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

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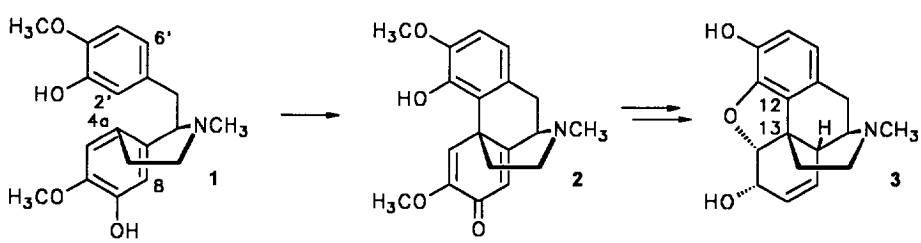
Abstract: Two intramolecular aryl-aryl-coupling reactions of 2'-bromoreticulines are described. Their regioselectivity depends on the cyclization method. The palladium(0) catalyzed reaction of **22** leads preferentially to the salutaridine derivative **27**, whilst via the photochemically induced $S_{RN}1$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

Introduction

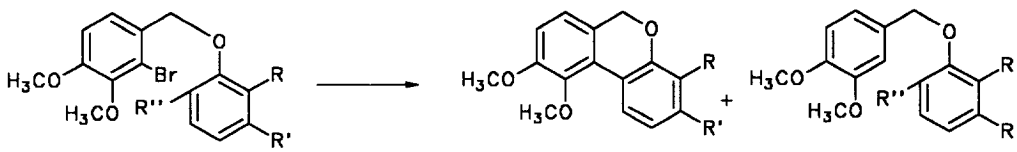
For decades the synthesis of morphine (**3**) has presented a continuous challenge in organic synthesis.[1] Cyclization between C-12 and C-13 has been the key step in a number of approaches. An efficient way to form this bond is the acid catalyzed intramolecular electrophilic aromatic substitution of 1-benzyloctahydroisoquinolines, the Grewe cyclization.[2] A recent approach uses the Heck reaction to form the quarternary center at C-13.[3] In the biosynthesis[4] of morphine the C-12 - 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 C-4a - C-2' 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 C-4a - C-2' coupling of 2'-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 $S_{RN}1$ 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 C-4a - C-2' coupling in 2'-bromoreticulines since the C-4a 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).



