An Efficient Synthesis of 5-(or 6-)Arylbenzoindolizidine and -quinolizidine Derivatives

Stéphane Lebrun,[a] Axel Couture,*[a] Eric Deniau,[a] and Pierre Grandclaudon[a]

Keywords: Horner reaction / Enamides / Reductions / Cyclizations / Alkaloids

A new methodology for the synthesis of (hetero)arylated benzoindolizidine and benzoquinolizidine derivatives through sequential reduction of pyrrolidine- and piperidine-based aromatic enamides, and ultimate cyclization, is reported.

The benzo[*b*]indolizidine and benzo[*b*]quinolizidine ring systems represent the main structural subunit of a wide variety of highly condensed alkaloids which have been shown to display unique and interesting biological properties.[1] When these fused heterocyclic models are further equipped with a pendant aromatic unit at the 5 or 6 position of the central nucleus, i. e. **1** (n = 1) or **2** (*n* = 2), these new skeletons constitute the framework of an array of tetrahydroprotoberberine (berbine) alkaloids as exemplified by the 8-phenyl derivatives of tetrahydrocoptisine **3**,[2] tetrahydropalmatine **4**,[3] and the 8-phenyl analogues of coralydine **5**[4] and *O*-methylcorytenchirine **6**[4] (Figure 1).

On the other hand 6-arylbenzo[*b*]quinolizidine derivatives **2** (*n* = 2) have been recently suggested as promising alternative models to podophyllotoxin (**7**),[5] which has long been known to display antitumour and mitotoxic activities[6] but also ill-fated toxic side effects.[7] Indeed, such compounds in which the sp^3 C-2 atom is replaced by an sp^3 nitrogen atom embedded in the fused hydrocarbon rings offer the double advantage of avoiding epimerization at this site and eliminating any deleterious effects attributable to the highly reactive nature of the γ-lactone moiety.

Paradoxically, the synthesis of the fused polyheterocyclic compounds **1** (*n* = 1), **2** (*n* = 2) has not elicited great synthetic efforts from the scientific community. An elegant and skilful route to the benzoquinolizidine derivatives **2** by application of the CN(RS) method involving alkylation of 2-cyano-6-phenyloxazolopiperidine followed by reduction and cyclization has been recently reported, but this route has been confined to the six-membered models.[8]

In our continuing study aimed at the involvement of *N*-acyl enamine derivatives in the elaboration of alkaloids and natural products[9−12] we wish to report here a conceptually and tactically new approach to benzoindolizidine and -quinolizidine derivatives **1** and **2**, arylated or heteroarylated at the 5-(6-)position of the heterocyclic framework.

Retrosynthetic analysis, depicted in Scheme 1, suggested that the 5-(or 6-)arylbenzoindo(or quino)lizidine derivatives

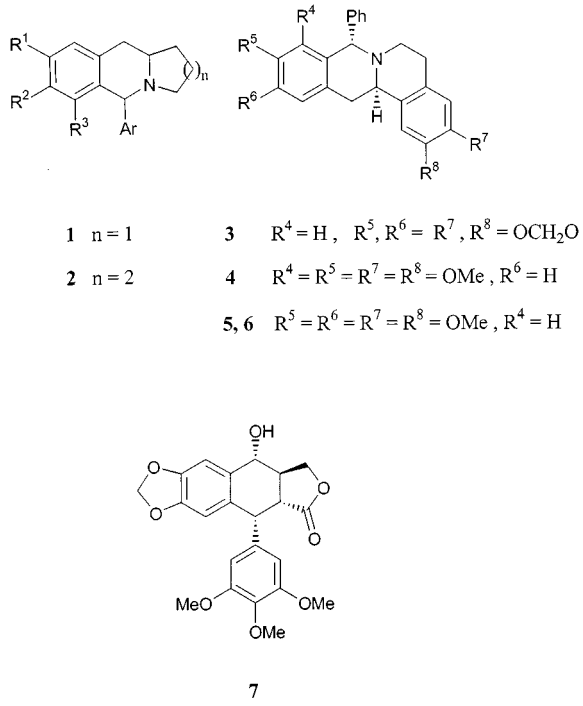


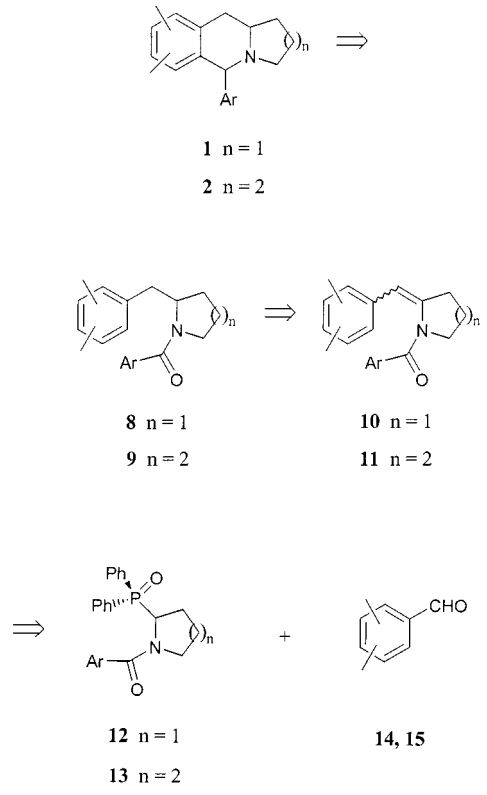
Figure 1

1 (*n* = 1) or **2** (*n* = 2), as well as various heterocyclic analogues, should be accessible by a semisynthetic strategy wherein the aromatic enamide **10** or **11** would be a key intermediate which could be derived from the Horner reaction between the phosphorylated *N*-acylpyrrolidine or -piperidine derivatives **12** (*n* = 1) or **13** (*n* = 2) and a suitably substituted aromatic carboxaldehyde **14** or **15**. The present work, which offers a number of undoubted advantages, originated from the following premises. The Pictet−Spengler cyclization of aromatic aldehydes, which enables access to the isoquinoline framework, requires the presence of a *para*-hydroxy group on the benzene ring.[13][14] When this is not the case, the Bischler−Napieralski reaction represents an interesting alternative approach and, in this regard, *N*-acyl-2-arylmethylpyrrolidine **8** (*n* = 1) or -piperidine **9** (*n* = 2) should be excellent candidates for this carboannulation process. On the other hand, the scheme might be extended to the preparation of heteroaryl derivatives **1** or **2** (Ar =

[a] Laboratoire de Chimie Organique Physique, UPRES A 8009, UST Lille 1,
F-59655 Villeneuve d'Ascq Cedex, France
Fax: (internat.) +33-3/20336309
E-mail: Axel.Couture@univ-lille1.fr

  1434−193X/99/0909−2345 $ 17.50+.50/0

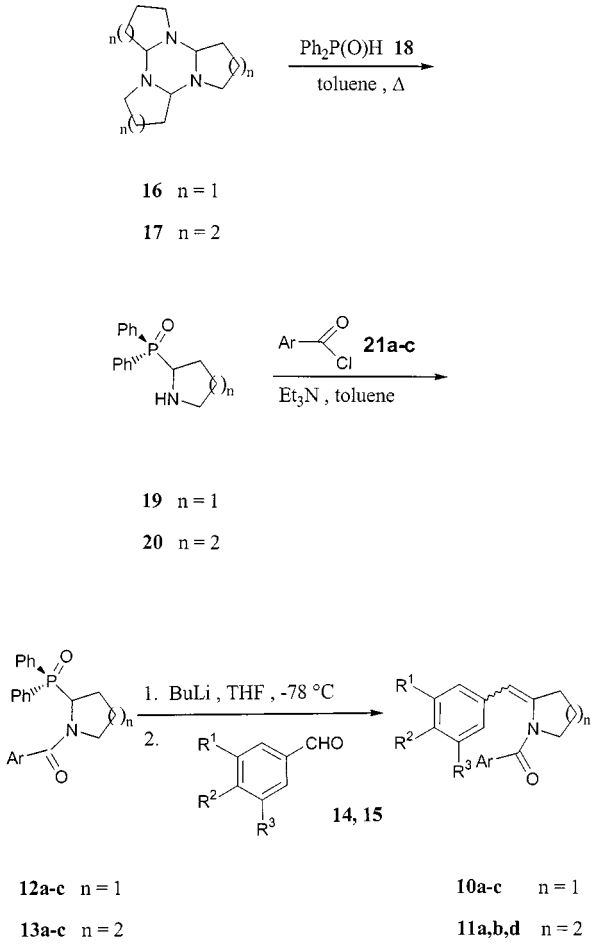
heteroaryl) owing to the ready accessibility of the phosphorylated cyclic *N*-acylamines **12** or **13**. Most interesting of all, the possibility of controlling a priori the stereochemical outcome of the appended arylmethylene unit of the enamides **10** or **11** set the stage for an investigation of the enantioselective reduction of these dehydro precursors which might address the problem of stereocontrol at the chiral centre adjacent to the nitrogen atom embedded in the skeleton of the fused compounds **1** and **2**.



