Tetrahedron Vol. 49, No. 19, pp. 3995-4006, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

ASYMMETRIC SYNTHESIS XXVIII[1] : HYDROXYLATED BENZOQUINOLIZIDINE ANALOGUES OF PODOPHYLLOTOXIN VIA THE CN(R,S) METHOD.

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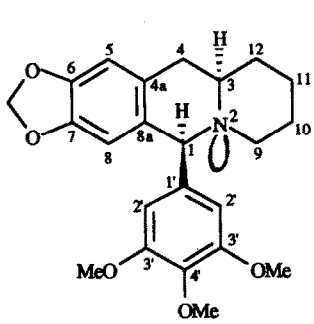
(*Received in Belgium* 1 *February* 1993)

Key Words : Asymmetric synthesis; benzoquinolizidine; podophyllotoxin analogues; CN(R,S) method, α-aminonitrile, α-aminoether, stereocontrolled alkylation of iminium ion.

Abstract : The condensation of 2-cyano-6-phenyloxazolopiperidine synthon (-)-5 with piperonal, gave after reduction, the optically pure pivotal amino-alcohol 8. Two strategies were developed to prepare the epimeric azapodophyllotoxin analogues 2 and 3 via Grignard reactions on an iminium ion generated from the common intermediate 8. The first strategy was based on an intramolecular reaction while the second involved a stereocontrolled addition reaction on iminium ion 20.

In the last few years, a great interest has developed for the synthesis of aza-analogues of podophyllotoxin because of their antitumor activity [2,3]. In the course of a program aimed at the preparation of benzoquinolizidine analogues of podophyllotoxin we have already reported the synthesis of parent compound 1 in optically pure form[2].



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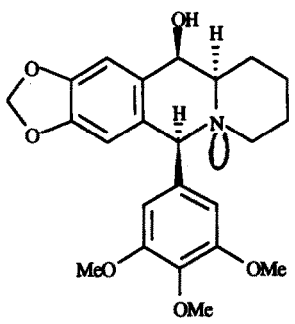

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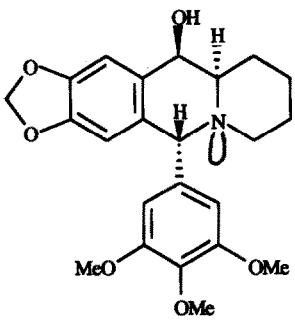

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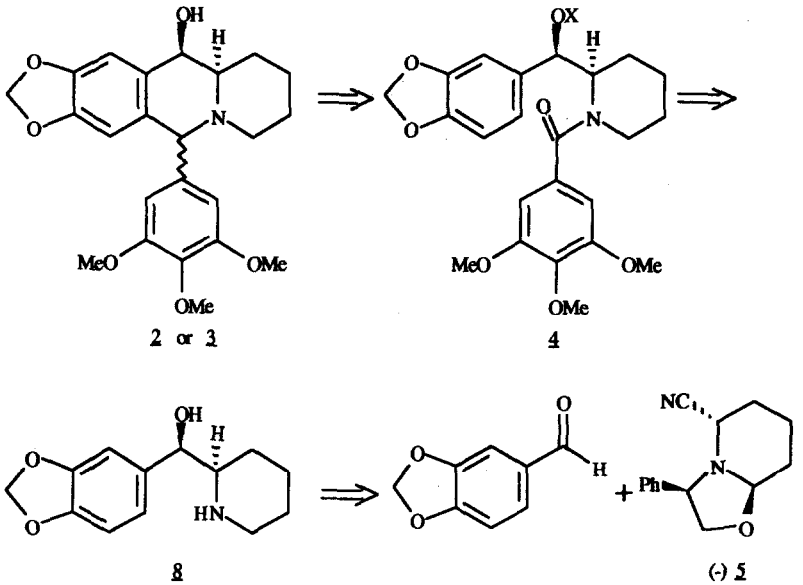
Our strategy was based on an application of the CN(R,S) method starting from synthon (-)-5 [4] which can provide a common route to a large range of functionalizations. Especially attractive was the possibility of introducing a hydroxyl function at C-4, typical for podophyllotoxin. It was also important to control the stereochemistry of the three asymmetric centres C-1, C-3 and C-4.

The most straightforward way to obtain such products was the direct oxidation of compound 1 previously obtained in our laboratory [2]. Unfortunately, all attempts to oxidize selectively the C-4 position

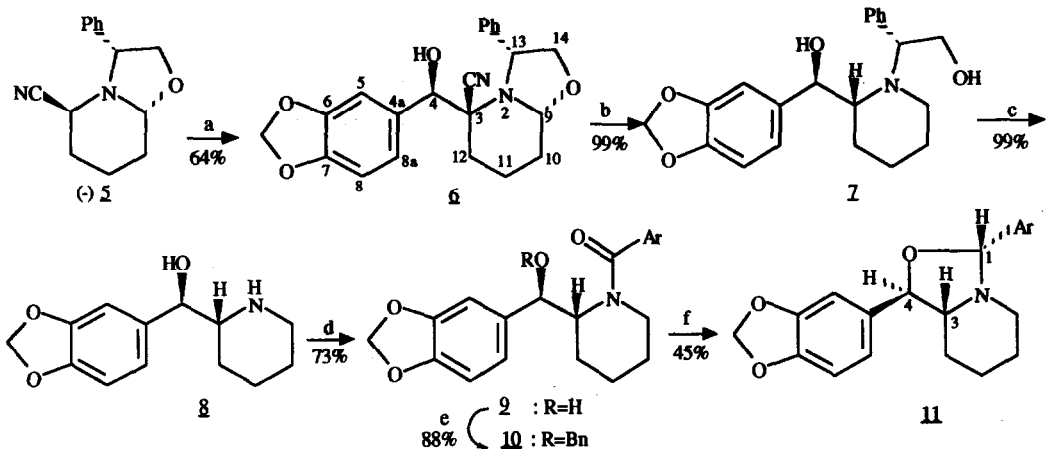
failed. DDQ in acetic acid[5] furnished exclusively the N-C-1 iminium salt. The use of other oxidizing agents ($Pb(OAc)_4$, NBS) gave the same result or led to degradation products.



SCHEME I

It was therefore necessary to introduce the oxy-function earlier in the synthesis, and we turned our attention to the retrosynthetic strategy presented in Scheme I. We envisaged formation of the desired product by a Bischler-Napieralsky reaction of the amide 4, obtained from the aminoalcohol 8, itself prepared by the CN(R,S) method as previously described from other aldehydes[6]. The main problem was to find a protective group for the hydroxyl function which was compatible with the cyclization conditions.