	R	R'	R''
4	H	H	H
5	CH_3	H	CH_3
6	CH_3	OH	H

	R	R'
7	H	H
8	CH_3	OH

	R	R'	R''
9	H	H	H
10	CH_3	H	CH_3
11	CH_3	OH	H

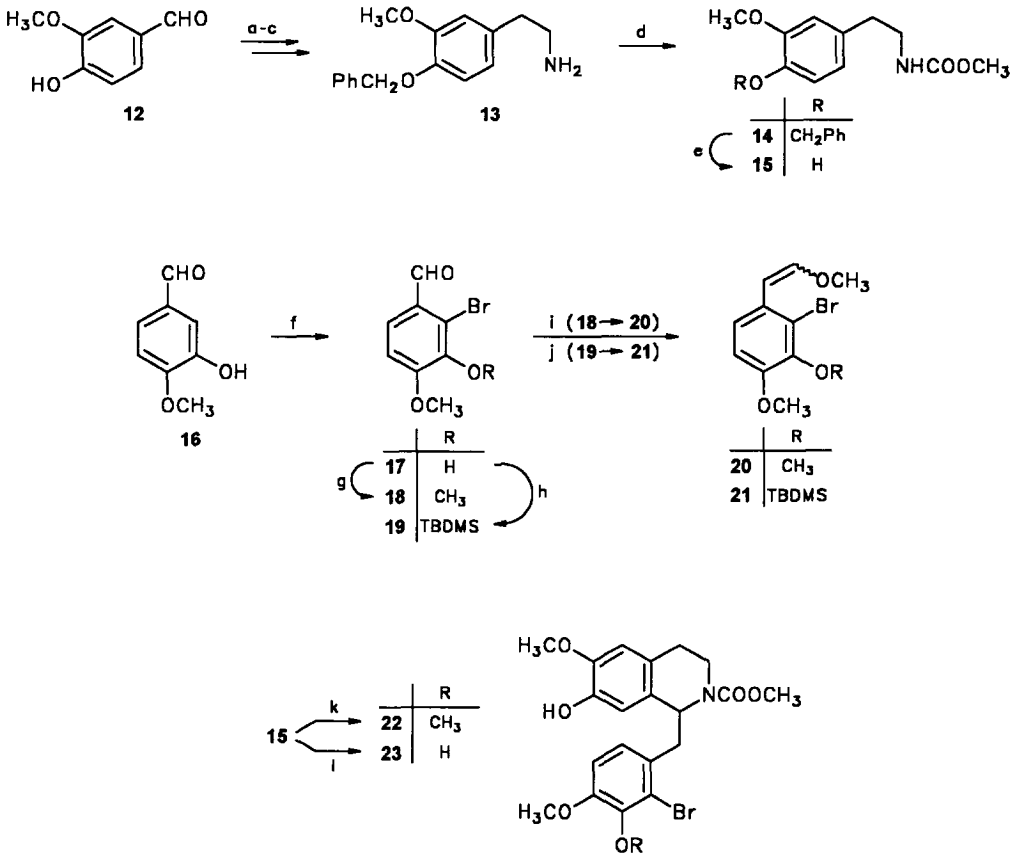
Scheme 2

The reaction conditions published by *Ames*[9] (palladium(II) chloride, potassium carbonate, dimethylformamide, 140 °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 $S_{RN}1$ reaction of aromatic compounds Ar-X with nucleophiles 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 (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 C-13 center in morphine appears to be possible by a $S_{RN}1$ 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 **4**, **5** and **6** were now transferred to a 2'-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 %.

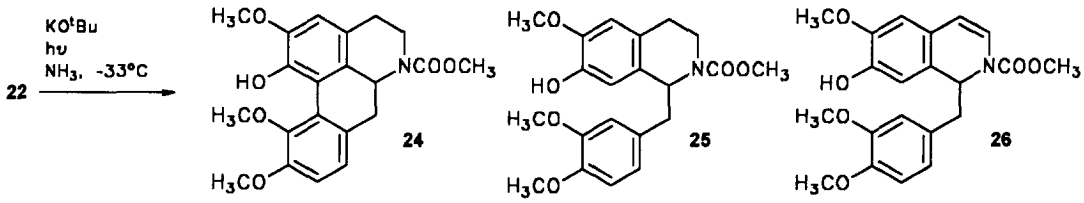
However, a conversion of **23** could neither be observed under the most favorable conditions for the palladium(0) catalyzed cyclization nor under those for the $S_{RN}1$ reaction. **23** differs from **4**, **5** and **6** since both aromatic rings are negatively charged owing to the phenolate formation. 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: $PhCH_2Cl$, KOH, Δ (90 %); b: CH_3NO_2, HOAc, Δ (86 %); c: $LiAlH_4$, tetrahydrofuran (81 %); d: $ClCOOCH_3$, NEt_3 (75 %); e: H_2, Pd/charcoal, CH_3OH (97 %); f: Br_2, Fe, HOAc, NaOAc (56 %); g: CH_3I, KOH, dmso (96 %); h: TBDMSCl, NEt_3, 4,4-dimethylaminopyridine (94 %); i: $Ph_3PCH_2OCH_3{}^+Cl^-$, KO^tBu, dioxane, Δ (79 %); j: $Ph_3PCH_2OCH_3{}^+Cl^-$, KO^tBu, dioxane, Δ (86 %); k: **20**, $POCl_3$, CH_2Cl_2, Δ (87 %); l: **21**, $POCl_3$, CH_2Cl_2, Δ (89 %).

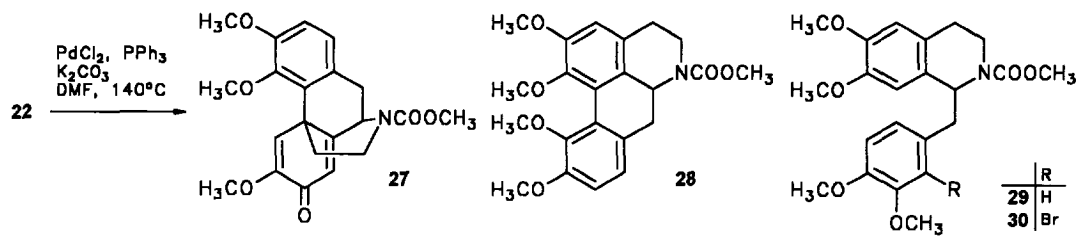
Scheme 3

Therefore the reticuline derivative **22**, in which the 3'-hydroxy substituent of **23** is replaced by a 3'-methoxy group, was synthesized in the same sequence as **23** in nine steps and 17% overall yield. The photoinitiated $S_{RN}1$ reaction of **22** in liquid ammonia afforded at complete conversion the C-8 - C-2' 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 σ-aryl radical, **26** is possibly formed via an intramolecular 1,5-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 μm) 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 high-pressure vapor lamp was employed.

