# A new route to ene carbamates, precursors to benzoindolizinones through sequential asymmetric hydrogenation and cyclization

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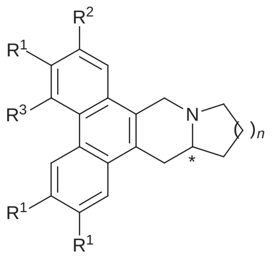
**New pyrrolidine-based ene carbamates have been efficiently synthesized and the first example of asymmetric hydrogenation of this kind of substrate is reported, leading to the preparation of 2-arylmethylpyrrolidine precursors to benzoindolizinones in high yields and enantioselectivities up to 57%.**

## Introduction

A variety of stereogenic centres is found in natural products, especially in alkaloids, but a particularly common feature of these architecturally sophisticated compounds is the presence of a chiral centre adjacent to nitrogen in a five- or six-membered ring. In particular a large variety of alkaloids such as tylocrebine **1**, tylophorine **2**, antofine **3** and cryptopleurine **4**



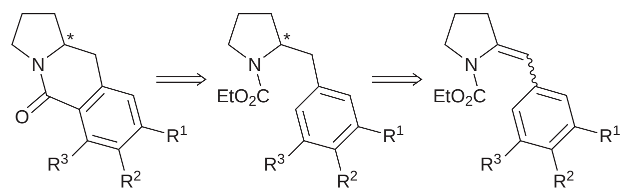
**1** $n = 1$, $R^1 = R^3 = OMe$, $R^2 = H$
**2** $n = 1$, $R^1 = R^2 = OMe$, $R^3 = H$
**3** $n = 1$, $R^1 = OMe$, $R^2 = R^3 = H$
**4** $n = 2$, $R^1 = OMe$, $R^2 = R^3 = H$

possess a 2-arylmethyl-pyrrolidine or -piperidine unit with a stereogenic centre and it is important for organic chemists to solve the problem of stereocontrol at this centre.

The enantioselective alkylation α to nitrogen in a number of acyclic systems or saturated heterocycles has attracted considerable attention over the last decade. Groups that have tackled this challenge have adopted cation methodology[1] or radical chemistry[2] but methods based on carbanion chemistry have enjoyed increasing popularity in recent years.[3] Generally the process involves activation of the nitrogen by an electron withdrawing group followed by deprotonation of diastereotopic protons and electrophilic attack of the intermediate dipole-stabilized carbanions. The generation of the asymmetric centre α to N is generally achieved by stoichiometric chirality transfer from a chiral precursor[4] or by mediation of the metallation–alkylation sequence with enantiopure inductors such as (−)-sparteine.[5] However to our knowledge application of these concepts to stereoselective incorporation of arylmethyl groups *via* their halide or trifluoromethanesulfonate derivatives has been mainly confined to *N*-alkoxycarbonyl protected benzylamines.[5,6]

## Results and discussion

In the course of our continuing efforts towards the synthesis and reactivity of *N*-acyl enamine derivatives[7] we launched a project related to the asymmetric catalytic synthesis of *N*-protected 2-arylmethylpyrrolidine derivatives assuming that these compounds could be accessible by enantioselective hydrogenation of dehydro-precursors. A survey of the literature revealed that since the pioneering work of Takaya and Noyori,[8] there have been only a few known examples of simple enamides which have been reduced with high enantioselectivity.[9] On the other hand the harsh acidic conditions required to regenerate the free amine have often plagued the tertiary carboxamide systems. For these different reasons we first turned our attention to a non-reported process so far, *i.e.* the enantioselective hydrogenation of ene carbamates and particularly of the *N*-ethoxycarbonyl derivatives **7** (retrosynthetic Scheme 1) which might



**5** **6** **7**

**Scheme 1**

offer, if feasible, a double advantage. Indeed the *N*-ethoxycarbonyl group of the hydrogenated compounds **6** can be easily removed under mild basic conditions. It may also be involved in an annulation process giving rise to the tricyclic isoquinolinones **5** and after reduction to the benzoindolizine ring system with stereocontrol of the chiral centre embedded in the skeleton.[10]