Condensation of the anion of (-) 5 with piperonal under kinetic conditions (-78°C, 10min) gave only one detectable isomer of 6 (Scheme II), while under thermodynamic conditions (0°C, 2h) the reaction furnished a mixture of products. The configuration of the newly created centre C-4 in 6 was assumed to be *R* on the basis of previous results[7]. The next step was the reductive cleavage of the aminoether and aminonitrile functions. This was achieved by use of $NaBH_4$ in EtOH, affording a single product 7. The reduction of the aminonitrile function occured with retention of stereochemistry[7] giving an R configuration at C-3. The C-4 configuration was confirmed by examination of the ^1H NMR spectra. It is known[8] that the vicinal coupling constant for *threo* β-aminoalcohols is larger (J=8-10Hz) than that for *erythro* isomer (J=5Hz). In our case the coupling constant observed in compound 7 (J=10Hz) is in agreement with the proposed *threo* configuration of the aminoalcohol. The same reaction performed on a mixture of the two alcohols obtained under thermodynamic conditions led to two non-separable epimeric alcohols. A ^1H NMR spectrum of the mixture gave a value of J (H-3, H-4) =5.4 Hz for the minor *erythro* derivative. Hydrogenolysis of compound 7 gave the aminoalcohol 8 which was reacted with 3,4,5-trimethoxybenzoyl chloride in a biphasic system (CH_2Cl_2/ NaOH-H_2O).



Ar = 3,4,5-trimethoxyphenyl

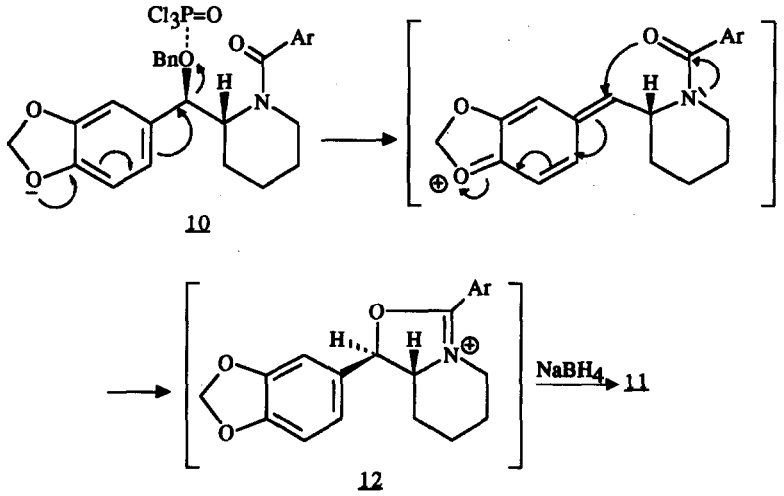
Reagents : (a) LDA, THF, -78°C, piperonal, 10 min; (b) $NaBH_4$, EtOH, reflux, 12h; (c) H_2 (1 atm, Pd/C, HCl (cat), EtOH, 12h ; (d) 3,4,5-trimethoxybenzoyl chloride, CH_2Cl_2, H_2O, NaOH, rt, 2h ; (e) NaH, benzyl bromide, THF, rt, 3h; (f) $POCl_3$, CH_3CN, reflux, 2h then $NaBH_4$, MeOH, 0°C, 1h.

SCHEME II

The secondary alcohol was then benzylated and the resulting compound 10 subjected to Bischler-Napieralsky reaction conditions. In order to prevent the side reactions due to participation of the benzyloxy function we used the mild conditions developed by Vandewalle[3g] and Itoh[9]. Neither of these methods gave the expected cyclised product, so we decided to use the classical method ($POCl_3$, acetonitrile, reflux) followed by reduction of the anticipated iminium intermediate. A single product 11 was formed in 45% yield in which the disappearance of the benzyloxy protecting group is noteworthy. This result may be explained by the formation of a cation at C-4, stabilized by the aromatic ring, which reacts with the carbonyl group of the amide to furnish the oxazolidinium ion 12 (Scheme III). Such reactivity of aromatic benzyl ethers has been used by Brown[10] in the synthesis of α-conidendrine. In this case the activation of the ether was effected by a Lewis acid ($BF_3.Et_2O$).

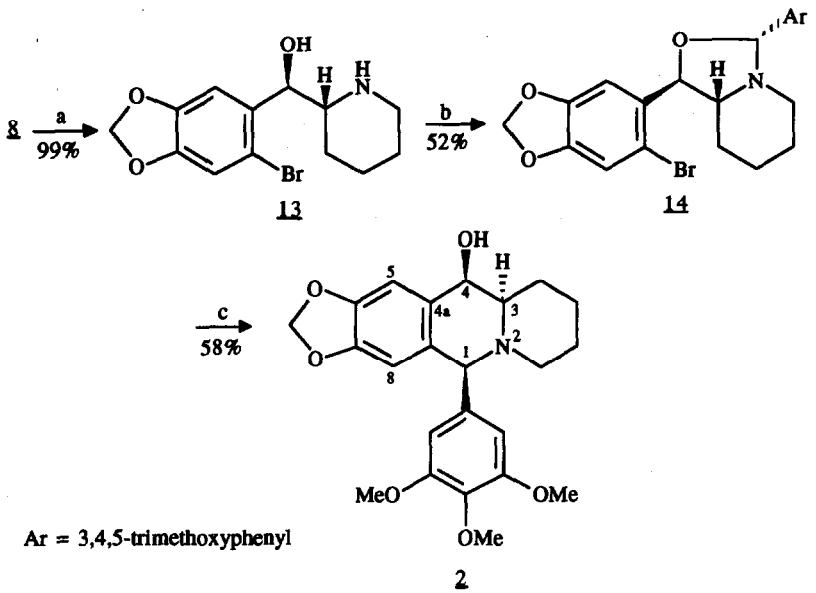
The relative stereochemistry of the three asymmetric centres of 11 was elucidated by NMR studies and by comparison with authentic product obtained independantly by condensation of aminoalcohol 8 with trimethoxybenzaldehyde. This result demonstrated that the stereogenic centres C-3 and C-4 possess the *R* configuration. The relative configuration of carbons C-1 and C-3 was obtained by a NOE-Diff experiment which indicated a *cis* relationship for the two protons H-1 and H-3. Thus the oxazolidine 11 possessed the absolute configuration 1R, 3R, 4R.

As the classical methods did not allow the preparation of the cyclised product we decided to develop a new scheme involving activation of the aromatic ring. The cyclisation could be achieved by the intramolecular reaction of a Grignard reagent on the iminium ion generated from an oxazolidine.