Palladium(0) catalyzed cyclizations of the aryl halides 4, 5 and 6

0.500 mmol of the aryl halide, 0.125 mmol $PdCl_2$, 0.375 mmol 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 °C. After complete conversion of the aryl halide (20 - 48 h) the mixture was poured into 20 ml 2 N HCl and the reaction products were extracted with diethyl ether (3 × 10 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 mmol, 66%); IR (KBr): $\tilde{\nu}$ 1493, 1265, 1242, 1103 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.76, 3.91 (s, 6 H, $ArOC\underline{H}_3$), 4.94 (s, 2 H, $ArC\underline{H}_2OR$), 6.85, 6.89 (d, $J_{3,4}$ = 8.3 Hz, 2 H, 3-H and 4-H), 7.01 (dd, $J_{9,10}$ = 8.3 Hz, $J_{8,10}$ = 1.5 Hz, 1 H, 10-H), 7.07 (ddd, $J_{7,8}$ = 7.9 Hz, $J_{8,9}$ = 7.5 Hz, $J_{8,10}$ = 1.5 Hz, 1 H, 8-H), 7.23 (ddd, $J_{9,10}$ = 8.3 Hz, $J_{8,9}$ = 7.5 Hz, $J_{7,9}$ = 1.5 Hz, 1 H, 9-H), 8.45 (dd, $J_{7,8}$ = 7.9 Hz, $J_{7,9}$ = 1.5 Hz, 1 H, 7-H); MS (70 eV): *m/z* (%) 242 (100) [M^+], 241 (87) [M^+ - H]; HRMS (M^+) calcd 242.0943, found 242.0937; mp 83 - 85 °C.

O-Phenyl-3,4-dimethoxybenzyl alcohol (9):

145.6 mg **4**, base: NaOAc, Yield: 5.3 mg **9** (0.025 mmol, 5%); IR (film): $\tilde{\nu}$ 1498, 1240 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89, 3.89 (s, 6 H, $ArOC\underline{H}_3$), 4.99 (s, 2 H, $ArC\underline{H}_2OR$), 6.87 (d, $J_{5,6}$ = 8.7 Hz, 1 H, 5-H), 6.95 - 6.99 (m, 5 H, 2-H, 6-H, 2'-H, 4'-H and 6'-H), 7.27 - 7.31 (m, 2 H, 3'-H and 5'-H); MS (70 eV): *m/z* (%) 244 (11) [M^+], 151 (100) [$(H_3CO)_2C_6H_3CH_2^+$]; HRMS (M^+) calcd 244.1099, found 244.1093.

O-(2,6-Dimethylphenyl)-3,4-dimethoxybenzyl alcohol (10):

175.7 mg **5**, base: K_2CO_3, Yield: 56.2 mg **10** (0.206 mmol, 41%); IR (film): $\tilde{\nu}$ 1516, 1262, 1197 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 6 H, $ArC\underline{H}_3$), 3.88, 3.91 (s, 6 H, $ArOC\underline{H}_3$), 4.76 (s, 2 H, $ArC\underline{H}_2OR$), 6.88 (d, $J_{5,6}$ = 7.9 Hz, 1 H, 5-H), 6.91 - 7.05 (m, 5 H, 2-H, 6-H, 3'-H, 4'-H and 5'-H); MS (70 eV): *m/z* (%) 151 (100) [$(H_3CO)_2C_6H_3CH_2^+$]; 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: K_2CO_3, Yield: 76.5 mg **8** (0.281 mmol, 56%); IR (KBr): $\tilde{\nu}$ 3378, 2936, 1489, 1406, 1261, 1071 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.17 (s, 3 H, $ArC\underline{H}_3$), 3.72, 3.88 (s, 6 H, $ArOC\underline{H}_3$), 4.93 (s, 2 H, 2-H), 5.07 (s, 1 H, OH), 6.53 (d, $J_{7,8}$ = 8.6 Hz, 1 H, 8-H), 6.79, 6.86 (d, $J_{3,4}$ = 8.2 Hz, 2 H, 3-H and 4-H), 8.18 (d, $J_{7,8}$ = 8.6 Hz, 1 H, 7-H); MS (70 eV): *m/z* (%) 272 (100) [M^+]; microanalysis calcd C 70.57, H 5.92, found C 70.40, H 6.06; mp = 167 - 173 °C.