Scheme 1. Retrosynthetic scheme

To establish the generality and versatility of the synthetic approach depicted in Scheme 1, the elaboration of a number of aromatic and heteroaromatic models, contiguously and differentially substituted by phenolic methoxy or methylenedioxy groups on the aromatic moieties, was explored.

Initially, a variety of 1-aroyl- and -heteroaroyl-2-diphenylphosphinoylpyrrolidine and -piperidine derivatives, **12a−c** and **13a−c**, respectively, were easily and almost quantitatively formed by Schotten−Baumann reaction of the appropriate carboxylic chlorides **21a−c** with the phosphorylated cyclic amines **19** and **20**, readily obtained by addition of diphenylphosphane oxide **18** to the triazines **16** and **17**[10][15] (Scheme 2). Compounds **12a−c** and **13a−c** were then smoothly deprotonated at −78°C with *n*BuLi in THF and subsequently treated with suitably substituted aldehydes **14** or **15**. Warming of the reaction mixture to room temperature ensured completion of the reaction, and the 1-aroyl- and -heteroaroyl-2-arylmethylenepyrrolidines **10a−c** and -piperidines **11a**,**b**,**d** were isolated in high yields (Scheme 2, Table 1). Curiously, the stereochemistry of the arylmethylene unit was strongly influenced by the size of the aza heterocycle (Table 1). Thus, enamides **10a−c** were invariably obtained as a mixture of (*Z*) and (*E*) isomers, with (*E*) isomers predominating, whereas a high degree of stereoselectivity was observed with the piperidine derivatives **11a**,**b**,**d** which were obtained exclusively in the (*E*) form. The (*Z*) and (*E*) isomers were in all cases separable by repeated flash chromatography on silica gel.



Scheme 2. Synthesis of 1-aroyl- and -heteroaroyl-2-arylmethylenepyrrolidines and -piperidines

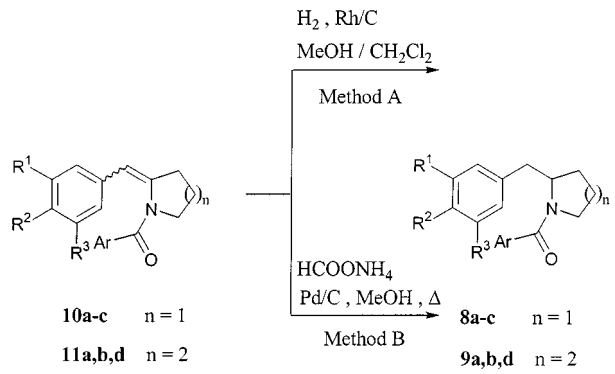
The stereochemistry was unambiguously determined by NMR spectroscopy. Thus, the signals of the *N*-aroyl protons of the (*Z*) isomers occur at a higher field, owing to aromatic shielding, than those of the (*E*) isomers. The (*Z*) stereochemistry was further confirmed by a one-dimensional difference nuclear Overhauser experiment wherein irradiation of the vinylic proton led to an increased intensity of the allylic proton signal of the pyrrolidine ring.

Two different methods were then adopted to convert the dehydro precursors **10a−c** and **11a**,**b**,**d** into the 1-aroyl- and -heteroaroyl-2-arylmethylpyrrolidines **8a−c** and -piperidines **9a**,**b**,**d** (Scheme 3). Catalytic hydrogenation (H_2, Rh/C, method A) afforded the desired aromatic and heteroaromatic carboxamides **8a−c** and **9a**,**b**,**d** which were also accessible by a more rarely employed method, making use of Pd on C and ammonium formate[16][17] (method B). The

Table 1. 1-Aroyl(heteroaroyl)-2-arylmethylenepyrrolidines **10a–c** and -piperidines **11a**,**b**,**d**

Product	Starting amide	*n*	Ar	Starting aldehyde	R^1	R^2	R^3	Yield (%)	(*E*)/(*Z*)
10a	**12a**	1	3,4-dimethoxyphenyl	**14**	$O-CH_2-O$		H	62	75:25
10b	**12b**	1	3,4,5-trimethoxyphenyl	**14**	$O-CH_2-O$		H	72	60:40
10c	**12c**	1	2-furyl	**15**	OCH_3	OCH_3	OCH_3	70	80:20
11a	**13a**	2	3,4-dimethoxyphenyl	**14**	$O-CH_2-O$		H	70	100:0
11b	**13b**	2	3,4,5-trimethoxyphenyl	**14**	$O-CH_2-O$		H	67	100:0
11d	**13c**	2	2-furyl	**14**	$O-CH_2-O$		H	60	100:0

results of a representative series of compounds which we have prepared following these two protocols are presented in Table 2, where it may be seen that these simple procedures afford excellent yields of the 2-arylmethylpyrrolidine and -piperidine derivatives **8a–c** and **9a**,**b**,**d**, respectively.



Scheme 3. Synthesis of 1-aroyl- and -heteroaroyl-2-arylmethylpyrrolidines and -piperidines

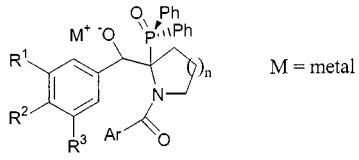
At this stage we focused our attention on the asymmetric hydrogenation of the *N*-acyl enamines **10–11** with asymmetric Ru catalysts in order to solve the problem of stereocontrol of the chiral centre adjacent to the nitrogen atom in the five- or six-membered ring of **1** or **2**. Enantioselective alkylation α to the nitrogen atom remains a challenging synthetic task, which has been tackled by several groups but which has been only partly addressed by adopting cation[18] or radical chemistry.[19] Methods based on carbanion chemistry have been developed in recent years and the creation of the asymmetric centre α to N is generally achieved either by stoichiometric chirality transfer from a chiral precursor[20][21] or by performing the metallation-alkylation sequence in the presence of enantiopure inductors.[22] However, these concepts have been mainly applied to the stereoselective connection of arylmethyl groups via their halide or trifluoromethanesulfonate derivatives on *N*-benzylcarbamates.[22][23]

A survey of the literature revealed that since the pioneering work of Takaya and Noyori[24] only a few known examples of *N*-acyl enamines have been successfully reduced with a high degree of enantioselectivity.[25][26] We were then cautiously optimistic about the chances for success of the asymmetric hydrogenation of the enamide derivatives even though high enantioselectivities have been obtained with models incorporating a styrene moiety.[24–27] Initially, of crucial importance was the stereoselective preparation of the (*Z*)-configured substrates because (*E*) stereomers are inactive to the hydrogenation conditions. Assuming that (*Z*)/(*E*) stereoselectivity might be strongly affected by the Horner reaction conditions, namely the nature of the counterion[28–32] in the primary adduct **22** (Figure 2), deprotonation of **12** or **13** with bases such as KHMDS, *n*BuLi/*t*BuOK, KHMDS and 18-crown-6 ether, which should maximize kinetic control and favour formation of the (*Z*) product, was examined.[28–32] These experiments revealed that the phosphorylated amides **12a–c** or **13a–c** were exclusively deprotonated with lithiated bases like *n*BuLi and LDA. Furthermore, all attempts to isolate the initially formed alcohols deriving from **22** (Figure 2, M = Li), which could be dephosphorylated with sodium or potassium bases (Figure 2; **22**, M = Na or K), met with no success, probably due to the high degree of conjugation of the final compounds. Consequently, we opted to study the photoinduced (*E*) → (*Z*) interconversion. Exposure of a solution of **10a–c** (*n* = 1) in diethyl ether at 25°C for 4 h to UV light resulted in the formation of a photostationary 3:2 mixture of the (*E*) and (*Z*) isomers, whereas the six-membered congeners were photochemically unreactive. The

Table 2. 1-Aroyl(heteroaroyl)-2-arylmethylpyrrolidines **8a–c** and -piperidines **9a**,**b**,**d**

Product	Starting enamide	*n*	Ar	R^1	R^2	R^3	Method A Yield (%)	Method B Yield (%)
8a	**10a**	1	3,4-dimethoxyphenyl	$O-CH_2-O$		H	90	93
8b	**10b**	1	3,4,5-trimethoxyphenyl	$O-CH_2-O$		H	86	91
8c	**10c**	1	2-furyl	OCH_3	OCH_3	OCH_3	–	89
9a	**11a**	2	3,4-dimethoxyphenyl	$O-CH_2-O$		H	87	90
9b	**11b**	2	3,4,5-trimethoxyphenyl	$O-CH_2-O$		H	–	88
9d	**11d**	2	2-furyl	$O-CH_2-O$		H	–	89

formation of several minor by-products, arising probably from photo Fries rearrangement[33–35] or photocyclization[36] of the highly conjugated parent models, was also observed but in negligible amounts. Repetition of this procedure two times and separation by flash chromatography gave pure stereoisomeric (*Z*)-**10a–c**.