SCHEME III

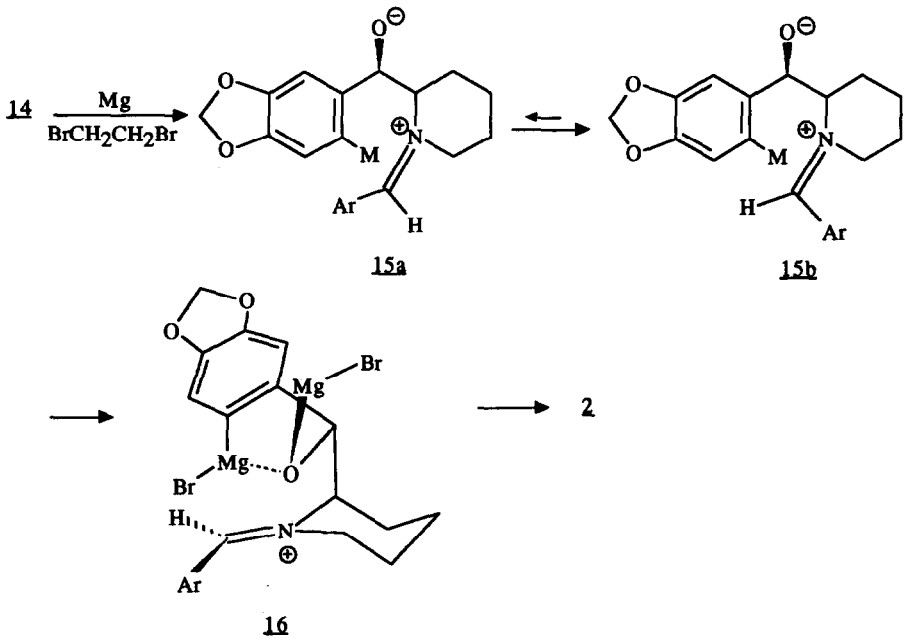
Bromination of the aminoalcohol 8 (Br_2, AcOH) furnished exclusively the bromo derivative 13 (Scheme IV) which was reacted with 3,4,5-trimethoxybenzaldehyde to give oxazolidine 14 in 52% yield.



Reagents : (a) Br_2, AcOH, r.t., 4h; (b) 3,4,5-trimethoxybenzaldehyde, TsOH, toluene, reflux; (c) Mg, 1,2-dibromoethane, THF, reflux, 3h.

SCHEME IV

The stereochemistry of 14 was the same as that for compound 11 as indicated by the chemical shifts and coupling constants values of H-1, H-3 and H-4. For the key-step it was necessary to find conditions for generation of the organometallic and the iminium salt from the oxazolidine. We thought that the formation of a Grignard reagent in the presence of an excess of dibromoethane might furnish the desired intermediate. Under these conditions, magnesium bromide is generated and can behave as a Lewis acid towards oxazolidine. Indeed, when compound 14 was treated with a large excess of magnesium and dibromoethane in THF, the cyclized product 2 was obtained in 58 % yield as a single isomer. Its IR spectrum showed Bohlmann bands indicating a *trans* quinolizidine system[11]. The axial and equatorial positions of H-3 and H-4 respectively were confirmed by their coupling constant values ($J_{H\text{-}3,H\text{-}12ax}$ = 9.3 Hz and $J_{H\text{-}3,H\text{-}4}$ = 1.0 Hz). The *cis* relationship between H-1 and H-3 was proved by the presence of a NOE between these two protons; the equatorial position of the trimethoxybenzene ring was confirmed by the shielding of H-8 (δ=6.18ppm). To explain the stereochemistry of C-1 it is necessary to consider the intermediate iminium ion 15 which can adopt two conformations 15a and 15b. From the work of Cook and Welvart[12], it is known that the E configuration 15b of such iminium ions is favoured (Scheme V).



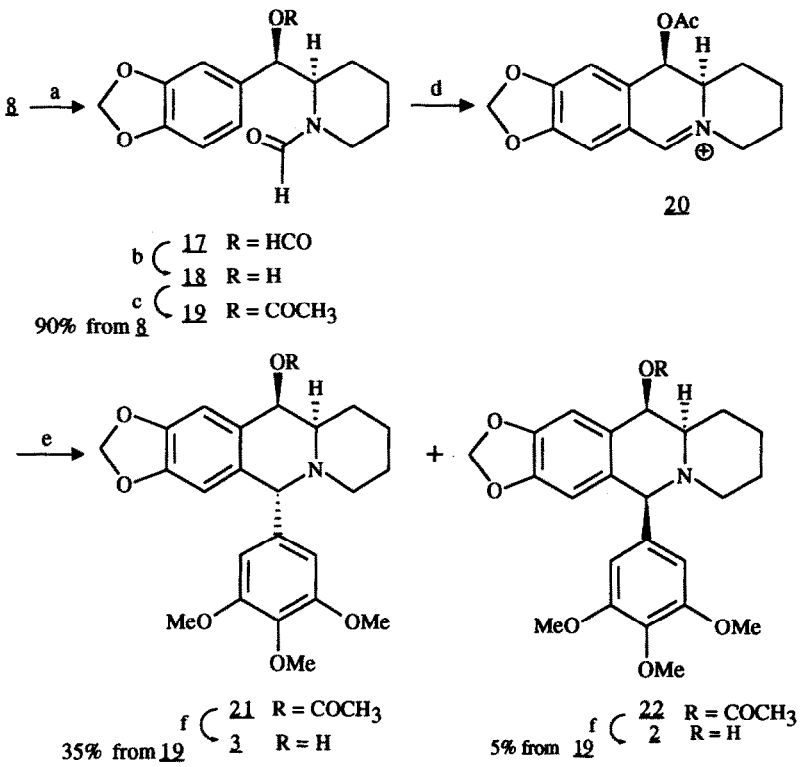
SCHEME V

The benzyl chain α to the nitrogen might adopt an axial position to minimise the steric interactions, while a chelation effect involving the magnesium atom and the alcoholate would stabilize the intermediate. Product 2 results from an approach of the aromatic ring on the Re face.

In order to study the influence of stereochemistry at C-1 on the biological activity of the new products, it was decided to elaborate an alternative strategy which would allow the stereoselective introduction

of an aromatic ring with opposite configuration at C-1. We thought that an iminium ion such as 20 could react with an organometallic species under stereoelectronic control (Scheme VI) to furnish compound 21 which possesses an axial aromatic ring. We encountered some difficulties in preparing such an iminium from aminoalcohol 8.

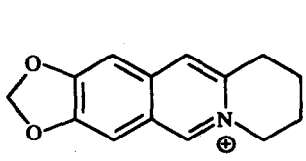
Tsuda[13] protected a hydroxyl function as an acetate during a synthesis involving a Bischler-Napieralsky reaction, so, we decided to use the same protective group. The amine was reacted first with acetic formic anhydride[14] to generate an amide (Scheme VI).