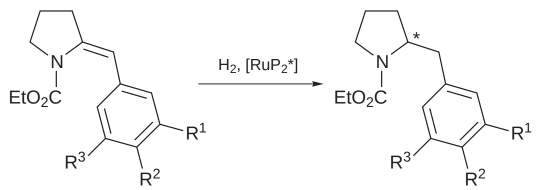
Initially the ene carbamates **7a–d** were prepared in the three step sequence depicted in Scheme 2.[11] The phosphorylated cyclic amine **10** readily prepared by addition of diphenylphosphine oxide **9** to the triazine **8** was treated with ethyl chloroformate to afford the phosphorylated carbamate **11** quantitatively. Compound **11** was then smoothly deprotonated at −78 °C with Bu$^n$Li in THF and then treated with suitably substituted aldehydes **12a–d**. Warming the reaction mixture to room temperature ensured completion of the reaction and the *N*-ethoxycarbonyl-2-arylmethylenepyrrolidines **7a–d** were quantitatively formed and isolated in high yields by this protocol (Scheme 2, Table 1). Ene carbamates **7a–d** were invariably obtained as mixtures of *Z*- and *E*-isomers which fortunately were interconvertible by irradiation. Exposure of the initial mixture of *Z*- and *E*-isomers to UV light (Rayonet RPR208, 254 nm, $Et_2O$, 4 h) afforded a photostationary 1:1 mixture of the *Z*- and *E*-isomers which were easily separated by flash chromatography. Repetition of this procedure twice on the *E*-

**Table 1** Ene carbamates **7a–d** and 2-arylmethylpyrrolidines **6a–d** prepared

| | | | | Ene carbamates | | | 2-Arylmethylpyrrolidines | | |
|---|---|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | Aldehyde | | *E*/*Z* ratio (Yield %)[a] | Photoisomerization, *Z*, Yield (%)[b] | | Method A[c] Yield (%) | Method B[d] Yield (%) |
| $OCH_2O$ | | H | **12a** | **7a** | 75:25 (85%) | 62 | **6a** | 85 | 92 |
| $OCH_3$ | $OCH_3$ | H | **12b** | **7b** | 70:30 (80%) | 67 | **6b** | 89 | 95 |
| $OCH_3$ | $OCH_3$ | $OCH_3$ | **12c** | **7c** | 80:20 (75%) | 65 | **6c** | 80 | 86 |
| H | H | H | **12d** | **7d** | 75:25 (85%) | 70 | **6d** | 91 | 93 |

[a] Isolated yield calculated on the basis of **11**. [b] Yield calculated after three photoisomerization processes. [c] Method A: 5% Rh/C, MeOH, 25 atm $H_2$, 80 °C, 4–15 h. [d] Method B: 10% Pd/C, $HCO_2NH_4$, MeOH, reflux, 2 h.

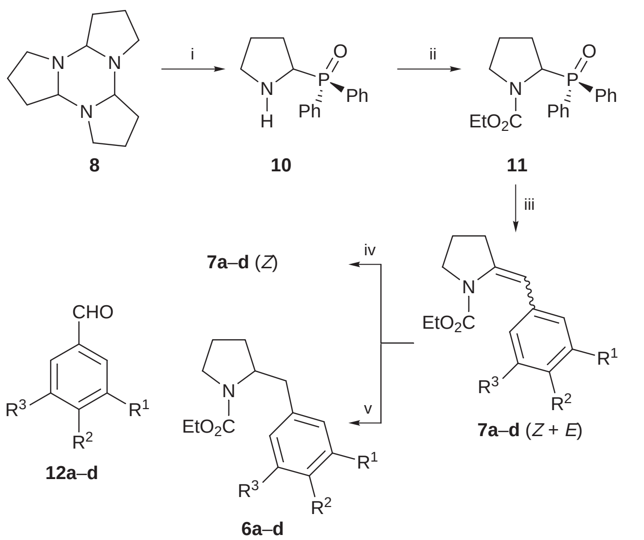
**Table 2** Asymmetric hydrogenation of ene carbamates **7a–d** into **6a–d**[a]