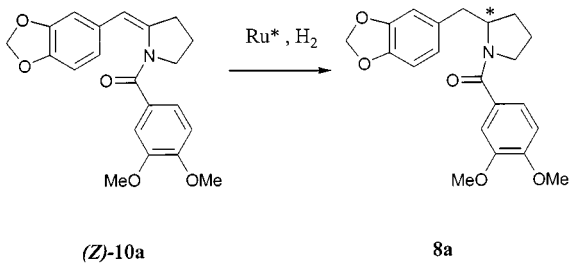


22

Figure 2. Primary adduct of the Horner reaction

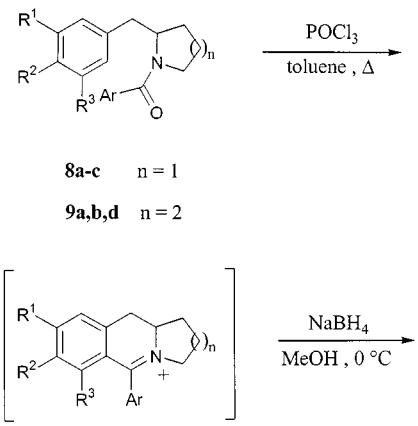
The efficiency of the catalyst and reaction conditions was examined by hydrogenation of (*Z*)-**10a** as substrate giving the 2-(benzo[1,3]dioxol-5-yl)methyl-1-(3,4-dimethoxybenzoyl)pyrrolidine **8a** (Scheme 4). Table 3 lists the results of the screening experiments. We first used the BINAP-Ru complexes as catalysts which exhibited excellent chiral efficiency in asymmetric hydrogenation of 1-acyl-2-alkylidenetetrahydroisoquinolines.[27] Thus, the reaction of (*Z*)-**10a** in a mixture of methanol and dichloromethane, which appeared to be the best medium for the asymmetric reduction of related systems,[24] at 30°C under an initial hydrogen pressure of 5 atm gave **8a** in 96% yield but with modest enantioselectivity (entry 1). By increasing the hydrogen pressure and reducing the reaction time, the chiral efficiency remained virtually unchanged. Variation of the atropisomeric chiral ligands in freshly prepared [$RuBr_2$(diphosphane)]-type catalysts led to comparable *ee* values (entries 3, 4). Use of TolBINAP–Ru complexes as well as Ru^{I-I}–dicarboxylato–BINAP complexes (entries 5,6 and 7,8) decreased the selectivity to a great extent, as under 5 atm the *ee* was lowered to 20%. These results confirm the erratic nature of the asymmetric hydrogenation of enamides, which can be performed exclusively on the rather sterically constrained (*Z*) stereoisomer, and which is strongly influenced by the degree of aromatic substitution, the nature of the substituents and the geometry of the parent models.

Compounds **8a–c** and **9a**,**b**,**d** were then subjected to Bischler–Napieralski reaction conditions. Thus, treatment of these compounds with $POCl_3$ in toluene at reflux and subsequent reduction of the intermediary iminium salts with $NaBH_4$ in methanol delivered fairly good yields of the cyclocondensed products **1a–c** and **2a**,**b**,**d** which were in-



(Z)-**10a** **8a**

Scheme 4. Enantioselective hydrogenation of (*Z*)-**10a**



8a-c n = 1

9a,b,d n = 2

1a-c n = 1 10 : 1

2a,b,d n = 2 10 : 1

Scheme 5. Synthesis of 5-(or-6-)arylbenzoindolizidines and -quinolizidines

Table 3. Asymmetric hydrogenation of enamide (*Z*)-**10a** into **8a**[a]

Entry	Catalyst	$p(H_2)$ [atm]	t[b] [h]	Yield[c] (%)	ee[d] (%)
1	$\{RuCl_2[(S)\text{-BINAP}]\}_2 \cdot NEt_3$	5	24	96	40 (–)
2	$\{RuCl_2[(S)\text{-BINAP}]\}_2 \cdot NEt_3$	10	14	95	41 (–)
3	$RuBr_2$[(*S*)-MeOBIPHEP]	10	16	90	41 (–)
4	$RuBr_2$[(*S*)-MeOBIPHEP]	100	3	95	42 (–)
5	$RuBr_2$[(*S*)-TolBINAP]	5	21	97	20 (–)
6	$RuBr_2$[(*S*)-TolBINAP]	100	3	93	20 (–)
7	$Ru(OAc)_2$[(*R*)-BINAP]	5	16	95	20 (+)
8	$Ru(TFA)_2$[(*R*)-BINAP]	5	4	90	18 (+)

[a] Reaction conditions: 30°C, substrate/catalyst, 200:1, ca. 0.5–1.0 mmol of substrate in 12 mL of MeOH/CH_2Cl_2 (5:1). – [b] Non-optimized reaction times for quantitative conversion of (*Z*)-**10a** into **8a** as determined by ^{1}H-NMR and HPLC analysis. – [c] Yield determined after purification by column chromatography. – [d] Enantiomeric excesses were determined by HPLC analysis with a Supelcosil (*R*)-DNBPG column (hexane/2-propanol, 95:5), 1 mL/min, UV detector 254 nm.

Table 4. Arylated benzoindolizidines **1a−c** and benzoquinolizidines **2a,b,d**

	n	Ar	R^1	R^2	R^3	Yield[a] (%)
1a	1	3,4-dimethoxyphenyl	$O-CH_2-O$		H	70
1b	1	3,4,5-trimethoxyphenyl	$O-CH_2-O$		H	75
1c	1	2-furyl	OCH_3	OCH_3	OCH_3	65
2a	2	3,4-dimethoxyphenyl	$O-CH_2-O$		H	68
2b	2	3,4,5-trimethoxyphenyl	$O-CH_2-O$		H	72
2d	2	2-furyl	$O-CH_2-O$		H	65

[a]Yield determined before separation of diastereomers.

variably obtained as a mixture of diastereomers in the ratio 10:1 (Scheme 5, Table 4). The structure of the major diastereomer was deduced from the ^{1}H-NMR spectrum, namely by the presence of long-range coupling between the mono- and dibenzylic protons attributable to their axial relationship.[13][14]

In conclusion, we have developed a general and versatile method for the preparation of benzoindolizidines and quinolizidines flanked indifferently with aromatic or heteroaromatic units on the central heteroring unit. The enamide synthesis, consecutive hydrogenation and subsequent cyclization reactions proceed in high yields even though the enantioselectivities of the hydrogenation products of enamides are rather modest. The reported protocol could undoubtedly be broadened to include the synthesis of a variety of alkaloids containing the 5-(or 6-)arylbenzoindo(or quino)lizidine skeleton.

Experimental Section

General: Methanol was distilled from magnesium turnings. Tetrahydrofuran (THF) and ether (Et_2O) were predried with anhydrous Na_2SO_4 and distilled from sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica-gel 60 (230−400 mesh ASTM) was used. The melting points were taken on a Reichert-Thermopan apparatus and are not corrected. − NMR: Bruker AM 300 (300, 75 and 121 MHz, for ^{1}H, ^{13}C and ^{31}P, respectively). For ^{1}H and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard; for ^{31}P NMR, $CDCl_3$ as solvent, H_3PO_4 as external standard. − Microanalyses were performed by the CNRS microanalysis centre. − Triazines **16**,[37] **17**[38] and diphenylphosphane oxide **18**[39] were prepared according to the literature methods.

Phosphorylated Amides: The phosphorylated amines **19**,[15] **20**[10] and amides **12a−c**, **13a−c**[9] were synthesized according to already reported procedures.