Reagents (a) $HCOOCOCH_3$, CH_3CN, HCOONa, r.t., 3h; (b) $NaHCO_3$, H_2O, CH_3OH, rt, 12h; (c) $(CH_3CO)_2O$, DMAP, CH_2Cl_2, r.t., 3h; (d) $POCl_3$, pyridine (1eq), toluene, r.t., 4h; (e) 3,4,5-trimethoxy phenyl magnesium bromide, THF, -78°C (1h) to r.t.(5h), 1h; (f) K_2CO_3, MeOH, H_2O, 1h.

SCHEME VI

Under these conditions, partial esterification of the alcohol was observed,and a mixture of amides 17 and 18 was obtained. Subsequent treatment in basic medium furnished only alcohol 18 which was protected without purification as the acetate 19. When this amide was subjected to classical Bischler-Napieralsky conditions ($POCl_3$, toluene, reflux) only benzoquinolizinium ion 23 was obtained.



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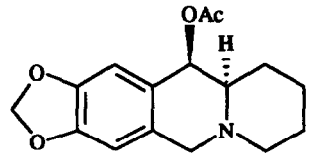

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Finally, we observed that treatment of 19 with an excess of $POCl_3$ in the presence of pyridine (1 equivalent) in toluene at room temperature yielded iminium salt 20. In the ^1H NMR spectra, iminium proton H-1 appears as a singlet at δ=7.80 ppm and H-4 as a doublet (J=5.8 Hz, δ=6.12 ppm). The signals for the two aromatic protons H-5 and H-8 are singlets at δ=7.22 and 7.45 ppm. The ^{13}C NMR spectrum corroborated this assignment and particulary significant is the iminium carbon with a typical chemical shift (δ=162.5 ppm). Reduction of iminium 20 with $NaBH_4$ furnished benzoquinolizidine 24 (2xH-1, δ=3.26 and 3.90 ppm, J=15.3 Hz).

The next step was the introduction of the aromatic substituent at C-1 which was achieved by addition of 3,4,5-trimethoxyphenyl magnesium bromide in THF. Two compounds 21 and 22 were formed in a ratio 85/15. They were not separated but the acetate function was hydrolysed (K_2CO_3, MeOH, H_2O) furnishing a mixture of alcohols in the same ratio which could be separated by flash-chromatography. The minor isomer was identical with compound 2 previously obtained (MS, ^1H and ^{13}C NMR). The major product 3 resulted from an axial attack of the nucleophile on the double bond of the iminium salt. The axial position of the aromatic ring was confirmed by the chemical shifts of the H-2' protons which appeared at 6.18 ppm (6.48 ppm for 2) indicating that these protons are experiencing the anisotropy of the other aromatic ring. The *trans* relationship of benzoquinolizidine was proved by the presence of Bohlmann bands (2890, 2850 and 2830 cm^{-1}) in the IR spectrum.

In conclusion, during this study, the asymmetric synthesis of two aza-analogues of podophyllotoxin has been achieved with control of stereochemistry using new methods for the elaboration of an aryl substituted tetrahydroisoquinoline skeleton based on stereocontrolled addition to an iminium ion. Compound 3 possesses the same absolute configuration as natural podophyllotoxin. Although 2 possesses the opposite absolute configuration of the known isopodophyllotoxin, its enantiomer is in principle available from synthon (+)-5.

EXPERIMENTAL

Melting points are given uncorrected. Infrared (IR) spectra were taken with a Nicolet 205 FT spectrometer in $CHCl_3$ solution. Mass spectra (MS) were recorded on a AEI MS-50 spectrometer, high-resolution mass spectra (HRMS) on a Kratos MS-80 RF spectrometer. Proton and carbon nuclear magnetic resonance (^1H NMR) (^{13}C NMR) spectra were recorded on Bruker AC-200, Bruker AC-250 or Bruker WM-400 spectrometers in $CDCl_3$ or CD_3OD.

Aminonitrile 6. To a solution of LDA prepared from 5.25ml (3.75 10^{-2} mol) of diisopropylamine and 28.5

ml of 1.6M BuLi in hexane ($3.75\ 10^{-2}$ mol) in THF (50ml) at -78°C was added a solution of compound 5 (5.7 g, $2.5\ 10^{-2}$ mol) in THF (10ml). After stirring for 45 min, piperonal (7.5 g, $5.0\ 10^{-2}$ mol) in THF (10ml) was added. After 10 min, the mixture was hydrolysed with a saturated NH_4Cl aqueous solution, then extracted with CH_2Cl_2. Classical work-up and purification by silicagel flash-chromatography furnished the alcohol 6 (6.06 g, 64%) as white crystals. mp=114°C (ether- heptane), $[\alpha]_D^{20}$= -173° ($CHCl_3$, c=0.9), IR (cm^{-1}) : 3503, 2955, 2851, 2200, 1490, 1420, 1220, 1050, 1020. MS (EI) m/z (%) : 379 (6), 352 (100), 202 (7), 151 (75), 133 (10). ^1H NMR (200 MHz) ($CDCl_3$) 1.60-2.20 (m, 6H), 2.00 (d, J=4.0 Hz, OH), 3.71 (dd, J=8.4 and 3.5 Hz, H-13), 4.05 (d, J=4.0 Hz, H-4), 4.20 (m, 2xH-14), 4.55 (dd, J=8.8 and 3.4 Hz, H-9), 5.92 (s, OCH_2O), 6.70 (m, H-5 and H-8), 6.90 (m, H-8a), 7.20-7.60 (m, 5 aromatic H). ^{13}C NMR (50.33 MHz) 19.9, 29.5, 34.8 (C-10, C-11, C-12), 61.1 (C-13), 66.2 (C-3), 74.9 (C-14), 76.5 (C-4), 92.3 (C-9), 101.3 (OCH_2O), 107.8 and 108.0 (C-5 and C-8), 116.9 (CN), 121.3 (C-8a), 126.8, 128.7, 129.2 (CH, aromatic), 133.0, 145.8, 148.0, 148.1 (Cq aromatic). Elemental analysis calc. for $C_{22}H_{22}N_2O_4$: C: 69.82, H: 5.85, N: 7.40, found : C: 69.87, H: 5.75, N: 7.49.