O-(2-Hydroxy-3-methylphenyl)-3,4-dimethoxybenzyl alcohol (11):
176.5 mg **6**, base: K_2CO_3, Yield: 6.4 mg **11** (0.023 mmol, 5%); IR (KBr): $\tilde{\nu}$ 3458, 1517, 1463, 1091, 1078 cm^{-1}; ^1H NMR ([D_6]Aceton): δ 2.13 (s, 3 H, $ArC\underline{H}_3$), 3.81, 3.83 (s, 6 H, $ArOC\underline{H}_3$), 5.00 (s, 2 H, $ArC\underline{H}_2OR$), 6.50, 6.54 (d, ^3J = 8.2 Hz, 2 H, 4'-H and 6'-H), 6.91 - 6.97 (m, 2 H, 5-H and 5'-H), 7.00 (dd, $J_{5,6}$ = 8.1 Hz, $J_{2,6}$ = 1.9 Hz, 1 H, 6-H), 7.10 (d, $J_{2,6}$ = 1.9 Hz, 1 H, 2-H); MS (70 eV, NH_3-DCI): *m/z* (%) 151 (100) $[(H_3CO)_2C_6H_3CH_2^+]$; microanalysis calcd C 70.06, H 6.61, found C 69.92, H 6.65; mp = 144 - 146 °C.

Photochemically induced $S_{RN}1$ reaction of 5
The aryl halide **5** (10.3 mg, 0.029 mmol) and KO^{t}Bu (11.7 mg, 0.104 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 × 20 ml), dried and after evaporation of the solvent purified by flash column chromatography (petroleum ether / diethyl ether = 1 : 1). 6.2 mg (0.023 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 g, 11.7 mmol), chloroformic acid methyl ester (0.87 ml, 12.8 mmol) and triethylamine (1.85 ml, 14.0 mmol) in 30 ml dichloromethane was stirred at 0 °C for 30 min. Concentration and flash column chromatography (petroleum ether / diethyl ether = 10 : 1) gave **14** (2.76 g, 8.8 mmol, 75%) as a white solid. IR (KBr): $\tilde{\nu}$ 3380, 3347, 1686, 1521, 1274, 1237 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.74 (t, $J_{1,2}$ = 7.0 Hz, 2 H, 2-H), 3.41 (m, 2 H, 1-H), 3.66 (s, 3 H, $COOCH_3$), 3.88 (s, 3 H, $ArOC\underline{H}_3$), 4.64 (s, br., 1 H, NH), 5.13 (s, 2 H, $OC\underline{H}_2Ph$), 6.65 (dd, $J_{5',6'}$ = 8.3 Hz, $J_{2',6'}$ = 1.9 Hz, 1 H, 6'-H), 6.72 (d, $J_{2',6'}$ = 1.9 Hz, 1 H, 2'-H), 6.82 (d, $J_{5',6'}$ = 8.3 Hz, 1 H, 5'-H), 7.29 - 7.45 (m, 5 H, 2"-H - 6"-H); MS (70 eV): *m/z* (%) 315 (19) [M^+], 91 (100) [$C_7H_7^+$]; microanalysis calcd C 68.55, H 6.71, N 4.44, found C 68.55, H 6.72, N 4.35; mp = 74 °C.

2-(4-Hydroxy-3-methoxyphenyl)-ethyl-N-methoxycarbonylamine (15):
To a solution of **14** (1.00 g, 3.2 mmol) in 40 ml methanol was added palladium on charcoal (10% Pd, 0.12 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 g **15**, 3.1 mmol, 97%). IR (KBr): $\tilde{\nu}$ 3356, 1700, 1516, 1270, 1237, 1202, 1033 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.73 (t, $J_{1,2}$ = 6.8 Hz, 2 H, 2-H), 3.35 - 3.42 (m, 2 H, 1-H), 3.48 (s, 1 H, OH), 3.67 (s, 3 H, $COOCH_3$), 3.87 (s, 3 H, $ArOC\underline{H}_3$), 4.73 (s, br., 1 H, NH), 6.65 - 6.72 (m, 2 H, 2'-H and 6'-H), 6.84 (d, $J_{5',6'}$ = 7.9 Hz, 1 H, 5'-H); MS (70 eV): *m/z* (%) 225 (24) [M^+], 150 (100) [M^+ - NH_2COOCH_3 (McL)], 137 (98) $[CH_2C_6H_3(OH)(OCH_3)^+]$; microanalysis calcd C 58.66, H 6.71, N 6.22, found C 58.53, H 6.89, N 6.11; mp = 66 - 69 °C.

2-Bromo-3,4-dimethoxybenzaldehyde (18):
Powdered sodium hydroxide (4.63 g, 82.5 mmol) was stirred in 35 ml dimethyl sulfoxide for exactly 5 min. To this suspension a solution of **17**[23] (7.63 g, 33.0 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 × 100 ml) and dried. Flash column chromatography (petroleum ether / diethyl ether = 1 : 1) afforded **18** as a white solid (7.78 g, 31.8 mmol, 96%). IR (KBr): $\tilde{\nu}$ 1679, 1583, 1490, 1282, 1258, 1023 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.88, 3.97 (s, 6 H, $ArOC\underline{H}_3$), 6.97 (d, $J_{5,6}$ = 8.7 Hz, 1 H, 5-H), 7.70 (d, $J_{5,6}$ = 8.7 Hz, 1 H, 6-H), 10.23 (s, 1 H, CHO); MS (70 eV): *m/z* (%) 244/246 (100/93) [M^+], 243/245 (67/94) [M^+ - H]; microanalysis calcd C 44.11, H 3.70, Br 32.60, found C 44.05, H 3.67, Br 32.64; mp = 83 - 84 °C.