Phosphorylated Amide 12a: 75%, m.p. 125−126°C. − IR (KBr): $\tilde{\nu}$ = 1623 cm^{-1} (CO), 1172 (PO). − ^{1}H NMR: δ = 1.73−1.92 (m, 1 H, CH_2), 1.97−2.35 (m, 2 H, CH_2), 2.41−2.60 (m, 1 H, CH_2), 3.42−3.51 (m, 1 H, NCH_2), 3.58−3.66 (m, 1 H, NCH_2), 3.81 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.51−5.59 (m, 1 H, CH-P), 6.68−6.81 (m, 3 H, aromatic H), 7.32−7.41 (m, 3 H, aromatic H), 7.45−7.58 (m, 3 H, aromatic H), 7.73−7.88 (m, 2 H, aromatic H), 8.06−8.13 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 24.7, 25.8, 50.9, 55.7 (d, J_{CP} = 80 Hz), 55.9 (s, OCH_3), 110.1, 110.8, 120.8, 127.9, 128.0 (d, J_{CP} = 11.5 Hz), 128.7 (d, J_{CP} = 11.5 Hz), 130.5 (d, J_{CP} = 95 Hz), 131.4 (d, J_{CP} = 8.5 Hz), 131.8 (d, J_{CP} = 3 Hz), 132.1 (d, J_{CP} = 3 Hz), 148.4, 150.7, 170.2 (s, C=O). − ^{31}P NMR: δ = 34.3. − $C_{25}H_{26}NO_4P$ (435.5): calcd. C 68.96, H 5.98, N 3.22; found C 69.10, H 5.83, N 3.45.

Phosphorylated Amide 12b: 78%, m.p. 148−149°C. − IR (KBr): $\tilde{\nu}$ = 1638 cm^{-1} (CO), 1168 (PO). − ^{1}H NMR: δ = 1.82−1.94 (m, 1 H, CH_2), 1.97−2.15 (m, 1 H, CH_2), 2.19−2.30 (m, 1 H, CH_2), 2.45−2.60 (m, 1 H, CH_2), 3.31−3.59 (m, 2 H, NCH_2), 3.73 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 5.53−5.56 (m, 1 H, CH-P), 6.28 (s, 2 H, aromatic H), 7.31−7.45 (m, 3 H, aromatic H), 7.47−7.55 (m, 3 H, aromatic H), 7.82−7.90 (m, 2 H, aromatic H), 8.05−8.11 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 24.9, 25.5, 50.6, 55.9 (s, OCH_3), 56.0 (d, J_{CP} = 79 Hz), 60.8 (s, OCH_3), 104.6, 128.2 (d, J_{CP} = 10 Hz), 128.9 (d, J_{CP} = 9 Hz), 130.6, 131.4 (d, J_{CP} = 9 Hz), 131.5 (d, J_{CP} = 94 Hz), 131.8 (d, J_{CP} = 8 Hz), 146.3, 152.8, 170.1 (s, C=O). − ^{31}P NMR: δ = 34.6. − $C_{26}H_{28}NO_5P$ (465.5): calcd. C 67.09, H 6.02, N 3.01; found C 67.18, H 5.93, N 2.88.

Phosphorylated Amide 12c: 77%, m.p. 147−148°C. − IR (KBr): $\tilde{\nu}$ = 1635 cm^{-1} (CO), 1173 (PO). − ^{1}H NMR: δ = 1.72−2.08 (m, 2 H, CH_2), 2.36−2.51 (m, 2 H, CH_2), 3.68−3.84 (m, 2 H, NCH_2), 5.46 (br. s, 1 H, CH-P), 6.34 (br. s, 1 H, furanic H), 6.78 (br. s, 1 H, furanic H), 7.21−7.56 (m, 7 H, 6 aromatic H + 1 furanic H), 7.66−7.79 (m, 2 H, aromatic H), 8.03−8.12 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 24.8, 26.4, 48.8, 57.3 (d, J_{CP} = 78 Hz), 111.3, 116.1, 127.9 (d, J_{CP} = 12 Hz), 128.7 (d, J_{CP} = 11 Hz), 130.3 (d, J_{CP} = 89 Hz), 131.3 (d, J_{CP} = 10 Hz), 131.6 (d, J_{CP} = 9 Hz), 132.0, 144.6, 159.8 (s, C=O). − ^{31}P NMR: δ = 33.9. − $C_{21}H_{20}NO_3P$ (365.4): calcd. C 69.04, H 5.48, N 3.83; found C 69.16, H 5.39, N 3.88.

Phosphorylated Amide 13a: 76%, m.p. 156−157°C. − IR (KBr): $\tilde{\nu}$ = 1621 cm^{-1} (CO), 1178 (PO). − ^{1}H NMR: δ = 1.26−1.43 (m, 1 H, CH_2), 1.61−1.98 (m, 3 H, CH_2), 2.06−2.18 (m, 1 H, CH_2), 2.37−2.56 (m, 1 H, CH_2), 3.47−3.55 (m, 1 H, NCH_2), 3.71−3.73 (m, 4 H, OCH_3 + 1 H NCH_2), 3.81 (s, 3 H, OCH_3), 5.84 (br. s, 1 H, CH-P), 6.29 (s, 1 H, aromatic H), 6.37 (d, J = 9.0 Hz, 1 H, aromatic H), 6.68 (d, J = 9.0 Hz, 1 H, aromatic H), 7.38−7.53 (m, 6 H, aromatic H), 7.88−8.05 (m, 4 H, aromatic H). − ^{13}C NMR: δ = 20.5, 24.2, 26.2, 46.6, 48.1 (d, J_{CP} = 82.5 Hz), 55.8 (s, OCH_3), 109.8, 110.5, 119.5, 127.5, 128.8 (d, J_{CP} = 10.5 Hz), 130.9 (d, J_{CP} = 9 Hz), 131.0 (d, J_{CP} = 9 Hz), 131.8 (d, J_{CP} = 15 Hz), 131.9 (d, J_{CP} = 92 Hz), 148.6, 150.0, 170.5 (s, C=O). − ^{31}P NMR: δ = 31.8. − $C_{26}H_{28}NO_4P$ (449.5): calcd. C 69.49, H 6.24, N 3.12; found C 69.61, H 6.38, N 3.01.

Phosphorylated Amide 13b: 75%, m.p. 131−132°C. − IR (KBr): $\tilde{\nu}$ = 1637 cm^{-1} (CO), 1171 (PO). − ^{1}H NMR: δ = 1.23−1.41 (m, 1 H, CH_2), 1.60−2.05 (m, 4 H, 2 CH_2), 2.32−2.50 (m, 1 H, CH_2), 3.54 (m, 1 H, NCH_2), 3.66 (td, J = 13.1, 2.4 Hz, 1 H, NCH_2), 3.86

(s, 6 H, 2 × OCH_3), 3.91 (s, 3 H, OCH_3), 5.84 (br. s, 1 H, CH-P), 6.13 (s, 2 H, aromatic H), 7.32−7.55 (m, 6 H, aromatic H), 7.86−8.12 (m, 4 H, aromatic H). − ^{13}C NMR: δ = 20.8, 24.5, 26.3, 46.5, 49.1 (d, J_{CP} = 76.5 Hz), 56.1 (s, OCH_3), 60.6 (s, OCH_3), 104.3, 128.6 (d, J_{CP} = 9 Hz), 129.3 (d, J_{CP} = 8.5 Hz), 130.8 (d, J_{CP} = 83 Hz), 131.2, 131.3 (d, J_{CP} = 8.5 Hz), 131.7 (d, J_{CP} = 8 Hz), 147.1, 152.7, 169.9 (s, C=O). − ^{31}P NMR: δ = 32.3. − $C_{27}H_{30}NO_5P$ (479.5): calcd. C 67.64, H 6.26, N 2.92; found C 67.48, H 6.39, N 3.06.

Phosphorylated Amide 13c: 83%, m.p. 112−113°C. − IR (KBr): $\tilde{\nu}$ = 1631 cm^{-1} (CO), 1177 (PO). − ^{1}H NMR: δ = 1.37−2.06 (m, 5 H, CH_2), 2.38−2.55 (m, 1 H, CH_2), 3.77 (br. t, *J* = 12.7 Hz, 1 H, NCH_2), 4.08 (br. d, *J* = 12.7 Hz, 1 H, NCH_2), 5.69 (br. s, 1 H, CH-P), 6.37 (dd, *J* = 3.8, 1.8 Hz, 1 H, furanic H), 7.14−7.46 (m, 7 H, 6 aromatic H + furanic H), 7.65−7.98 (m, 5 H, 4 aromatic H + furanic H). − ^{13}C NMR: δ = 20.7, 24.6, 26.3, 45.7, 49.0 (d, J_{CP} = 75.5 Hz), 110.9, 115.4, 128.2 (d, J_{CP} = 11.5 Hz), 128.8 (d, J_{CP} = 11 Hz), 130.6 (d, J_{CP} = 90.5 Hz), 131.0 (d, J_{CP} = 8 Hz), 131.7 (d, J_{CP} = 13 Hz), 143.8, 145.8, 160.5 (s, C=O). − ^{31}P NMR: δ = 32.7. − $C_{22}H_{22}NO_3P$ (379.4): calcd. C 69.65, H 5.80, N 3.69; found C 69.58, H 5.92, N 3.60.