Aminoalcohol 7. To a solution of compound 6 (6.41 g, $1.69\ 10^{-2}$ mol) in EtOH (200ml) was added $NaBH_4$ (6 g) portionwise. The solution was heated at reflux for 12h. After classical work-up, aminoalcohol 7 was obtained as a white powder (5.94 g, 99%). mp=100-102°C (CH_2Cl_2- heptane), $[\alpha]_D^{20}$= -62° ($CHCl_3$, c=1.2), IR (cm^{-1}) : 3010, 1510, 1490, 1125, 1090. MS (CI isobutane) : 356 (MH^+, 70), 277 (80), 186 (75), 185 (100). ^1H NMR (200 MHz) ($CDCl_3$) 1.20-1.70 (m, 7H), 2.54 (ddd, J=10.0, 4.7 and 1.2 Hz, H-3), 3.12 (m, H-9 eq.), 3.88 (dd, J=11.0 and 6.2 Hz, H-14), 4.03 (dd, J=11.0 and 5.2 Hz, H-14), 4.16 (dd, J=6.2 and 5.2 Hz, H-13), 4.74 (d, J=10.0 Hz, H-4), 5.87 (s, OCH_2O),6.50-6.70 (m, H-5, H-8 and H-8a), 7.36-7.42 (m, 5 aromatic H). ^{13}C NMR (50.33 MHz) 19.3, 20.2 and 20.4 (C-10, C-11, C-12), 43.7 (C-9), 60.0 (C-3), 64.6 (C-13), 66.0 (C-14), 70.0 (C-4), 100.9 (OCH_2O), 107.2 and 107.8 (C-5 and C-8), 120.9 (C-8a), 128.2, 128.6 and 129.0 (CH, aromatic), 136.7, 140.5, 147.0 and 147.7 (Cq aromatic). Elemental analysis calc. for $C_{21}H_{25}NO_4$: C: 70.96, H: 7.09, N: 3.94, found : C: 71.02, H: 6.90, N: 3.81.

Aminoalcohol 8 : A solution of compound 7 (3.78 g, $1.06\ 10^{-2}$ mol) in EtOH (50 ml) was stirred under 1 atm of H_2 in the presence of 10% Pd/C (0.37 g) for 12h. After elimination of the catalyst by filtration and evaporation of the solvent, crude material was dissolved in 10% HCl and the solution washed with CH_2Cl_2. After basic treatment ($NaHCO_3$) of the aqueous phase and extraction with $CHCl_3$, organic layers were evaporated. 8 (2.47 g, 99%) was obtained as an oil, $[\alpha]_D^{20}$= -19° ($CHCl_3$, c=1.6), IR (cm^{-1}) : 3300, 2901, 1600, 1490, 1420, 1220, 1010. MS (EI) m/z (%) : 235 (30), 218 (64), 216 (44), 186 (65), 149 (70), 85 (100). ^1H NMR (250 MHz) (CD_3OD) 0.90-1.80 (m, 6H), 2.59 (td, J=8.6 and 2.7 Hz, H-3), 2.65 (td, J=11.7 and 2.9 Hz, H-9ax), 3.11 (dt, J=11.7 and 1.0 Hz, H-9eq), 4.23 (d, J=8.6 Hz, H-4), 5.95 (s, OCH_2O), 6.70-6.82 (m, H-5, H-8 and H-8a). ^{13}C NMR (50.33 MHz) 24.3, 25.9 and 28.4 (C-10, C-11 and C-12), 46.4 (C-9), 67.2 (C-3), 77.1 (C-4), 101.1 (OCH_2O), 107.3 and 108.0 (C-5 and C-8), 120.4 (C-8a), 136.8 (C-4a), 147.7 and 147.8 (C-6 and C-7). Elemental analysis calc. for $C_{13}H_{17}NO_3$: C: 66.34, H: 7.28, N:5.95, found : C: 66.27, H: 7.16, N: 6.08.

Benzamide 9 : To a solution of aminoalcohol 8 (90 mg, $3.8\ 10^{-4}$ mol) in CH_2Cl_2 (3ml), was added 3,4,5-trimethoxybenzoyl chloride (88 mg, $3.8\ 10^{-4}$ mol) in CH_2Cl_2 (3ml) and 0.25 ml of NaOH 10%. Stirring was maintained for 2h. After habitual work-up, crude material was purified by silicagel flash-chromatography (CH_2Cl_2/MeOH: 95/5) eluting amide 9 as an oil (120 mg, 73%). $[\alpha]_D^{20}$= -46° ($CHCl_3$, c=1.1), IR (cm^{-1}) : 3310, 2943, 1609, 1585, 1505, 1463, 1327, 1238, 1041. MS m/z (%) : 429 (30), 412 (40), 279 (100), 278

(98), 196 (91), 195 (95). ^{1}H NMR (200 MHz) ($CDCl_3$) 1.10-2.00 (m, 7H), 2.70-3.62 (m, H-3 and H-9eq), 3.85 (s, 3xOMe), 4.53 (m, H-4), 5.85 (s, OCH_2O), 6.50-7.10 (m, 5H, aromatic). ^{13}C NMR (50.33 MHz) 19.6, 25.6, 35.1 (C-10, C-11, C-12), 44.7 (C-9), 56.2 (2xOMe), 60.8 (OMe), 73.1 (C-4), 101.0 (OCH_2O), 104.8 and 106.9 (C-5 and C-8), 108.1 (2xC-2'), 120.1 (C-8a), 125.8, 128.1, 147.3, 147.9 and 153.2 (Cq, aromatic), 171.2 (C=O).

O-Benzyl derivative 10 : To a suspension of NaH (60% dispersion in oil) (40 mg) in THF (3ml), was added a solution of amide 9 (120 mg, 2.79 10^{-4} mol) in THF (2ml). The mixture was stirred at rt for 2h, then benzyl bromide (400µl, 2.9 10^{-4} mol) was added. After 1h, usual work-up and purification by silicagel flash-chromatography (CH_2Cl_2, CH_3OH: 99/1) gave 10 as a colourless oil (96 mg, 66%). $[\alpha]_D^{20}$=-54° ($CHCl_3$, c=1.0); IR (cm^{-1}) : 2945, 1615, 1580, 1510, 1462, 1327, 1239, 1020. MS (EI) m/z (%) : 519, (1), 429 (8), 412 (3), 411 (2), 280 (80), 198 (100), 197 (79), 152 (51). ^{1}H NMR (200 MHz) ($CDCl_3$) : 1.10-1.20 (m, 7H), 2.70-3.00 (m, H-3, H-9eq), 3.50-4.00 (m, 3xOMe), 4.20-4.30 (m, OCH_2Ph), 4.65 (d, J=5.5 Hz, H-4), 5.90 (s, OCH_2O), 6.50-7.50 (m, 10H, aromatic). ^{13}C NMR (50.33 MHz): 19.7, 25.1 and 25.8 (C-10, C-11 and C-12), 43.5 (C-9), 53.8 (C-3), 55.9 (2xOMe), 59.6 (OCH_2Ph), 60.7 (OMe), 70.9 (C-4), 101.1 (OCH_2O), 104.9 and 106.2 (C-5 and C-8), 108.2 (2xC-2'), 121.2 (C-8a), 127.3, 127.8, 128.3 (CH), 132.6, 133.1, 137.7, 147.7, 148.2, 152.9 (Cq), 171.9 (C=O).