**7a–d** (*Z*)-isomer **6a–d**

| Entry | Substrate | Catalyst | $H_2$ (atm) | *T*/h | Product (Yield %) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | (*Z*)-**7a** | {[(*S*)-BINAP]$RuCl_2$}$_2$·$NEt_3$ | 5 | 24 | **6a** (100) | 31 (−) |
| 2 | (*Z*)-**7a** | {[(*S*)-BINAP]$RuCl_2$}$_2$·$NEt_3$ | 25 | 24 | **6a** (100) | 15 (−) |
| 3 | (*Z*)-**7a** | [(*S*)-BINAP](*p*-Cym)RuCl | 5 | 18 | **6a** (98) | 33 (−) |
| 4 | (*Z*)-**7a** | [(*S*)-TolBINAP]$RuBr_2$ | 5 | 24 | **6a** (95) | 39 (−) |
| 5 | (*Z*)-**7a** | [(*S*)-MeOBIPHEP]$RuBr_2$ | 10 | 20 | **6a** (98) | 35 (−) |
| 6 | (*Z*)-**7a** | [(*R*)-BINAP]Ru$(OAc)_2$ | 5 | 21 | **6a** (100) | 53 (+) |
| 7 | (*Z*)-**7a** | [(*R*)-BINAP]Ru$(TFA)_2$ | 5 | 18 | **6a** (100) | 57 (+)[d] |
| 8 | (*E*)-**7a** | [(*R*)-BINAP]Ru$(TFA)_2$ | 5 | 24 | **6a** (0) | — |
| 9 | (*Z*)-**7b** | [(*R*)-BINAP]Ru$(TFA)_2$ | 5 | 46 | **6b** (100) | 37 (+) |
| 10 | (*Z*)-**7c** | [(*R*)-BINAP]Ru$(TFA)_2$ | 5 | 48 | **6c** (100) | 18 (+) |
| 11 | (*Z*)-**7d** | [(*R*)-BINAP]Ru$(TFA)_2$ | 5 | 18 | **6d** (100) | 54 (+) |

[a] Reaction conditions unless otherwise stated: 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*)-**7a–d** into **6a–d** as determined by $^1H$ NMR spectroscopy and HPLC analysis. [c] Enantiomeric excesses were determined by HPLC analysis of the *N*-1-naphthoyl derivative with a SUPELCOSIL (*R*)-DNBPG column (hexane–propan-2-ol 95:5, 1 ml min$^{-1}$, UV detector 254 nm). [d] $[\alpha]_D^{25}$ (*c* 1, $CHCl_3$) +3.




**Scheme 2** *Reagents and conditions*: i, $Ph_2P(O)H$ **9**, toluene, reflux; ii, $ClCO_2Et$, $NEt_3$, toluene, 0 °C; iii, BuLi, THF, −78 °C then **12a–d**, THF, −78 °C to rt; iv, *hν*, $Et_2O$, 254 nm; v, $H_2$, Rh/C, MeOH, 80 °C (Method A) or $HCO_2NH_4$, Pd/C, MeOH, reflux (Method B)

isomer allowed the stereoselective preparation of *Z*-configured 2-arylmethylene substrates with very satisfactory yields (Table 1).

Our preliminary results for the asymmetric hydrogenation of ene carbamates **7a–d** giving the protected 2-arylmethylpyrrolidines **6a–d** are reported in Table 2. Enantiomeric excesses were determined using racemic samples which were easily obtained in quantitative yield with heterogeneous catalysts (5% Rh/C, MeOH, 25 atm $H_2$, 80 °C, 4–15 h or 10% Pd/C, $HCO_2NH_4$, MeOH, reflux, 2 h) (Scheme 2, Table 1). The efficiency of the enantioselective ruthenium-based catalyst† and reaction conditions was examined using substrate **7a**. In direct agreement with previous results obtained in asymmetric hydrogenation of enamides,[8] the *Z*-configured olefin was found to be much more reactive than the corresponding *E*-stereoisomer, justifying the above described selective preparation of *Z*-ene carbamates **7a–d**. Thus, the reaction of (*Z*)-**7a** in a mixture of methanol–dichloromethane (5:1) at 30 °C under an initial hydrogen pressure of 5 atm in the presence of 0.5 mol% of commercially available {[(*S*)-BINAP]$RuCl_2$}$_2$·$NEt_3$ gave (−)-**6a** in 100% yield but in only 31% ee (entry 1). Increase in hydrogen pressure decreased the enantioselectivity to a great extent, as under 25 atm the ee was lowered to 15% (entry 2). Use of another purchased catalyst precursor [(*S*)-BINAP](*p*-Cymene)RuCl as well as variation of the atropisomeric chiral ligand in freshly prepared $RuBr_2$(diphosphine) type catalysts[12] led to comparable ee values ranging from 33–39% ee (entries 3–5). A slight improvement in terms of enantioselectivity was gained with $Ru^{II}$-dicarboxylato-BINAP complexes[13] which afforded (+)-**6a** in up to 57% ee (entries 6 and 7). Also, structural modification at the aryl moiety of the substrate was found to affect the catalyst

† Attempted hydrogenation experiments with Rh(COD)[(*R*)-BINAP]-$(ClO_4)$ failed to give **6a**.