General Procedure for the Synthesis of *N*-Acyl Enamines 10−11: A solution of *n*BuLi (1.6 M in hexanes, 1.7 mL, 2.75 mmol) was added dropwise to a solution of the phosphorylated amide **12−13** (2.5 mmol) in THF (30 mL) at −78°C with stirring under Ar. The orange solution was stirred for an additional 15 min and a solution of the appropriate aldehyde **14** or **15** (2.5 mmol) in THF (5 mL) was then slowly added. After being stirred at −78°C for 15 min the reaction mixture was allowed to come to room temperature over 2 h. Aqueous NH_4Cl was added and the organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. The crude products were analysed by ^{1}H NMR in order to determine the (*E*)/(*Z*) isomer ratio and compounds **10a−c** [(*E*) and (*Z*) isomers] and **11a**,**b**,**d** [(*E*) isomers] were finally purified by flash column chromatography with AcOEt/hexane (60:40) as eluent and recrystallized from hexane/toluene.

***N*-Acyl Enamine 10a**: (*E*) isomer, m.p. 129−130°C. − ^{1}H NMR: δ = 1.86−1.98 (m, 2 H, CH_2), 2.83 (td, *J* = 7.5, 2.0 Hz, 2 H, = CCH_2), 3.71 (t, *J* = 6.9 Hz, 2 H, NCH_2), 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.91 (s, 2 H, OCH_2O), 6.66−6.74 (m, 3 H, 2 aromatic H + vinylic H), 6.83 (d, *J* = 8.0 Hz, 1 H, aromatic H), 7.06−7.12 (m, 3 H, aromatic H). − ^{13}C NMR: δ = 22.8, 30.4, 51.9, 56.0 (s, OCH_3), 100.9, 108.1, 108.4, 110.3, 110.8, 113.1, 120.3, 122.0, 130.5, 132.1, 139.8, 145.7, 147.5, 149.5, 151.6, 169.1 (s, C=O); (*Z*) isomer, oil. − ^{1}H NMR: δ = 1.81−1.99 (m, 2 H, CH_2), 2.49 (t, *J* = 7.3 Hz, 2 H, =CCH_2), 3.62 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.71 (t, *J* = 7.0 Hz, 2 H, NCH_2), 5.55 (s, 1 H, vinylic H), 5.67 (s, 2 H, OCH_2O), 6.13 (s, 1 H, aromatic H), 6.28 (d, *J* = 7.9 Hz, 1 H, aromatic H), 6.41 (d, *J* = 7.9 Hz, 1 H, aromatic H), 6.52 (d, *J* = 8.3 Hz, 1 H, aromatic H), 6.60 (s, 1 H, aromatic H), 6.81 (d, *J* = 8.3 Hz, 1 H, aromatic H). − ^{13}C NMR: δ = 20.9, 31.8, 49.5, 55.4 (s, OCH_3), 55.9 (s, OCH_3), 100.6, 107.6, 107.7, 109.6, 111.3, 112.2, 120.5, 120.9, 129.1, 131.0, 138.3, 145.4, 147.2, 148.3, 150.7, 168.7 (s, C=O). − $C_{21}H_{21}NO_5$ (367.4): calcd. C 68.66, H 5.72, N 3.81; found C 68.57, H 5.81, N 3.66.

***N*-Acyl Enamine 10b:** (*E*) isomer, m.p. 125−126°C. − ^{1}H NMR: δ = 1.83−1.93 (m, 2 H, CH_2), 2.84 (td, *J* = 7.3, 1.8 Hz, 2 H, = CCH_2), 3.68 (t, *J* = 6.9 Hz, 2 H, NCH_2), 3.84 (s, 9 H, 3 × OCH_3), 5.91 (s, 2 H, OCH_2O), 6.66−6.75 (m, 4 H, 3 aromatic H+ vinylic H), 7.18−7.27 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 22.8, 30.4, 51.5, 56.2 (s, OCH_3), 60.9 (s, OCH_3), 100.9, 104.3, 108.2, 108.4, 113.2, 122.1, 130.7, 132.0, 133.0, 139.6, 145.6, 147.5, 153.1, 169.2 (s, C=O); (*Z*) isomer, m.p. 108−109°C. − ^{1}H NMR: δ = 1.98−2.13 (m, 2 H, CH_2), 2.66 (t, *J* = 7.6 Hz, 2 H, =CCH_2), 3.73 (s, 6 H, 2 × OCH_3), 3.82 (s, 3 H, OCH_3), 3.87 (t, *J* = 7.5 Hz, 2 H, NCH_2), 5.70 (s, 1 H, vinylic H), 5.85 (s, 2 H, OCH_2O), 6.19 (s, 1 H, aromatic H), 6.43 (d, *J* = 8.2 Hz, 1 H, aromatic H), 6.45 (s, 2 H, aromatic H), 6.57 (d, *J* = 8.2 Hz, 1 H, aromatic H). − ^{13}C NMR: δ = 20.8, 31.8, 49.0, 55.9 (s, OCH_3), 60.7 (s, OCH_3), 100.7, 105.2, 107.7, 107.9, 112.5, 121.0, 128.6, 130.5, 130.8, 138.5, 145.5, 147.3, 152.3, 168.6 (s, C=O). − $C_{22}H_{23}NO_6$ (397.4): calcd. C 66.50, H 5.79, N 3.53; found C 66.41, H 5.70, N 3.69.

***N*-Acyl Enamine 10c:** (*E*) isomer, oil. − ^{1}H NMR: δ = 1.78−1.92 (m, 2 H, CH_2), 2.81 (td, *J* = 7.3, 1.9 Hz, 2 H, =CCH_2), 3.68 (t, *J* = 6.8 Hz, 2 H, NCH_2), 3.89 (s, 9 H, 3 × OCH_3), 6.42 (dd, *J* = 3.4, 1.5 Hz, 1 H, furanic H), 6.82 (s, 2 H, aromatic H), 7.04 (dd, *J* = 3.4, 0.8 Hz, 1 H, furanic H), 7.31 (s, 1 H, vinylic H), 7.42 (dd, *J* = 1.5, 0.8 Hz, 1 H, furanic H). − ^{13}C NMR: δ = 22.7, 30.6, 50.7, 56.0 (s, OCH_3), 60.9 (s, OCH_3), 102.4, 108.3, 111.6, 115.8, 130.6, 137.6, 141.3, 142.7, 147.4, 150.1, 169.7 (s, C=O); (*Z*) isomer, oil. − ^{1}H NMR: δ = 1.81−2.02 (m, 2 H, CH_2), 2.65 (t, *J* = 6.9 Hz, 2 H, =CCH_2), 3.75 (s, 6 H, 2 × OCH_3), 3.80 (s, 3 H, OCH_3), 3.86 (t, *J* = 7.2 Hz, 2 H, NCH_2), 5.78 (s, 1 H, vinylic H), 6.46 (d, *J* = 3.3 Hz, 1 H, furanic H), 6.54 (s, 2 H, aromatic H), 7.08 (d, *J* = 3.3 Hz, 1 H, furanic H), 7.45 (br. s, 1 H, furanic H). − ^{13}C NMR: δ = 21.2, 31.7, 50.1, 55.6 (s, OCH_3), 60.8 (s, OCH_3), 102.6, 108.0, 111.2, 115.9, 130.9, 137.2, 141.2, 142.9, 147.8, 150.2, 169.6 (s, C=O). − $C_{19}H_{21}NO_5$ (343.4): calcd. C 66.47, H 6.12, N 4.08; found C 66.41, H 5.98, N, 4.16.

***N*-Acyl Enamine 11a:** (*E*) isomer, m.p. 97−98°C. − ^{1}H NMR: δ = 1.65−1.82 (m, 4 H, CH_2), 2.44 (t, *J* = 5.8 Hz, 2 H, =CCH_2), 3.65 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.74 (m, 2 H, NCH_2), 5.63 (s, 1 H, vinylic H), 5.92 (s, 2 H, OCH_2O), 6.21 (s, 1 H, aromatic H), 6.25 (s, 1 H, aromatic H), 6.29−6.58 (m, 4 H, aromatic H). − ^{13}C NMR: δ = 25.2, 25.6, 28.2, 46.1, 56.0 (s, OCH_3), 100.9, 107.2, 108.3, 108.7, 113.3, 122.1, 124.3, 124.5, 130.3, 130.5, 136.2, 147.7, 148.6, 150.7, 158.4, 170.2 (s, C=O). − $C_{22}H_{23}NO_5$ (381.4): calcd. C 69.29, H 6.03, N 3.67; found C 69.41, H 5.95, N 3.59.