Oxazolidine 11 : a) from amide 10. To a solution of benzamide 10 (95 mg, 1.79 10^{-4} mol) in CH_3CN (5ml) was added $POCl_3$ (340 µl, 3.64 10^{-3} mol). The mixture was heated at reflux for 2h. After cooling, water (10ml) was added. Extraction with $CHCl_3$, then evaporation of the organic phases furnished an oil which was dissolved in CH_3OH (5ml) then reacted with $NaBH_4$ (100 mg) at 0°C for 1h. Usual work-up and purification by silicagel flash chromatography (CH_2Cl_2/ MeOH : 99/1) furnished oxazolidine 11 (34 mg, 45%) as a colourless oil.

b) from aminoalcohol 8: A solution of aminoalcohol 8 (500 mg, 2.1 10^{-3} mol), 3,4,5-trimethoxy benzaldehyde (440 mg, 2.2 10^{-3} mol) and para-toluenesulfonic acid (10 mg) in toluene (100 ml) was heated at reflux in a Dean-Stark apparatus. After 12h, the solvent was evaporated and crude material purified by silicagel flash-chromatography yielding oxazolidine 11 (700 mg, 80%). IR (cm^{-1}) : 3654, 3630, 3204, 2418, 1702, 1590, 1505, 1390, 1110, 900. MS (EI) m/z (%) : 413 (3), 412 (5), 301 (48), 263 (100), 262 (46), 248 (30), 210 (46), 196 (19), 135 (6).^{1}H NMR (250 MHz) ($CDCl_3$) : 1.10-1.90 (m, 6H), 2.07 (td, J=10.9 and 3.2 Hz, H-9 ax), 2.22 (td, J=8.8 and 2.2 Hz, H-3), 2.82 (dt, J=10.9 and 1.0 Hz, H-9eq), 3.81 (s, OMe), 3.85 (s, 2xOMe), 4.68 (d, J=8.8 Hz, H-4), 4.86 (s, H-1), 5.95 (s, OCH_2O) 6.70-7.10 (m, 5H). ^{13}C NMR (62.6 MHz) : 23.5, 24.7 and 26.4 (C-10, C-11 and C-12), 47.5 (C-9), 56.2 (2xOMe), 60.8 (OMe), 70.8 (C-3), 84.3 (C-4), 97.3 (C-1), 101.1 (OCH_2O), 105.0 and 107.0 (C-5 and C-8), 108.3 (2xC-2'), 120.8 (C-8a), 134.1, 134.6, 147.3, 147.8, 153.3 and 153.7 (Cq).

Bromo derivative 13 : To a solution of aminoalcohol 8 (548 mg, 2.33 10^{-3} mol) in AcOH at rt (10ml) was added bromine (178µl, 3.49 10^{-3} mol). The solution was stirred for 4h. AcOH was distilled off, then the residue was washed with 10% NaOH. The aqueous phase was extracted three times with CH_2Cl_2. Organic layers were dried over Na_2SO_4. Evaporation of the solvent furnished bromo derivative 13 (730 mg, 99%) as white crystals. mp= 92°C (MeOH, Et_2O), $[\alpha]_D^{20}$=-10° ($CHCl_3$, c=2.2); IR (cm^{-1}) : 3310, 3023, 2939, 1504, 1477, 1240, 1225, 1219, 1200, 1040. MS (CI, isobutane) (%) : 371, 369 (M+57, 16), 315, 313 (MH+, 100), 298, 296 (10), 151 (30). ^{1}H NMR (250 MHz, CD_3OD): 1.20-1.80 (m, 6H), 2.62-2.72 (m, H-3 and H-9ax), 3.13 (dt, J=11.6 and 4.3 Hz, H-9 eq), 3.35 (m, H-4), 6.00 (d, J=1.4 Hz, OCH_2O), 7.00 and

7.02 (2s, H-5 and H-8). ^{13}C NMR (62.5 MHz, CD_3OD) : 25.0, 26.0 and 28.2 (C-10, C-11 and C-12), 47.7 (C-9), 64.1 (C-3), 75.7 (C-4), 103.3 (OCH_2O), 109.0 (C-5), 112.9 (C-8), 114.4 (C-8a), 132.1 (C-4a), 147.6 and 147.8 (C-6 and C-7). Elemental analysis : calc. for $C_{13}H_{16}BrNO_3$: C: 49.85, H: 4.82, N: 4.47; found C: 49.66, H: 5.11, N: 4.26.

Bromo oxazolidine 14: Condensation of 13 (300 mg, 9.45 10^{-4}mol) and 3,4,5-trimethoxybenzaldehyde (185 mg, 9.45 10^{-4} mol) in the conditions described for compound 11 furnished the bromo oxazolidine 14 (240 mg, 52%) as a colourless oil. $[\alpha]_D^{20}$= -12° ($CHCl_3$, c=1.5); IR (cm^{-1}) : 3653, 3640, 3204, 2402, 1701, 1598, 1504, 1380, 1210, 1153, 1110, 900. MS m/z (%): 492, 490 (5), 381, 379 (10), 300 (10), 263 (100), 248 (30). HRMS: calc. for $C_{23}H_{26}BrNO_6$: 492.0838 and 490.0859; found :492.0802 and 490.0884. ^1H NMR(250 MHz) ($CDCl_3$): 1.10-1.90 (6H), 2.00 (td, J=10.5 and 3.4 Hz, H-9ax), 2.27 (td, J=8.8 and 2.6 Hz, H-3), 2.83 (dt, J=10.5 and 3.1 Hz, H-9eq), 3.86 (s, OMe), 3.91 (s, 2xOMe), 4.91 (s, H-1), 5.25 (d, J=8.8 Hz, H-4), 5.97 (s, OCH_2O), 6.80 (s, 2xH-2'), 6.96 and 7.14 (2s, H-5 and H-8). ^{13}C NMR (50.33 MHz) : 22.7, 23.6 and 24.5 (C-10, C-11 and C-12), 47.5 (C-9), 56.2 (2xOMe), 60.8 (OMe), 71.8 (C-3), 82.4 (C-4), 97.6 (C-1), 101.8 (OCH_2O), 104.9, 108.3 and 112.3 (C-5, C-8 and 2xC-2'), 112.9 (C-4a), 132.8, 134.3, 147.7, 147.9 and 153.3 (Cq).

