \mathrm{mmol}$ ) and potassium carbonate ( 186.2 mg , 1.347 mmol ). The resulting suspension was stirred for 13 h at $140^{\circ} \mathrm{C}$ and poured into 30 ml 2 N HCl . It was extracted with dichloromethane ( $5 \times 20 \mathrm{ml}$ ), dried and the solvent was evaporated. After flash column chromatography (diethyl ether / methanol $=40: 1$ ) it was necessary to purify the products by HPLC (petroleum ether/ ethyl acetate $/$ methanol $=10: 2: 1$ ).

O-Methyl-N-methoxycarbonylnorsalutaridine (27):
Yield of 27: $22.9 \mathrm{mg}, 0.060 \mathrm{mmol}, 17 \%$. IR (KBr): $\tilde{\mathbf{v}} 2962,1699,1675,1652,1232,1100,1017 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 1.58-1.69(\mathrm{~m}, 2 \mathrm{H}, 2 \times 15-\mathrm{H}), 2.35-2.45(\mathrm{~m}, 1 \mathrm{H}, 1 \times 16-\mathrm{H}), 2.80\left(\mathrm{dt}, J_{\mathrm{gem}}=13.1 \mathrm{~Hz}\right.$, $\left.J_{15,16}=3.8 \mathrm{~Hz}, 1 \mathrm{H}, 1 \times 16-\mathrm{H}\right), 3.10-3.25(\mathrm{~m}, 2 \mathrm{H}, 2 \times 10-\mathrm{H}), 3.70,3.77(\mathrm{~s}, \mathrm{br}$., integration of all signals in the range of $\left.3.70-3.97 \mathrm{ppm}: 12 \mathrm{H}, \mathrm{COOCH}_{3}\right), 3.78,3.87,3.97\left(\mathrm{~s}, 3 \times \mathrm{ArOCH}_{3}\right), 5.02,5.16(\mathrm{~s}, \mathrm{br} ., 1 \mathrm{H}, 9-\mathrm{H})$, $6.32,6.35(\mathrm{~s}, \mathrm{br} ., 1 \mathrm{H}, 8-\mathrm{H}), 6.84(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}$ and $2-\mathrm{H}), 7.25(\mathrm{~s}, 1 \mathrm{H}, 5-\mathrm{H}) ; \mathrm{MS}(70 \mathrm{eV}): \mathrm{m} / \mathrm{z}(\%) 386$ (100) $\left[\mathrm{M}^{+}+\mathrm{H}\right]$; HRMS $\left(\mathrm{M}^{+}\right)$calcd 385.1525 , found $385.1516 ; \mathrm{mp}=76-77^{\circ} \mathrm{C}$.

O,O-Dimethyl-N-methoxycarbonylnorcorytuberine (28):
Yield of 28: $11.1 \mathrm{mg}, 0.027 \mathrm{mmol}, 8 \%$. $\mathrm{IR}(\mathrm{KBr}): \tilde{v} 1696,1399,1247 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 2.58-2.66$, $2.80-3.00(\mathrm{~m}, 5 \mathrm{H}, 2 \times 4-\mathrm{H}, 1 \times 5-\mathrm{H}, 2 \times 8-\mathrm{H}), 3.67,3.70,3.75,3.88,3.89\left(\mathrm{~s}, 15 \mathrm{H}, 4 \times \mathrm{ArOCH}_{3}\right.$ and $\left.\mathrm{COOCH}_{3}\right), 4.40-4.47(\mathrm{~m}, 1 \mathrm{H}, 1 \times 5-\mathrm{H}), 4.57\left(\mathrm{dd}, J_{8 \mathrm{a}, 7}=12.9 \mathrm{~Hz}, J_{8 \mathrm{~b}, 7}=3.1 \mathrm{~Hz}, 1 \mathrm{H}, 7-\mathrm{H}\right), 6.69(\mathrm{~s}, 1 \mathrm{H}$, $3-\mathrm{H}), 6.85,6.95\left(\mathrm{~d}, J_{9,10}=8.2 \mathrm{~Hz}, 2 \mathrm{H}, 9-\mathrm{H}\right.$ and $\left.10-\mathrm{H}\right) ; \mathrm{MS}(70 \mathrm{eV}): m / z(\%) 399(91)\left[\mathrm{M}^{+}\right], 311(100)\left[\mathrm{M}^{+}\right.$-$\mathrm{CH}_{2}=\mathrm{NH}-\mathrm{COOCH}_{3}$ ]; HRMS $\left(\mathrm{M}^{+}\right)$calcd 399.1682, found 399.1670; $\mathrm{mp}=165-166^{\circ} \mathrm{C}$.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (29):
Yield of 29: $4.1 \mathrm{mg}, 0.010 \mathrm{mmol}, 3 \%$. IR (KBr): $\tilde{v} 1697,1514,1462,1452,1261,1242,1230,1207,1100$ $\mathrm{cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.47-2.57,2.66-2.81,2.85-3.00,3.04-3.11,3.17-3.34(\mathrm{~m}, 11 \mathrm{H}, 1 \times 3-\mathrm{H}$ ( a and b ), $1 \times 3-\mathrm{H}(\mathrm{a}$ or b$), 2 \times 4-\mathrm{H}(\mathrm{a}$ and b$)$ and $2 \times \alpha-\mathrm{H}(\mathrm{a}$ and b$)$ ), $3.52\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{COOCH}_{3}(\mathrm{a})\right), 3.59(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{COOCH}_{3}(\mathrm{~b})\right), 3.68,3.74,3.77,3.80\left(\mathrm{~s}, 24 \mathrm{H}, 4 \times \mathrm{ArOCH}_{3}(\mathrm{a}\right.$ and b$\left.)\right), 4.05-4.14(\mathrm{~m}, 1 \mathrm{H}, 1 \times 3-\mathrm{H}(\mathrm{a}$ or b$)$ ), 5.07-5.12 (m, 1 H, 1-H (a)), 5.18-5.23 (m, 1 H, 1-H (b)), 6.16(s, 1 H, 8-H (a)), $6.32(\mathrm{~s}, 1 \mathrm{H}, 8-\mathrm{H}(\mathrm{b})), 6.54-$ $6.75\left(\mathrm{~m}, 2 \times 4 \mathrm{H}, 5-\mathrm{H}, 2^{\prime}-\mathrm{H}, 5^{\prime}-\mathrm{H}\right.$ and $6^{\prime}-\mathrm{H}(\mathrm{a}$ and b$)$ ) (most signals are doubled because of the hindered rotation around the amide linkage, the main rotamer is marked with an a); MS (70 eV): m/z (\%) $250(100)\left[\mathrm{M}^{+}\right.$$\mathrm{CH}_{2} \mathrm{C}_{6} \mathrm{H}_{6}\left(\mathrm{OCH}_{3}\right)_{2}$; microanalysis calcd C $65.82, \mathrm{H} 6.78$, N 3.49 , found $\mathrm{C} 65.74, \mathrm{H} 6.98, \mathrm{~N} 3.37$; mp $=110^{\circ} \mathrm{C}$.