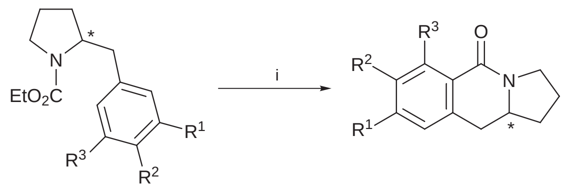
**Table 3** Benzoindolizinones **5a–c** prepared from **6a–c**

| 5 | $R^1$ | $R^2$ | $R^3$ | Yield (%) | $[\alpha]_D^{25}$ | ee (%) |
|---|---|---|---|---|---|---|
| **a** | $OCH_2O$ | | H | 78 | −66[a] | 57 |
| **b** | $OCH_3$ | $OCH_3$ | H | 70 | −34[a] | 37 |
| **c** | $OCH_3$ | $OCH_3$ | $OCH_3$ | 76 | +15[b] | 18 |

[a] $[\alpha]_D^{25}$ (*c* 1, $CHCl_3$). [b] $[\alpha]_D^{25}$ (*c* 0.54, $CHCl_3$).

enantioselectivity. Namely, di- and tri-methoxy derivatives **6b** and **6c** were produced in only 37 and 18% ee, respectively, while the enantioselectivity for the unsubstituted-phenyl compound **6d** was almost unchanged compared to that of **6a** (entries 9–11).

The cyclization of the enantio-enriched 2-arylmethylpyrrolidines **6a–c** under the usual Bischler–Napieralski reaction conditions which are known to occur without racemization[14] proceeded uneventfully and, as anticipated, treatment of compounds **6a–c** with phosphorous oxychloride in refluxing toluene delivered the benzoindolizinones **5a–c** with fairly good yields (Scheme 3). Table 3 summarizes the yields, ees and optical rotation values obtained for these compounds.



**6a–c** **5a–c**

**Scheme 3** *Reagents and conditions*: i, $POCl_3$, toluene, reflux

## Conclusion

In conclusion, the ene carbamate synthesis, consecutive hydrogenation and subsequent cyclization reactions reported herein proceed in high yields and afford an efficient access to benzoindolizine ring systems. Unfortunately the enantioselectivities (so far obtained with the catalysts used) of the hydrogenation products of ene carbamates are significantly lower than those obtained under similar conditions for some enamides.[8,9a] This could be due to the different coordinating ability of the carbamate moiety onto the metal centre compared to *N*-formyl and *N*-acyl functions, and/or to the structural peculiarity of compounds **7a–d**. Further work in this direction is in progress.

## Experimental

### General methods

Mps were determined on a Reichert-Thermopan apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrometer. $^1H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer and were referenced against internal tetramethylsilane; $^{31}P$ NMR (121 MHz) spectra were referenced against $H_3PO_4$ as external standard. Coupling constants ($J$) are given in Hz and rounded to the nearest 0.1 Hz. Mass spectral analyses were performed on a Ribermag 10-10 mass spectrometer. Elemental analyses were determined by the CNRS microanalysis centre. TLC was performed with plates coated with Kieselgel G (Merck). The plates were developed with hexane–ethyl acetate. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use and dichloromethane ($CH_2Cl_2$) was distilled from $CaH_2$. Toluene was distilled from Na under Ar and methanol, ethanol and isopropanol from magnesium turnings.

### Starting materials

Triazine **8**[15] and diphenylphosphine oxide **9**[16] were prepared according to the literature methods.