(E)- and (Z)-1-(2-Bromo-3,4-dimethoxyphenyl)-2-methoxyethene (20):
Methoxymethyltriphenylphosphonium chloride (4.20 g, 12.2 mmol) and KO^{t}Bu (1.44 g, 12.8 mmol) were suspended in 35 ml freshly distilled dioxane. After 60 min **18** (2.00 g, 8.2 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 × 50 ml). The solvent was completely removed and the residue was redissolved in 5 ml dichloromethane. PPh_3O 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 g, 6.4 mmol, 79%). IR (film): $\tilde{\nu}$ 1486, 1277, 1256, 1218, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3 H, *(Z)* =CH-OC$\underline{H}_3$), 3.74 (s, 3 H, *(E)* =CH-OC$\underline{H}_3$), 3.83, 3.84, 3.84, 3.85 (s, 3 H, *(E)*- and *(Z)*-ArOC$\underline{H}_3$), 5.55 (d, $J_{1,2}$ = 7.2 Hz, 1 H, *(Z)*-1-H), 6.03 (d, $J_{1,2}$ = 12.9 Hz, 1 H, *(E)*-1-H), 6.17 (d, $J_{1,2}$ = 7.2 Hz, 1 H, *(Z)*-2-H), 6.77 - 6.86 (m, 3 H, *(E)*-2-H, *(E)*- and *(Z)*-5'-H), 7.03 (d, $J_{5',6'}$ = 8.6 Hz, 1 H, *(E)*-6'-H), 7.77 (d, $J_{5',6'}$ = 8.8 Hz, 1 H, *(Z)*-6'-H); MS (70 eV): *m/z* (%) 272/274 (91/91) [M$^+$], 178 (100) [M$^+$ - Br - CH_3]; microanalysis calcd C 48.37, H 4.80, found C 48.19, H 4.86.

2-Bromo-3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (19):
17[23] (2.02 g, 8.7 mmol), *tert*-butyldimethylsilyl chloride (1.32 g, 8.7 mmol), triethylamine (2.31 ml, 17.5 mmol) and a catalytic amount of 4-*N',N'*-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 g, 8.2 mmol, 94%). IR (film): $\tilde{\nu}$ 1685, 1577, 1489, 1310, 1279, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.21 (s, 6 H, OSi$(CH_3)_2$), 1.04 (s, 9 H, OSiC$(CH_3)_3$), 3.86 (s, 3 H, ArOC$\underline{H}_3$), 6.86 (d, $J_{5,6}$ = 8.8 Hz, 1 H, 5-H), 7.55 (d, $J_{5,6}$ = 8.8 Hz, 1 H, 6-H), 10.23 (s, 1 H, CHO); MS (70 eV): *m/z* (%) 287/289 (89/89) [M$^+$ - C_4H_9], 272/274 (98/100) [M$^+$ - CH_3 - C_4H_9]; microanalysis calcd C 48.70, H 6.13, found C 48.40, H 6.27.