I-(2-Bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (30):
Yield of $\mathbf{3 0}: 5.8 \mathrm{mg}, 0.012 \mathrm{mmol}, 4 \%$. IR (KBr): $\tilde{\mathrm{v}} 1698,1487,1448,1255,1034 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 2.65-2.73,2.85-3.04,3.19-3.54$ ( m , integration of all signals in the range of $2.65-3.54 \mathrm{ppm}: 14 \mathrm{H}, 1 \times$ $3-\mathrm{H}(\mathrm{a}$ and b$), 1 \times 3-\mathrm{H}(\mathrm{a}$ or b$), 2 \times 4-\mathrm{H}$ (a and b), $2 \times \alpha-\mathrm{H}$ (a and b)), $3.30\left(\mathrm{~s}, \mathrm{COOCH}_{3}(\mathrm{a})\right), 3.66(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{COOCH}_{3}(\mathrm{~b})\right), 3.82,3.85,3.86,3.87\left(\mathrm{~s}, 24 \mathrm{H}, 4 \times \mathrm{ArOCH}_{3}(\mathrm{a}\right.$ and b)$), 4.28-4.35(\mathrm{~m}, 1 \mathrm{H}, 1 \times 3-\mathrm{H}(\mathrm{a}$ or b$))$,
$5.34-5.39\left(\mathrm{~m}, 2 \mathrm{H}, 1-\mathrm{H}(\mathrm{a}\right.$ and b$)$ ), $6.26(\mathrm{~s}), 6.59-6.87\left(\mathrm{~m}, 8 \mathrm{H}, 5-\mathrm{H}, 8-\mathrm{H}, 5 \mathrm{~S}^{\prime}-\mathrm{H}\right.$ and $6 \mathrm{H}-\mathrm{H}(\mathrm{a}$ and b$)$ ) (most signals are doubled because of the hindered rotation around the amide linkage, the main rotamer is marked with an a); MS (70 eV, $\left.\mathrm{NH}_{3}-\mathrm{DCI}\right): ~ m / z(\%) 497 / 499(100 / 98)\left[\mathrm{M}^{+}+\mathrm{NH}_{3}+\mathrm{H}\right], 480 / 482(83 / 83)\left[\mathrm{M}^{+}+\mathrm{H}\right], 400(52)$ $\left[\mathrm{M}^{+}-\mathrm{Br}\right], 250(100)\left[\mathrm{M}^{+}-\left(\mathrm{H}_{3} \mathrm{CO}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3} \mathrm{CH}_{2}\right.$ ]; microanalysis calcd C 55.01, H 5.46, N 2.92, found C 54.99, H 5.34, N 2.92; $\mathrm{mp}=61-62^{\circ} \mathrm{C}$.

## ACKNOWLEDGEMENT

We thank the Fonds der chemischen Industrie for financial support of this work. The engaged technical assistance of Mrs M. Rother is gratefully acknowledged.

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