2-Diphenylphosphinylpyrrolidine **10** was prepared in the following manner. A solution of triazine **8** (2.07 g, 10 mmol) and diphenylphosphine oxide **9** (6.06 g, 30 mmol) in toluene (100 ml) was refluxed for 3 h. Toluene was removed under vacuum and the crude product was triturated with $Et_2O$, filtered and finally purified by recrystallization from hexane–toluene (7.6 g, 94%), mp 109–110 °C (Found: C, 70.7; H, 6.8; N, 5.0. $C_{16}H_{18}NOP$ requires C, 70.85; H, 6.7; N, 5.2%); $\nu_{max}$(KBr)/cm$^{-1}$ 3420 (NH), 1431 (PPh) and 1191 (PO); $\delta_H$($CDCl_3$) 1.62–1.86 (2 H, m, $CH_2$), 1.85–2.22 (3 H, m, $CH_2$ + N-H), 2.85–3.04 (2 H, m, $NCH_2$), 3.86 (1 H, td, *J* 8.3, 3.5, CH-P), 7.34–7.62 (6 H, m, $H_{arom}$), 7.73–8.05 (4 H, m, $H_{arom}$); $\delta_C$($CDCl_3$) C, 131.3 (d, *J* 95.8); CH, 56.6 (d, *J* 85.7), 128.4 (d, *J* 11.5), 130.4 (d, *J* 11.5), 131.0 (d, *J* 8.5), 131.7 (d, *J* 8.5); $CH_2$, 26.2 (d, *J* 6.1), 26.4, 48.1 (d, *J* 8.5); $\delta_P$($CDCl_3$) 31.4; *m*/*z* 271 ($M^+$, 2%), 201 (12) and 71 (100).

2-Diphenylphosphinyl-1-ethoxycarbonylpyrrolidine **11** was prepared in the following manner. A solution of ethyl chloroformate (2.4 g, 22 mmol) in dry toluene (10 ml) was added dropwise under Ar to a cooled (0 °C) solution of the phosphorylated amine **10** (5.42 g, 20 mmol) and $Et_3N$ (2.02 g, 20 mmol) in toluene (30 ml). Stirring was maintained for 3 h at 0 °C, the reaction mixture was filtered and the filtrate washed twice with water (2 × 30 ml) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography using acetone–hexane (4:1) as eluent. Recrystallization from hexane–toluene afforded the phosphorylated carbamate **11** (5.83 g, 85%), mp 81–82 °C (Found: C, 66.4; H, 6.4; N, 4.1. $C_{19}H_{22}NO_3P$ requires C, 66.5; H, 6.45; N, 4.1%); $\nu_{max}$(KBr)/cm$^{-1}$ 1690 (CO) and 1185 (PO); $\delta_H$($CDCl_3$: this compound was a mixture of two rotational isomers, ratio 3:2) 0.98 (3/5 × 3 H, br s, $CH_3$), 1.09 (2/5 × 3 H, t, *J* 7.0, $CH_3$), 1.66–2.34 (4 H, m, 2 × $CH_2$), 3.34 (2/5 × 2 H, q, *J* 7.0, $CO_2CH_2$), 3.27–3.51 (3/5 × 4 H, m, $NCH_2$ + $CO_2CH_2$), 3.72–3.83 (2/5 × 2 H, br s, $NCH_2$), 4.61–4.66 (3/5 × 1 H, br s, CH-P), 4.72–4.78 (2/5 × 1 H, br s, CH-P), 7.09–7.72 (10 H, m, $H_{arom}$); $\delta_C$($CDCl_3$) C, 130.7 (d, *J* 90.8), 150.1 (CO); CH, 57.5 (d, *J* 72.6), 57.7 (d, *J* 76.9), 128.6 (d, *J* 11.0), 130.9 (d, *J* 8.0), 131.4 (d, *J* 7.3); $CH_2$, 23.8, 25.0, 26.3, 27.2, 46.8, 47.4, 61.0; $CH_3$, 14.5; $\delta_P$($CDCl_3$: mixture of two rotational isomers, ratio 3:2) 30.8 (minor isomer), 31.4 (major isomer); *m*/*z* 343 ($M^+$, 5%), 201 (21) and 71 (100).