(E)- and (Z)-1-(2-Bromo-3-(tert-butyldimethylsilyloxy)-4-methoxyphenyl)-2-methoxyethene (21):
19 (2.50 g, 7.2 mmol), methoxymethyltriphenylphosphonium chloride (4.19 g, 12.2 mmol) and KO^{t}Bu (1.37 g, 12.2 mmol) in 30 ml dioxane were by analogy to the preparation of **20** converted into **21**. The flash column chromatography was carried out with petroleum ether / diethyl ether = 40 : 1 as eluent and yielded **21** as a colourless oil (2.31 g, 6.2 mmol, 86%). IR (film): $\tilde{\nu}$ 1649, 1487, 1412, 1256, 1103, 1038, 855 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.26 (s, 6 H, *(Z)*-OSi$(CH_3)_2$), 0.26 (s, 6 H, *(E)*-OSi$(CH_3)_2$), 1.09 (s, 9 H, *(Z)*-OSiC$(CH_3)_3$), 1.09 (s, 9 H, *(E)*-OSiC$(CH_3)_3$), 3.72 (s, 3 H, *(E)* =CH-OC$\underline{H}_3$), 3.75 (s, 3 H, *(Z)* =CH-OC$\underline{H}_3$), 3.79, 3.80 (s, 6 H, *(E)*- and *(Z)*-ArOC$\underline{H}_3$), 5.63 (d, $J_{1,2}$ = 7.2 Hz, 1 H, *(Z)*-1-H), 6.11 (d, $J_{1,2}$ = 12.7 Hz, 1 H, *(E)*-1-H), 6.17 (d, $J_{1,2}$ = 7.2 Hz, 1 H, *(Z)*-2-H), 6.74 (d, $J_{5',6'}$ = 8.5 Hz, 1 H, *(E)*-5'-H), 6.79 (d, $J_{5',6'}$ = 8.7 Hz, 1 H, *(Z)*-5'-H), 6.86 (d, $J_{1,2}$ = 12.7 Hz, 1 H, *(E)*-2-H), 6.92 (d, $J_{5',6'}$ = 8.5 Hz, 1 H, *(E)*-6'-H), 7.67 (d, $J_{5',6'}$ = 8.7 Hz, 1 H, *(Z)*-6'-H); MS (70 eV): *m/z* (%) 315/317 (97/100) [M$^+$ - C_4H_9], 300/302 (80/88) [M$^+$ - C_4H_9 - CH_3]; 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-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (22):
To a solution of **15** (1.41 g, 6.3 mmol) and **20** (1.67 g, 6.1 mmol) in 50 ml dichloromethane was added $POCl_3$ (1.70 ml, 18.2 mmol). After refluxing the mixture for 6 h it was quenched with 150 ml water and the product was extracted with dichloromethane (3 × 50 ml). Flash column chromatography (dichloromethane / ethyl acetate = 5 : 1) afforded **22** as a white solid (2.51 g, 5.4 mmol, 89%). IR (KBr): $\tilde{\nu}$ 1685, 1487, 1452, 1241, 1202, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.62 - 2.96, 3.21 - 3.35 (m, integration of all signals in the range of 2.62 - 3.60 ppm: 17 H, 1 × 3-H (a and b), 1 × 3-H (a or b), 2 × 4-H (a and b) and 2 × α-H (a and b)), 3.21 (s, $COOCH_3$ (a)), 3.60 (s, $COOCH_3$ (b)), 3.84, 3.86, 3.87 (s, 18 H, 3 × ArOC$\underline{H}_3$ (a and b)), 4.30 (ddd, ^2J = 13.3 Hz, ^3J = 6.2 Hz,

^3J = 1.9 Hz, 1 H, 1 × 3-H (a or b)), 5.33 (dd, J_{1,α_1} = 10.7 Hz, J_{1,α_2} = 3.3 Hz, 2 H, 1-H (a and b)), 5.68 (s, br., 2 H, OH (a and b)), 6.54 - 6.60 (m), 6.77 (s), 6.88 (s, integration of all signals in the range of 6.54 - 6.88 ppm: 8 H, 5-H, 8-H, 5'-H and 6'-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, NH_3-DCI): *m/z* (%) 483/485 (96/100) [M^+ + NH_3 + H]; microanalysis calcd C 54.09, H 5.19, N 3.00, found C 54.16, H 5.17, N 3.15; mp = 199-200 °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 mg, 0.888 mmol) and **21** (371.5 mg, 0.995 mmol) in 10 ml dichloromethane $POCl_3$ (0.33 ml, 3.5 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 × 10 ml). Purification by chromatography (diethyl ether / methanol = 20 : 1) afforded **23** as a white solid (350.0 mg, 0.774 mmol, 87%). IR (KBr): $\tilde{\nu}$ 1685, 1489, 1286, 1264, 1033 cm^{-1}; ^1H NMR ($CDCl_3$): δ 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 ppm: 17 H, 1 × 3-H (a and b), 1 × 3-H (a or b), 2 × 4-H (a and b) and 2 × α-H (a and b)), 3.12 (s, $COOCH_3$ (a)), 3.60 (s, $COOCH_3$ (b)), 3.86 (s, 12 H, 2 × $ArOC\underline{H}_3$ (a and b)), 4.30 (ddd, ^2J = 13.1 Hz, ^3J = 6.0 Hz, ^3J = 2.4 Hz, 1 H, 1 × 3-H (a or b)), 5.35 (dd, J_{1,α_1} = 10.7 Hz, J_{1,α_2} = 3.6 Hz, 2 H, 1-H (a and b)), 6.55 - 6.73 (m), 6.87 (s, integration of all signals in the range of 6.55 - 6.87 ppm: 8 H, 5-H, 8-H, 5'-H and 6'-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, NH_3-DCI): *m/z* (%) 452/454 (35/100) [M^+ + H]; microanalysis calcd C 53.11, H 4.90, found C 53.37, H 5.27; mp = 74 - 76 °C.