1-Aryl benzoquinolizidine 2 : To a suspension of magnesium (90 mg, 3.75 10^{-3} mol) in THF (5 ml) at reflux was added 1,2-dibromoethane (50 µl, 5.6 10^{-4} mol). After the reaction had commenced, a solution of oxazolidine 14 (92 mg, 1.8 10^{-4} mol) in THF (5 ml) was added slowly (1h). Dibromoethane (90 µl, 1.0 10^{-3} mol) was then added to the mixture with stirring at reflux. After 3h, the mixture was cooled and usual work-up furnished an oil which was purified by silicagel flash-chromatography (CH_2Cl_2/ MeOH : 98/2) eluting compound 2 (48 mg, 58%) as an oil. $[\alpha]_D^{20}$ = -35° ($CHCl_3$, c=2.1), IR (cm^{-1}) : 3054, 2890, 2854, 2803, 1604, 1484, 1243, 1129. MS, m/z (%) : 413 (38), 412 (40), 330 (90), 329 (100), 314 (85), 299 (78), 258 (86), 246 (87), 181 (80). HRMS : calc. for $C_{23}H_{27}NO_6$: 413.1839, found : 413.1833. ^1H NMR (250 MHz) ($CDCl_3$): 1.20-2.10 (m, 7H), 2.57 (dt, J=9.3 and 1.0 Hz, H-3), 2.80 (d, J=8.5 Hz, OH), 2.90 (dt, J=11.4 and 1.0 Hz, H-9eq), 3.81 (s, 2xOMe), 3.86 (s, OMe), 4.06 (s, H-1), 4.14 (dd, J=8.5 Hz and 1.0 Hz, H-4eq), 5.86 (d, J=6.3 Hz, OCH_2O), 6.18 (s, H-8), 6.48 (s, 2xH-2'), 6.75 (s, H-5). ^{13}C NMR (62.5 MHz) : 23.9, 25.8 and 28.5 (C-10, C-11 and C-12), 53.6 (C-9), 56.3 (2xOMe), 60.9 (OMe), 61.7 (C-3), 70.2 (C-4), 73.1 (C-1), 106.3 (2xC-2'), 107.8 and 108.2 (C-5 and C-8), 130.9, 131.2, 139.4 and 153.3 (Cq).

Formylamido ester 19: To a solution of aminoalcohol 8 (1.94g, 8.26 10^{-3} mol) and sodium formate (2g, 2.94 10^{-2} mol) in 50ml of CH_3CN/THF (1/1), was added formic acetic anhydride at rt [14]. Stirring was maintained for 3h, then usual work-up furnished a residue which was dissolved in 50ml of MeOH/H_2O (8/2). $NaHCO_3$ was added until pH 8. The solution was stirred for 12h, then after classical work-up, the residue was dissolved in CH_2Cl_2 (50ml), then treated with acetic anhydride (6.5 ml, 4.19 10^{-2}mol) and 20 mg of DMAP. After 3h at rt, the solvent was evaporated under reduced pressure. The amido-ester 19 was purified by silicagel flash-chromatography (CH_2Cl_2/ MeOH : 98/2). 2.28g (88%) of a colourless oil was obtained. $[\alpha]_D^{20}$ = -152° ($CHCl_3$, c=2.5). IR (cm^{-1}) : 2391, 1743, 1672, 1418, 1415, 1409. MS m/z (%) : 305 (78), 246 (30), 217 (25), 194 (50), 151 (100), 113 (97); HRMS calc. for $C_{16}H_{19}NO_5$: 305.1264, found : 305.1261. ^1H NMR (200 MHz) ($CDCl_3$): 1.20-1.90 (m, H-10, H-11 and H-12), 2.01 and 2.22 (2s, $COCH_3$), 2.79 (td, J=13.0 and 2.9 Hz, H-9 ax), 3.41 (m, H-9ax and H-9eq), 4.30 (ddd, J=13.0, 3.3 and 1.0 Hz, H-9eq), 3.79 and 4.83 (dt, J=10.5 and 3.6 Hz, H-3ax), 5.90-6.15 (m, H-4 and OCH_2O), 6.72-7.00 (m, H-9, H-13 and H-14), 8.10 (br. s, CHO). ^{13}C NMR (50.33 MHz) : 20.7 (CH_3CO), 20.0, 24.4, 24.7, 25.4 and 26.0 (C-10, C-11

and C-12), 36.6 and 43.0 (C-9), 51.2 and 58.0 (C-3), 71.7 and 78.0 (C-4), 101.3 (OCH_2O), 107.2, 107.7, 108.3 and 108.4 (C-5 and C-8), 121.2 and 121.5 (C-8a), 130.9, 131.1, 148.0, 148.1 (C-4a, C-6 and C-7), 162.1 and 162.5 (C-1), 169.6 ($\underline{C}OCH_3$).

Benzoquinolizidinium 20: To a solution of amide 19 (258 mg, 8.4 10^{-4} mol) and pyridine (66µl, 8.4 10^{-4} mol) in toluene (15ml) at 0°C, was added $POCl_3$ (2.3 ml, 2.46 10^{-3} mol) dropwise. The resulting mixture was stirred for 30 min at this temperature then 4h at rt. After evaporation of the solvent under reduced pressure, the residue was dissolved in methanol (20ml), then evaporated. This operation was repeated three times to eliminate traces of HCl. The residue was then dissolved in $CHCl_3$ and washed with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted three times with $CHCl_3$. Organic layers were dried over Na_2SO_4 and evaporation of the solvent furnished an oil (205mg) which was not purified. IR (cm^{-1}) : 3031, 2946, 1749, 1657, 1599, 1494, 1409, 1317, 1265, 1209, 1036. ^1H NMR (250 MHz) (CD_3OD) : 1.10-2.40 (m, H-10, H-11 and H-12), 2.11 (s, CH_3CO), 4.02 (m, H-3), 4.47 (m, 2xH-9), 6.12 (d, J=5.8 Hz, H-4), 6.14 (s, OCH_2O), 7.22 and 7.45 (2s, H-5 and H-8), 7.80 (s, H-1). ^{13}C NMR (62.5 MHz, CD_3OD): 20.4 ($\underline{C}H_3CO$), 22.0, 25.1 and 25.3 (C-10, C-11 and C-12), 58.6 (C-9), 61.1 (C-3), 67.6(C-4), 105.2 (OCH_2O), 110.7 and 113.3 (C-5 and C-8), 119.3, 132.1, 150.5 and 157.3 (C-4a, C-6, C-7 and C-8a), 165.2 (C-1), 170.5 ($CH_3\underline{C}O$).