***N*-Acyl Enamine 11b:** (*E*) isomer, m.p. 92−93°C. − ^{1}H NMR: δ = 1.71−1.88 (m, 4 H, CH_2), 2.53 (t, *J* = 6.1 Hz, 2 H, =CCH_2), 3.69 (t, *J* = 7.0 Hz, 2 H, NCH_2), 3.83 (s, 9 H, 3 × OCH_3), 5.71 (s, 1 H, vinylic H), 5.93 (s, 2 H, OCH_2O), 6.43−6.71 (m, 5 H, aromatic H). − ^{13}C NMR: δ = 25.1, 25.7, 29.1, 46.5, 55.8 (s, OCH_3), 60.1 (s, OCH_3), 100.8, 104.3, 108.1, 108.4, 113.2, 122.1, 130.5, 132.1, 133.0, 139.6, 145.6, 147.5, 153.1, 169.2 (s, C=O). − $C_{23}H_{25}NO_6$ (411.5): calcd. C 67.15, H 6.08, N 3.41; found C 67.09, H 6.19, N 3.38.

***N*-Acyl Enamine 11d:** (*E*) isomer, oil. − ^{1}H NMR: δ = 1.75−1.89 (m, 4 H, 2 CH_2), 2.61 (t, *J* = 6.5 Hz, 2 H, =CCH_2), 3.58 (t, *J* = 7.1 Hz, 2 H, NCH_2), 5.77 (s, 1 H, vinylic H), 5.90 (s, 2 H, OCH_2O), 6.25 (s, 1 H, aromatic H), 6.33−6.58 (m, 3 H, 2 aromatic H + furanic H), 7.08 (d, *J* = 3.4 Hz, 1 H, furanic H), 7.45 (d, *J* = 1.8 Hz, 1 H, furanic H). − ^{13}C NMR: δ = 24.9, 25.8, 29.3, 45.8, 100.9, 108.0, 108.8, 110.7, 111.8, 114.8, 122.2, 130.6, 131.8, 143.6, 147.3, 148.5, 148.7, 159.2 (s, C=O). − $C_{18}H_{17}NO_4$ (311.3): calcd. C 69.45, H 5.47, N 4.50; found C 69.53, H 5.38, N 4.53.

General Procedure for the Photoisomerization Process: A solution of the enamide (*E*)**-10a−c** (2 mmol) in Et_2O (200 mL) was purged by bubbling Ar through it for 0.5 h. Photolyses were carried out in a water-cooled quartz reactor equipped with a dry Ar inlet and a magnetic stirrer. The solution was placed in a Rayonet RPR 208 photochemical reactor containing eight RUL 2537 Å lamps. Degassing and stirring of the solution were maintained during irradiation. The photostationary state [(*Z*)/(*E*) = 2:3] was obtained after 4 h. The solvent was evaporated under vacuum and the resi-

due treated by flash column chromatography with AcOEt/hexanes (3:7) as eluent. Compounds (*Z*)-**10a−c** and (*E*)-**10a−c** were isolated and the photochemical protocol was repeated twice with the (*E*) isomer.

General Procedure for the Synthesis of *N*-Acylpyrrolidine and -piperidine Derivatives 8a−c and 9a,b,d. − Method A: A solution of the *N*-acyl enamine **10** or **11** (2 mmol) in a mixture of methanol/CH_2Cl_2 (5:1, 20 mL) was degassed by two freeze-thaw cycles and then transferred on the catalyst Rh/C (5×10^{-3} mmol) placed in a Schlenk tube. The resulting mixture was transferred to a 100-mL stainless steel autoclave. Hydrogen was introduced (25 atm) and the reaction mixture was magnetically stirred at 30°C during 20 h. The hydrogen was then removed and the solution was concentrated under vacuum to leave an oily product, which was purified by flash column chromatography with AcOEt/hexanes (1:1) as eluent. − **Method B:** A suspension of compounds **10** or **11** (2 mmol) in methanol (30 mL) was stirred with activated Pd/C (10%, 20 mg) and a solution of $HCOONH_4$ (640 mg, 10 mmol) in distilled water (5 mL) was slowly added. The reaction mixture was refluxed for 2 h, filtered through Celite® and water was added. Extraction with CH_2Cl_2 (3 × 20 mL), drying with $MgSO_4$ and concentration in vacuo left an oily product which was purified as described above.

***N*-Acylpyrrolidine 8a:** Oil. − ^{1}H NMR: δ = 1.53−1.97 (m, 4 H, 2 CH_2), 2.76 (dd, *J* = 13.2, 8.4 Hz, 1 H, CH_2Ar), 3.09 (br. d, *J* = 13.2 Hz, 1 H, CH_2Ar), 3.18−3.24 (m, 1 H, NCH_2), 3.33−3.42 (m, 1 H, NCH_2), 3.83 (s, 6 H, 2 × OCH_3), 4.31−4.39 (m, 1 H, NCH), 5.84 (s, 2 H, OCH_2O), 6.65−6.78 (m, 4 H, aromatic H), 7.03−7.15 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 20.9, 29.3, 38.4, 50.9, 55.9 (s, OCH_3), 58.6, 100.7, 108.0, 110.0, 110.2, 111.0, 120.5, 122.6, 127.8, 129.7, 146.0, 147.5, 148.7, 150.4, 169.5 (s, C=O). − $C_{21}H_{23}NO_5$ (369.4): calcd. C 68.29, H 6.23, N 3.79; found C 68.17, H 6.36, N 3.19.

***N*-Acylpyrrolidine 8b:** Oil. − ^{1}H NMR: δ = 1.38−1.66 (m, 2 H, CH_2), 1.73−1.85 (m, 2 H, CH_2), 2.76 (dd, *J* = 12.9, 8.1 Hz, 1 H, CH_2Ar), 2.96 (dd, *J* = 12.9, 2.2 Hz, 1 H, CH_2Ar), 3.03−3.15 (m, 1 H, NCH_2), 3.22−3.33 (m, 1 H, NCH_2), 3.71 (s, 3 H, OCH_3), 3.73 (s, 6 H, 2 × OCH_3), 4.21−4.36 (m, 1 H, NCH), 5.76 (s, 2 H, OCH_2O), 6.41−6.65 (m, 5 H, aromatic H). − ^{13}C NMR: δ = 20.9, 24.8, 38.1, 50.8, 56.1 (s, OCH_3), 58.4, 60.7 (s, OCH_3), 100.7, 104.6, 107.9, 110.0, 122.7, 132.1, 132.5, 139.3, 146.0, 147.5, 152.9, 169.4 (s, C=O). − $C_{22}H_{25}NO_6$ (399.45): calcd. C 66.16, H 6.26, N 3.51; found C 66.27, H 6.41, N 3.38.

***N*-Acylpyrrolidine 8c:** Oil. − ^{1}H NMR: δ = 1.66−2.03 (m, 4 H, 2 CH_2), 2.76 (dd, *J* = 12.9, 9.0 Hz, 1 H, CH_2Ar), 3.17 (dd, *J* = 12.9, 2.0 Hz, 1 H, CH_2Ar), 3.61−3.96 (m, 11 H, 3 × OCH_3 + NCH_2), 4.41−4.45 (m, 1 H, NCH), 6.41 (s, 2 H, aromatic H), 6.44 (dd, *J* = 3.3, 1.6 Hz, 1 H, furanic H), 7.02 (d, *J* = 1.6 Hz, 1 H, furanic H), 7.46 (br. s, 1 H, furanic H). − ^{13}C NMR: δ = 24.5, 28.1, 38.9, 48.5, 56.0 (s, OCH_3), 59.8, 60.8 (s, OCH_3), 106.3, 111.4, 115.9, 134.6, 144.1, 148.8, 153.0, 158.0, 172.3 (s, C=O). − $C_{19}H_{23}NO_5$ (345.4): calcd. C 66.09, H 6.66, N 4.06; found C 65.91, H 6.83, N 4.18.