Photochemically induced $S_{RN}1$ reaction of 22

22 (124.0 mg, 0.266 mmol) was dissolved in 20 ml of refluxing NH_3 (acetone / dry ice reflux condenser). KO^tBu (131.7 mg, 1.078 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. $NaHCO_3$, extracted with dichloromethane (4 × 15 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 mg, 0.050 mmol, 19%. IR (KBr): $\tilde{\nu}$ 1695, 1466, 1449, 1286, 1234 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.61 - 3.04 (m, 5 H, 2 × 4-H, 1 × 5-H, 2 × 8-H), 3.76, 3.76, 3.91, 3.92 (s, 12 H, $ArOC\underline{H}_3$ and $COOCH_3$), 4.40 - 4.44 (m, 1 H, 1 × 5-H), 4.67 (dd, $J_{8a,7}$ = 13.0 Hz, $J_{8b,7}$ = 3.1 Hz, 1 H, 7-H), 6.71 (s, 1 H, 3-H), 6.89, 7.09 (d, $J_{9,10}$ = 8.2 Hz, 2 H, 9-H and 10-H), 8.88 (s, 1 H, OH); MS (70 eV, NH_3-DCI): *m/z* (%) 403 (100) [M^+ + H + NH_3]; HRMS (M^+) calcd 385.1525, found 385.1516; mp = 200 - 202 °C.

1-(2-Bromo-3,4-dimethoxybenzyl)-7-hydroxy-6-methoxy-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (25):

Yield of **25**: 8.0 mg, 0.021 mmol, 8%. IR (KBr): $\tilde{\nu}$ 1685, 1515, 1263 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35 - 2.86, 2.96 - 3.21 (m, 11 H, 1 × 3-H (a and b), 1 × 3-H (a or b), 2 × 4-H (a and b), 2 × α-H (a and b)), 3.47 (s, integration of all signals in the range of 3.47 - 3.86 ppm: 24 H, $COOCH_3$ (a)), 3.69 (s, $COOCH_3$ (b)), 3.74, 3.80, 3.84, 3.86 (s, 3 × $ArOC\underline{H}_3$ (a and b)), 4.08 - 4.17 (m, 1 H, 1 × 3-H (a or b)), 5.10 - 5.14 (m, 1 H, 1-H (a)), 5.24 - 5.31 (m, 1 H, 1-H (b)), 5.53, 5.55 (s, br., 2 H, OH (a and b), 6.54 - 6.77 (m, 8 H, 5-H, 8-H, 5'-H and 6'-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) [M^+], 236 (100) [M^+ - $(H_3CO)_2C_6H_3CH_2$]; microanalysis calcd C 65.10, H 6.50, found C 65.18, H 6.65; mp = 57 - 58 °C.

1-(3,4-Dimethoxybenzyl)-7-hydroxy-6-methoxy-N-methoxycarbonyl-1,2-dihydroisoquinoline (26):
Yield of **26**: 8.2 mg, 0.021 mmol, 8%. IR (film): $\tilde{\nu}$ 1700, 1518, 1269 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.65 - 2.88 (m, 4 H, 2 × α-H (a and b)), 3.50, 3.66, 3.76, 3.78, 3.80, 3.85, 3.87, 3.89 (s, 24 H, $ArOC\underline{H}_3$ and $COOCH_3$ (a and b)), 5.21 - 5.25 (m, 1 H, 1-H (a or b)), 5.36 - 5.40 (m, 1 H, 1-H (a or b)), 5.46 - 5.82 (m, 2 H, 4-H (a and b)), 6.26 (s), 6.45 - 6.91 (m, 12 H, 3-H, 5-H, 8-H, 2'-H, 5'-H and 6'-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* (%) 234 (100) [M^+ - $(H_3CO)_2C_6H_3CH_2$]; HRMS (M^+) calcd 403.1869, found 403.1886.