Benzoquinolizidine 24: Reduction of iminium salt 20 (30 mg) in methanol (20 ml) with $NaBH_4$ (30 mg) furnished benzoquinolizidine 24 quantitatively. Oil, IR (cm^{-1}): 3017, 2944, 1727, 1502, 1487, 1465, 1372, 1347, 1242, 1042. MS (CI, isobutane) : 290 (MH^+, 75), 230 (100), 174 (20), 146 (5). ^1H NMR (200 MHz) ($CDCl_3$) : 1.21-1.89 (m, H-10, H-11, H-12 and H-9ax), 2.01 (CH_3CO), 2.39 (dt, J=10.2 and 4.6 Hz, H-3), 3.17 (ddd, J=11.2, 3.2 and 3.0 Hz, H-9eq), 3.26 (d, J=15.3, H-1ax), 3.90 (d, J=15.3Hz, H-1eq), 5.84 (d, J=4.6 Hz, H-4), 5.91 (s, OCH_2O), 6.50 and 6.78 (2s, H-5 and H-8). ^{13}C NMR (50.33 MHz): 21.3 ($\underline{C}H_3CO$), 24.2, 25.5 and 27.6 (C-10, C-11 and C-12), 56.5 and 58.3 (C-1 and C-9), 61.4 (C-3), 70.4 (C-4), 101.0 (OCH_2O), 105.6 and 109.2 (C-5 and C-8), 125.6, 129.2, 146.6 and 148.0 (C4'a, C-6, C-7 and C-8a), 171.3 (CH_3CO).

1-Aryl benzoquinolizidine 3: To the iminium salt 20 (obtained from 258 mg of 8), was added a 0.89 M solution of 3,4,5-trimethoxyphenyl magnesium bromide in THF (4.75ml, 4.23 10^{-3} mol) at -78°C. The mixture was stirred for 1h at -78°C, then at rt for 5h. After usual work-up, the resulting oil was dissolved in MeOH (20 ml). A saturated aqueous solution of K_2CO_3 (4 ml) was added and the resulting mixture was stirred for 1h at rt. Usual work-up furnished an oil which was purified by silicagel flash-chromatography (CH_2Cl_2/MeOH: 98/2), eluting 2 (18mg, 5%) as the minor product, identical with the previously described product and 3 as the major product (120mg, 35%). 3 : mp=66-68°C (CH_2Cl_2/ CH_3OH), $[\alpha]_D^{20}$=-79° ($CHCl_3$, C=0.3); IR (cm^{-1}): 3350, 3012, 2950, 1504, 1484, 1265, 1240. MS (EI) m/z (%) : 413 (4), 412 (13), 329 (20), 328 (18), 312 (12), 229 (13), 245 (13), 84 (100). HRMS calc for $C_{23}H_{27}NO_6$: 413.1839, found: 413.1832. ^1H NMR (250 MHz) ($CDCl_3$): 0.80-2.10 (m, H-10, H-11, H-12 and H-9ax), 2.75 (dt, J=11.5 and 1.1 Hz, H-9eq), 3.15 (dt, J=10.8 and 3.1 Hz, H-3ax), 3.77 (s, 2xOMe), 3.83 (s, OMe), 4.34 (d, J=1.1 Hz, H-4eq), 4.57 (br. s, J= 1.4 Hz, H-1eq), 5.90 (s, OCH_2O), 6.18 (s, 2xH-2'), 6.19 (s, H-5), 6.89 (s, H-8). ^{13}C NMR (62.6 MHz): 23.9, 24.9 and 26.3 (C-10, C-11 and C-12), 51.7 (C-9), 55.4 (C-3), 56.3 (2xOMe), 60.9 (OMe), 65.0 (C-1), 69.5 (C-4), 107.7, 108.0 and 108.1 (C-5, C-8, 2xC-2'), 130.1, 130.7, 131.6, 136.2, 146.6, 147.3, 152.8 (Cq).

References.

1) For Part XXVII see Aitken, D.J.; Guillaume, D.; Husson, H.-P. *Tetrahedron*, submitted for publication

2) Lienard, P.; Royer, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 2489.

3) a) Arai, Y.; Enomoto, K. Yakugaku Zasshi **1968**, *88*, 1197 and *Chem. Abstr.* **1969**, *70*, 27530e. b) Vandewalle, M.; Van der Eycken, J.; Van Wijngaarden, I.; Van Hes, R.; Hulkenberg, A.; Keet, C. Patent appl. A 87 C 73.149 EP 251.361, JP 87.283.960 and *Annual Drug Data Report* **1988**, *10*, 510. c) Pearce, H.L.; Bach, N.J.; Cramer, T.L. *Tetrahedron Lett.* **1989**, *30*, 907. d) Tomioka, K.; Kubota, Y.; Koga, K. *ibid*, **1989**, *30*, 2953. e) Kadow, J.F.; Vyas, D.M.; Doyle, T.W. *ibid*, **1989**, *30*, 3299. f) Tomioka, K.; Kubota, Y.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1989**, 1622. For asymmetric synthesis see also g) Van der Eycken, J.; Bosmans, J.P., Van Haver, D.; Vandewalle, M; Hulkenberg, A.; Veerman, W., Nieuwenhuizen, R. *Tetrahedron Lett.* **1989**, *30*, 3873. h) Bosmans, J.P.; Van der Eycken, J.; Vandewalle, M.; Hulkenberg, A.; Van Hes, R.; Veerman, W. *ibid*, **1989**, *30*, 3877.

4) Bonin, M.; Royer, J.; Grierson, D. S.; Husson, H.-P. Organic Syntheses **1991**, *70*, 54.

5) Rice, K.C.; Ripka, W.C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601.

6) a) Ratovelomanana, V.; Royer, J.; Husson, H.-P.*Tetrahedron Lett.***1985**, *26*, 3803.
b) Delgado, A.; Mauleon, D. *Synth. Commun.* **1988**, *18*, 823.

7) Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

8) Stork, G.; Jacobson, R.M.; Levitz, R. *Tetrahedron Lett.* **1979**, *20*, 771.

9) Itoh, N.; Sugasawa, S.*Tetrahedron* **1959**, *6*, 16.

10) Boissin, P.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 4371.

11) Bohlmann, F. *Angew. Chem.* **1957**, *69*, 641.

12) a) Ungemach, F.; Di Pierro, M.; Weber, R.; Cook, J.M. *J. Org. Chem* **1981**, *46*, 164. b) Deng, L.; Czerwinski, K.; Cook, J.M. *Tetrahedron Lett.* **1991**, *32*, 175. c) Maigrot, N.; Mazaleyrat, J.-P., Welvart, Z. *J. Chem. Soc. Chem. Commun.* **1984**, 40.

13) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153.

14) Krimen, L.I *Organic Syntheses*, **1970**,*50*, 1.