***N*-Acylpiperidine 9a:** Oil. − ^{1}H NMR: δ = 1.29−1.68 (m, 7 H, CH_2), 2.51−2.76 (m, 2 H, CH_2), 2.78 (dd, *J* = 13.6, 8.2 Hz, 1 H), 2.89−3.01 (m, 1 H), 3.64 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 5.68 (s, 2 H, OCH_2O), 6.30−6.72 (m, 6 H, aromatic H). − ^{13}C NMR: δ = 19.3, 25.8, 30.6, 35.7, 44.8, 54.9, 55.7 (s, OCH_3), 55.8 (s, OCH_3), 100.7, 107.9, 109.4, 110.2, 110.3, 119.1, 121.9, 129.0, 132.1, 145.9, 147.5, 148.7, 149.7, 170.6 (s, C=O). − $C_{22}H_{25}NO_5$ (383.45): calcd. C 68.93, H 6.53, N 3.65; found C 69.04, H 6.56, N 3.58.

***N*-Acylpiperidine 9b:** Oil.[18] − ^{1}H NMR: δ = 1.56−1.83 (m, 7 H, CH_2), 2.61−2.84 (m, 2 H, CH_2), 2.98 (dd, *J* = 13.7, 8.4 Hz, 1 H), 3.01−3.13 (m, 1 H), 3.80 (s, 6 H, 2 × OCH_3), 3.82 (s, 3 H, OCH_3), 5.89 (s, 2 H, OCH_2O), 6.31 (s, 2 H, aromatic H), 6.51−6.78 (m, 3 H, aromatic H). − ^{13}C NMR: δ = 19.2, 25.6, 30.8, 35.2, 45.1, 54.3, 56.1 (s, OCH_3), 60.9 (s, OCH_3), 100.9, 103.6, 108.2, 109.6, 122.1, 129.8, 132.2, 145.7, 147.6, 148.3, 153.2, 169.8 (s, C=O).

***N*-Acylpiperidine 9d:** Oil.[18] − ^{1}H NMR: δ = 1.42−1.75 (m, 6 H, CH_2), 2.70−2.76 (m, 1 H, CH_2), 2.72 (dd, *J* = 13.4, 8.8 Hz, 1 H), 2.98−3.13 (m, 1 H), 4.25−4.46 (br. s, 1 H), 4.58−4.73 (br. s, 1 H), 5.81 (s, 2 H, OCH_2O), 6.38 (dd, *J* = 3.4, 1.9 Hz, 1 H, furanic H), 6.56 (d, *J* = 1.9 Hz, 1 H, furanic H), 6.58−6.67 (m, 3 H, aromatic H), 7.41 (dd, *J* = 1.9, 0.8 Hz, 1 H, furanic H). − ^{13}C NMR: δ = 19.1, 25.8, 26.9, 36.0, 43.9, 54.8, 100.8, 108.1, 111.0, 112.7, 115.2, 122.0, 132.3, 141.8, 147.6, 148.3, 148.6, 159.9 (s, C=O).

Asymmetric Hydrogenation of (*Z*)-10a: The catalyst $\{RuCl_2[(S)\text{-BINAP}]\}_2 \cdot NEt_3$ is commercially available and the catalysts $RuBr_2[(S)$-MeOBiPHEP],[40] $RuBr_2[(S)$-TolBINAP],[40] $Ru(OAc)_2[(R)$-BINAP][41] and $Ru(TFA)_2[(R)$-BINAP][41] were freshly prepared as previously described. For the determination of the enantiomeric excesses the oily residue obtained after the hydrogenation experiment carried out as for Method A was analysed by HPLC with a Supelcosil (*R*)-DNBPG column with hexane-2-propanol (95:5) as eluent (flow rate 1 mL/min), UV detection at 254 nm, t_R of **8a** (−): 52.1 min and **8a** (+): 54.6 min.

General Procedure for the Synthesis of the Cyclocondensed Products 1a−c and 2a,b,d: A mixture of compound **8a−c** or **9a**,**b**,**d** (2 mmol), $POCl_3$ (1.53 g, 10 mmol) in dry toluene (30 mL) was refluxed for 6 h under Ar with stirring. The solvent and excess reagent were removed under vacuum and the residue was dissolved in dry methanol (20 mL). Sodium tetrahydroborate (0.38 g, 10 mmol) was then added portionwise until pH = 9, AcOEt (50 mL) was added and the organic layer washed with aqueous NaOH (10%) and dried ($MgSO_4$). Evaporation of the solvent left an oily residue, which was analysed by ^{1}H-NMR spectroscopy and finally purified by flash column chromatography with acetone/petroleum ether (1:1) as eluent and by recrystallization from Et_2O/hexane.

Benzoindolizidine 1a: Major isomer, m.p. 147−148°C. − ^{1}H NMR: δ = 1.54−1.78 (m, 4 H, CH_2), 1.95−2.13 (m, 2 H, CH_2Ar), 2.77−2.88 (m, 3 H, NCH_2 + NCH), 3.71 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.10 (s, 1 H, NCHAr), 5.75 (s, 2 H, OCH_2O), 6.06 (s, 1 H, aromatic H), 6.73−6.83 (m, 3 H, aromatic H). − ^{13}C NMR: δ = 21.1, 30.8, 35.9, 53.5, 55.8 (s, OCH_3), 55.9 (s, OCH_3), 61.2, 71.5, 100.6, 107.8, 108.0, 110.5, 111.8, 121.7, 128.1, 132.2, 135.9, 145.7, 145.9, 148.4, 149.1. − $C_{21}H_{23}NO_4$ (353.4): calcd. C 71.39, H 6.51, N 3.96; found C 71.58, H 6.33, N 3.82.

Benzoindolizidine 1b: Major isomer, m.p. 163−164°C. − ^{1}H NMR: δ = 1.54−1.80 (m, 3 H, CH_2), 1.99−2.11 (m, 2 H, CH_2), 2.54−2.54 (m, 1 H, CH_2Ar), 2.69−2.91 (m, 3 H, NCH_2 + NCH), 3.83 (s, 3 H, OCH_3), 3.85 (s, 6 H, 2 × OCH_3), 4.09 (s, 1 H, NCHAr), 5.82 (s, 2 H, OCH_2O), 6.16 (s, 1 H, aromatic H), 6.51 (s, 2 H, aromatic H), 6.54 (s, 1 H, aromatic H). − ^{13}C NMR: δ = 21.2, 31.0, 36.3, 53.7, 56.1 (s, OCH_3), 60.8 (s, OCH_3), 60.9, 72.1, 100.7, 106.0, 107.7, 108.1, 128.2, 132.3, 137.1, 139.7, 145.6, 145.8, 153.1. − $C_{22}H_{25}NO_5$ (383.45): calcd. C 68.93, H 6.53, N 3.65; found C 69.08, H 6.71, N 3.46.

Benzoindolizidine 1c: Major isomer, m.p. 78−79°C. − ^{1}H NMR: δ = 1.58−1.92 (m, 3 H, 2 CH_2), 2.01−2.36 (m, 2 H, CH_2), 2.48−2.56 (m, 1 H, CH_2Ar), 2.72−2.85 (m, 2 H, NCH_2), 3.09 (td, *J* = 8.3, 2.6 Hz, 1 H, NCH), 3.74 (s, 3 H, OCH_3), 3.82 (s, 6 H, 2 × OCH_3), 4.55 (s, 1 H, NCHAr), 6.17 (d, *J* = 2.8 Hz, 1 H, furanic H), 6.31 (dd, *J* = 2.8, 1.9 Hz, 1 H, furanic H), 6.43 (s, 1 H, aromatic H), 7.27 (d, *J* = 1.9 Hz, 1 H, furanic H). − ^{13}C NMR:

δ = 21.1, 30.6, 36.6, 53.0, 55.8 (s, OCH_3), 59.7 (s, OCH_3), 59.8, 60.4, 106.1, 107.1, 110.1, 122.0, 132.0, 140.3, 140.5, 151.1, 152.3, 157.0. − $C_{19}H_{23}NO_4$ (329.4): calcd. C 69.30, H 6.99, N 4.25; found C 69.45, H 7.12, N 4.11.

Benzoquinolizidine 2a: Major isomer, m.p. 132−133°C. − ^{1}H NMR: δ = 1.24−1.91 (m, 7 H, CH_2), 2.39 (td, *J* = 10.8, 3.3 Hz, 1 H, NCH), 2.60 (dd, *J* = 15.4, 3.3 Hz, 1 H, CH_2Ar), 2.81 (m, 2 H, 1 H CH_2Ar + 1 H NCH_2), 3.82 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.04 (s, 1 H, NCHAr), 5.79 (dd, *J* = 4.9, 1.3 Hz, 2 H, OCH_2O), 6.08 (s, 1 H, aromatic H), 6.49 (s, 1 H, aromatic H), 6.79 (d, *J* = 8.0 Hz, 1 H, aromatic H), 6.80 (s, 1 H, aromatic H), 6.86 (dd, *J* = 8.0, 1.9 Hz, 1 H, aromatic H). − ^{13}C NMR: δ = 24.3, 26.0, 33.8, 37.5, 53.8, 55.8 (s, OCH_3), 55.9 (s, OCH_3), 58.0, 71.8, 100.5, 107.1, 108.0, 110.5, 111.9, 121.8, 127.1, 131.7, 137.5, 145.5, 145.6, 149.1, 150.8. − $C_{22}H_{25}NO_4$ (367.45): calcd. C 71.93, H 6.81, N 3.81; found C 71.97, H 6.89, N 3.76.