Palladium(0) catalyzed reaction of 22
In 15 ml of freshly distilled dimethylformamide were dissolved **22** (162.7 mg, 0.349 mmol), palladium(II) chloride (5.9 mg, 0.033 mmol), triphenylphosphine (26.2 mg, 0.100 mmol) and potassium carbonate (186.2 mg, 1.347 mmol). The resulting suspension was stirred for 13 h at 140 °C and poured into 30 ml 2 N HCl. It was extracted with dichloromethane (5 × 20 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 mg, 0.060 mmol, 17%. IR (KBr): $\tilde{\nu}$ 2962, 1699, 1675, 1652, 1232, 1100, 1017 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 - 1.69 (m, 2 H, 2 × 15-H), 2.35 - 2.45 (m, 1 H, 1 × 16-H), 2.80 (dt, J_{gem} = 13.1 Hz, $J_{15,16}$ = 3.8 Hz, 1 H, 1 × 16-H), 3.10 - 3.25 (m, 2 H, 2 × 10-H), 3.70, 3.77 (s, br., integration of all signals in the range of 3.70 - 3.97 ppm: 12 H, $COOC\underline{H}_3$), 3.78, 3.87, 3.97 (s, 3 × $ArOC\underline{H}_3$), 5.02, 5.16 (s, br., 1 H, 9-H), 6.32, 6.35 (s, br., 1 H, 8-H), 6.84 (s, 2 H, 1-H and 2-H), 7.25 (s, 1 H, 5-H); MS (70 eV): *m/z* (%) 386 (100) [M^+ + H]; HRMS (M^+) calcd 385.1525, found 385.1516; mp = 76 - 77 °C.

O,O-Dimethyl-N-methoxycarbonylnorcorytuberine (28):
Yield of **28**: 11.1 mg, 0.027 mmol, 8%. IR (KBr): $\tilde{\nu}$ 1696, 1399, 1247 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.58 - 2.66, 2.80 - 3.00 (m, 5 H, 2 × 4-H, 1 × 5-H, 2 × 8-H), 3.67, 3.70, 3.75, 3.88, 3.89 (s, 15 H, 4 × $ArOC\underline{H}_3$ and $COOCH_3$), 4.40 - 4.47 (m, 1 H, 1 × 5-H), 4.57 (dd, $J_{8a,7}$ = 12.9 Hz, $J_{8b,7}$ = 3.1 Hz, 1 H, 7-H), 6.69 (s, 1 H, 3-H), 6.85, 6.95 (d, $J_{9,10}$ = 8.2 Hz, 2 H, 9-H and 10-H); MS (70 eV): *m/z* (%) 399 (91) [M^+], 311 (100) [M^+ - CH_2=NH-$COOCH_3$]; HRMS (M^+) calcd 399.1682, found 399.1670; mp = 165 - 166 °C.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (29):
Yield of **29**: 4.1 mg, 0.010 mmol, 3%. IR (KBr): $\tilde{\nu}$ 1697, 1514, 1462, 1452, 1261, 1242, 1230, 1207, 1100 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.47 - 2.57, 2.66 - 2.81, 2.85 - 3.00, 3.04 - 3.11, 3.17 - 3.34 (m, 11 H, 1 × 3-H (a and b), 1 × 3-H (a or b), 2 × 4-H (a and b) and 2 × α-H (a and b)), 3.52 (s, 3 H, $COOCH_3$ (a)), 3.59 (s, 3 H, $COOCH_3$ (b)), 3.68, 3.74, 3.77, 3.80 (s, 24 H, 4 × $ArOC\underline{H}_3$ (a and b)), 4.05 - 4.14 (m, 1 H, 1 × 3-H (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 (s, 1 H, 8-H (b)), 6.54 - 6.75 (m, 2 × 4 H, 5-H, 2'-H, 5'-H and 6'-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* (%) 250 (100) [M^+ - $CH_2C_6H_6(OCH_3)_2$]; microanalysis calcd C 65.82, H 6.78, N 3.49, found C 65.74, H 6.98, N 3.37; mp=110 °C.

1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-N-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (30):
Yield of **30**: 5.8 mg, 0.012 mmol, 4%. IR (KBr): $\tilde{\nu}$ 1698, 1487, 1448, 1255, 1034 cm^{-1}; ^1H NMR ($CDCl_3$): δ 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 ppm: 14 H, 1 × 3-H (a and b), 1 × 3-H (a or b), 2 × 4-H (a and b), 2 × α-H (a and b)), 3.30 (s, $COOCH_3$ (a)), 3.66 (s, 3 H, $COOCH_3$ (b)), 3.82, 3.85, 3.86, 3.87 (s, 24 H, 4 × $ArOC\underline{H}_3$ (a and b)), 4.28 - 4.35 (m, 1 H, 1 × 3-H (a or b)),

5.34 - 5.39 (m, 2 H, 1-H (a and b)), 6.26 (s), 6.59 - 6.87 (m, 8 H, 5-H, 8-H, 5'-H and 6'-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, NH_3-DCI): *m/z* (%) 497/499 (100/98) [$M^+ + NH_3 + H$], 480/482 (83/83) [$M^+ + H$], 400 (52) [M^+ - Br], 250 (100) [$M^+ - (H_3CO)_2C_6H_3CH_2$]; microanalysis calcd C 55.01, H 5.46, N 2.92, found C 54.99, H 5.34, N 2.92; mp = 61 - 62 °C.

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