### General procedure for the synthesis of ene carbamates 7a–d

A commercial solution of Bu$^n$Li (1.6 M in hexanes, 2 ml, 3.2 mmol) was added dropwise to a solution of **11** (1 g, 29 mmol) in THF (30 ml) at −78 °C under Ar. After completion of the addition the mixture was stirred at −78 °C for 15 min. A solution of the appropriate aldehyde **12a–d** (2.9 mmol) in THF (5 ml) was then added. After being stirred at −78 °C for 15 min the reaction mixture was allowed to come to room temperature over 2 h. Aqueous $NH_4Cl$ (10%, 50 ml) was added and the organic layer separated. The aqueous layer was extracted with $Et_2O$ (2 × 30 ml) and the combined organic layers were washed successively with water and brine and finally dried over $MgSO_4$. Evaporation of the solvent furnished an oily product which was purified by flash column chromatography using ethyl acetate–hexanes (50:50) as eluent.

**2-[3,4-(Methylenedioxy)phenylmethylene]-1-ethoxycarbonylpyrrolidine 7a.** This compound was a mixture of *E* and *Z* isomers. (*E*)-Isomer, mp 53–54 °C (Found: C, 65.6; H, 6.0; N, 4.9. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.2; N, 5.1%); $\delta_H$($CDCl_3$) 1.29 (3 H, t, *J* 7.1, $CH_3$), 1.78–1.84 (2 H, m, $CH_2$), 2.73 (2 H, td,

$J$ 7.4, 2.0, $=CCH_2$), 3.64 (2 H, t, $J$ 7.0, $NCH_2$), 4.20 (2 H, q, $J$ 7.1, $CO_2CH_2$), 5.89 (2 H, s, $OCH_2O$), 6.64–6.73 (3 H, m, $H_{arom}$), 7.08 (1 H, br s, =CH); $\delta_C(CDCl_3)$ C, 132.7, 139.5, 144.9, 147.3, 153.0 (CO); CH, 107.6 (=CH), 107.8, 108.3, 121.3; $CH_2$, 21.9, 30.0, 48.2, 60.9, 100.7; $CH_3$, 14.4. (*Z*)-Isomer (an oil); $\delta_H(CDCl_3)$ 0.89 (3 H, t, $J$ 7.3, $CH_3$), 1.88–1.96 (2 H, m, $CH_2$), 2.49 (2 H, td, $J$ 7.3, 1.5, $=CCH_2$), 3.70 (2 H, t, $J$ 7.1, $NCH_2$), 3.91 (2 H, q, $J$ 7.3, $CO_2CH_2$), 5.75 (1 H, s, =CH), 5.82 (2 H, s, $OCH_2O$), 6.63–6.71 (3 H, m, $H_{arom}$); $\delta_C(CDCl_3)$ C, 132.1, 136.5, 145.3, 147.0, 153.0 (CO); CH, 107.5, 107.7 (=CH), 110.2, 121.0; $CH_2$, 21.2, 32.9, 49.1, 61.2, 100.6 ($OCH_2O$); $CH_3$, 13.8.

**2-[(3,4-Dimethoxyphenyl)methylene]-1-ethoxycarbonylpyrrolidine 7b.** This compound was a mixture of *E* and *Z* isomers. (*E*)-Isomer, mp 66–67 °C (Found: C, 66.1; H, 7.1; N, 4.95. $C_{16}H_{21}NO_4$ requires C, 66.0; H, 7.3; N, 4.8%); $\delta_H(CDCl_3)$ 1.32 (3 H, t, $J$ 7.3, $CH_3$), 1.80–1.94 (2 H, m, $CH_2$), 2.81 (2 H, td, $J$ 7.3, 1.9, $=CCH_2$), 3.68 (2 H, t, $J$ 6.8, $NCH_2$), 3.86 (3 H, s, $OCH_3$), 3.87 (3 H, s, $OCH_3$), 4.23 (2 H, q, $J$ 7.3, $CO_2CH_2$), 6.71–6.93 (3 H, m, $H_{arom}$), 7.18 (1 H, br s, =CH); $\delta_C(CDCl_3)$ C, 131.6, 139.4, 148.0, 149.0, 153.5 (CO); CH, 108.3 (=CH), 111.1, 112.4, 121.5; $CH_2$, 23.9, 30.2, 48.4, 60.5; $CH_3$, 14.6, 55.7, 55.8. (*Z*)-Isomer (an oil); $\delta_H(CDCl_3)$ 0.71–0.86 (3 H, m, $CH_3$), 1.77–1.89 (2 H, m, $CH_2$), 2.44 (2 H, t, $J$ 7.1, $=CCH_2$), 3.66 (2 H, t, $J$ 6.6, $NCH_2$), 3.72 (3 H, s, $OCH_3$), 3.75 (3 H, s, $OCH_3$), 3.88 (2 H, q, $J$ 7.4, $CO_2CH_2$), 5.71 (1 H, s, =CH), 6.62–6.72 (3 H, m, $H_{arom}$); $\delta_C(CDCl_3)$ C, 131.0, 136.6, 147.0, 148.1, 153.6 (CO); CH, 109.9, 110.5 (=CH), 110.6, 120.2; $CH_2$, 21.4, 33.1, 49.4, 61.7; $CH_3$, 13.9, 55.7, 55.8.