Benzoquinolizidine 2b: Major isomer, m.p. 124−125°C (ref.[18] 123°C). − ^{1}H NMR: δ = 1.31−1.90 (m, 7 H, CH_2), 2.37 (td, *J* = 10.5, 3.3 Hz, 1 H, NCH), 2.61 (dd, *J* = 15.3, 3.3 Hz, 1 H, CH_2Ar), 2.79 (m, 2 H, 1 H CH_2Ar + 1 H NCH_2), 3.83 (s, 9 H, 3 × OCH_3), 4.03 (s, 1 H, NCHAr), 5.82 (s, 2 H, OCH_2O), 6.15 (s, 1 H, aromatic H), 6.50 (s, 1 H, aromatic H), 6.54 (s, 2 H, aromatic H). − ^{13}C NMR: δ = 24.3, 26.1, 33.8, 37.5, 53.9, 56.1 (s, OCH_3), 57.9, 60.9 (s, OCH_3), 72.5, 100.5, 106.1, 107.2, 107.8, 127.1, 131.3, 136.8, 140.6, 145.5, 145.6, 153.1.

Benzoquinolizidine 2d: Major isomer, m.p. 93−94°C (ref.[18] oil). − ^{1}H NMR: δ = 1.21−1.94 (m, 7 H, CH_2), 2.34 (tt, *J* = 10.8, 3.1 Hz, 1 H, NCH), 2.62 (dd, *J* = 16.1, 3.1 Hz, 1 H, CH_2Ar), 2.84 (m, 2 H, 1 H CH_2Ar + 1 H NCH_2), 4.31 (s, 1 H, NCHAr), 5.83 (dd, *J* = 5.0, 0.9 Hz, 2 H, OCH_2O), 6.19 (s, 1 H, aromatic H), 6.33 (m, 2 H, furanic H), 6.51 (s, 1 H, aromatic H), 7.36 (br. s, 1 H, furanic H). − ^{13}C NMR: δ = 24.2, 25.8, 33.5, 37.1, 54.2, 58.2, 65.2, 100.6, 106.8, 107.5, 109.6, 109.7, 127.4, 128.1, 142.3, 145.8, 146.1, 154.9.

Acknowledgments

We thank Dr. T. G. C. Bird (Zeneca Pharma) for helpful comments on the manuscript and Dr. J.-F. Carpentier for valuable discussions. This research was supported by the Centre National de la Recherche Scientifique and MENESR (grant to S. L.).

[1] [1a] I. S. de la Lande, *Aust. J. Exp. Biol. Med. Sci.* **1948**, *26*, 181−187. − [1b] A. Al-Shamma, S. D. Drake, L. E. Guagliardi, L. A. Mitscher, J. K. Swayze, *Phytochemistry* **1982**, *21*, 485−487. − [1c] E. Krmpotic, N. R. Farnsworth, W. M. Messner, *J. Pharm. Sci.* **1972**, *61*, 1508−1509. − [1d] J. J. Hoffman, D. J. Luzbetak, S. J. Torrance, J. R. Cole, *Phytochemistry* **1978**, *17*, 1448.
[2] A. R. Battersby, R. J. Francis, M. Hirst, E. A. Ruveda, J. Staunton, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1140−1147.
[3] R. S. Mali, S. D. Patil, S. L. Patil, *Tetrahedron* **1986**, *42*, 2075−2082.
[4] N. Sotomayor, E. Domínguez, E. Lete, *J. Org. Chem.* **1996**, *61*, 4062−4072.
[5] P. Lienard, J. C. Quirion, H. P. Husson, *Tetrahedron* **1993**, *49*, 3995−4006.
[6] [6a] S. B. Horwitz, J. D. Loike, *Lloydia* **1977**, *40*, 82−89. − [6b] S. G. Weiss, M. Tin-Wa, R. E. Perdue, N. R. Farnsworth, *J. Pharm. Sci.* **1975**, *64*, 95−98.
[7] F. Cortese, B. Bhattacharyya, J. Wolff, *J. Biol. Chem.* **1977**, *252*, 1134−1140.
[8] P. Lienard, J. Royer, J. C. Quirion, H. P. Husson, *Tetrahedron Lett.* **1991**, *32*, 2489−2492.
[9] A. Couture, E. Deniau, P. Grandclaudon, C. Hoarau, *J. Org. Chem.* **1998**, *63*, 3128−3132.
[10] A. Couture, E. Deniau, P. Grandclaudon, P. Woisel, *Tetrahedron* **1996**, *52*, 4433−4448.
[11] A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **1997**, *53*, 10313−10330.
[12] A. Couture, E. Deniau, P. Woisel, P. Grandclaudon, J. F. Carpentier, *Tetrahedron Lett.* **1996**, *37*, 3697−3700.
[13] T. Kametani, K. Fukumoto, *Heterocycles* **1975**, *3*, 311−341.
[14] L. E. Overman, M. Kakimoto, M. E. Okazaki, G. P. Meier, *J. Am. Chem. Soc.* **1983**, *105*, 6622−6629.
[15] A. Couture, E. Deniau, S. Lebrun, P. Grandclaudon, J. F. Carpentier, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1403−1407.
[16] C. Sonesson, M. Larhed, C. Nyqvist, A. Hallberg, *J. Org. Chem.* **1996**, *61*, 4756−4763.
[17] C. Sonesson, H. Wikstroem, M. W. Smith, K. Svensson, A. Carlsson, N. Waters, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 241−246.
[18] R. P. Polniaszek, S. E. Belmont, R. Alvarez, *J. Org. Chem.* **1990**, *55*, 215−223.
[19] R. A. Ewin, K. Jones, C. G. Newton, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1107−1111.
[20] T. K. Highsmith, A. I. Meyers, in *Advances in Heterocyclic Natural Product Synthesis* (Ed.: W. H. Pearson), JAI Greenwich, CT, **1990**, vol. 1, p. 95−135.
[21] R. E. Gawley, P. Zhang, *J. Org. Chem.* **1996**, *61*, 8103−8112.
[22] Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758.
[23] P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552−560.
[24] M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297−310.
[25] D. M. Tschaen, L. Abramson, D. Cai, R. Desmond, U. H. Dolling, L. Frey, S. Karady, Y.-J. Shi, T. R. Verhoeven, *J. Org. Chem.* **1995**, *60*, 4324−4330.
[26] T. Morimoto, N. Nakajima, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 75−78.
[27] R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117−7119.
[28] G. Lefèbvre, J. Seyden-Penne, *J. Chem. Soc., Chem. Commun.* **1970**, 1308−1309.
[29] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405−4408.
[30] S. K. Thompson, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 3386−3388.
[31] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863−927.
[32] H. J. Hensel, P. L. Fuchs, *Synth. Commun.* **1986**, *16*, 1285−1295.
[33] A. Couture, E. Deniau, P. Grandclaudon, S. Lebrun, *Tetrahedron Lett.* **1996**, *37*, 7749−7752.
[34] N. C. Yang, G. R. Lenz, *Tetrahedron Lett.* **1967**, 4897−4800.
[35] D. Bellus, *Adv. Photochem.* **1978**, *8*, 109−113.
[36] I. Ninomiya, T. Naito, *Alkaloids* **1983**, *22*, 189−279.
[37] K. Ogawa, Y. Nomura, Y. Takeuchi, S. Tomoda, *J. Chem. Soc., Perkin Trans. 1* **1982**, 3031−3035.
[38] G. P. Claxton, L. Allen, J. M. Grisar, *Org. Synth. Coll. Vol. VI* **1988**, 968−971.
[39] R. C. Miller, *J. Org. Chem.* **1959**, *24*, 2013−2015.
[40] J. P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, M. C. Caño de Andrade, J. A. Laffite, *Tetrahedron: Asymmetry* **1994**, *5*, 665−674.
[41] B. Heiser, E. A. Broger, Y. Crameri, *Tetrahedron: Asymmetry* **1991**, *2*, 51−62.

Received March 4, 1999
[O99149]