**2-[(3,4,5-Trimethoxyphenyl)methylene]-1-ethoxycarbonylpyrrolidine 7c.** This compound was a mixture of *E* and *Z* isomers. (*E*)-Isomer, mp 48–49 °C (Found: C, 63.7; H, 7.3; N, 4.2. $C_{17}H_{23}NO_5$ requires C, 63.55; H, 7.2; N, 4.35%); $\delta_H(CDCl_3)$ 1.32 (3 H, t, $J$ 7.1, $CH_3$), 1.82–1.94 (2 H, m, $CH_2$), 2.82 (2 H, td, $J$ 7.3, 1.9, $=CCH_2$), 3.69 (2 H, t, $J$ 7.1, $NCH_2$), 3.81 (6 H, s, $2 \times OCH_3$), 3.82 (3 H, s, $OCH_3$), 4.23 (2 H, q, $J$ 7.1, $CO_2CH_2$), 6.45 (2 H, s, $H_{arom}$), 7.13 (1 H, s, =CH); $\delta_C(CDCl_3)$ C, 134.5, 140.2, 152.8 (CO), 153.4, 153.5; CH, 105.3, 108.6 (=CH); $CH_2$, 22.1, 30.4, 48.5, 61.2; $CH_3$, 14.6, 55.9, 60.8. (*Z*)-Isomer (an oil); $\delta_H(CDCl_3)$ 0.79–0.91 (3 H, m, $CH_3$), 1.83–1.97 (2 H, m, $CH_2$), 2.45 (2 H, t, $J$ 7.0, $=CCH_2$), 3.62 (2 H, t, $J$ 7.2, $NCH_2$), 3.82 (6 H, s, $2 \times OCH_3$), 3.84 (3 H, s, $OCH_3$), 4.21 (2 H, q, $J$ 7.0, $CO_2CH_2$), 5.68 (1 H, s, =CH), 6.36 (2 H, s, $H_{arom}$); $\delta_C(CDCl_3)$ C, 133.8, 137.6, 152.6 (CO), 152.8, 153.5; CH, 104.6, 110.4 (=CH); $CH_2$, 21.3, 33.1, 49.4, 61.7; $CH_3$, 13.9, 55.9, 60.8.

**2-Phenylmethylene-1-ethoxycarbonylpyrrolidine 7d.** This compound was a mixture of *E* and *Z* isomers. (*E*)-Isomer, mp 58–59 °C (Found: C, 72.65; H, 7.3; N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%); $\delta_H(CDCl_3)$ 1.32 (3 H, t, $J$ 7.2, $CH_3$), 1.81–1.92 (2 H, m, $CH_2$), 2.81 (2 H, td, $J$ 7.2, 1.9, $=CCH_2$), 3.67 (2 H, t, $J$ 7.0, $NCH_2$), 4.24 (2 H, q, $J$ 7.2, $CO_2CH_2$), 7.08–7.35 (6 H, m, 5 $H_{arom}$ + =CH); $\delta_C(CDCl_3)$ C, 138.7, 140.6, 153.7 (CO); CH, 108.7 (=CH), 125.2, 128.1, 128.2; $CH_2$, 22.2, 30.3, 48.6, 61.6; $CH_3$, 14.7. (*Z*)-Isomer; $\delta_H(CDCl_3)$ 0.84 (3 H, t, $J$ 6.7, $CH_3$), 1.96–2.19 (2 H, m, $CH_2$), 2.65 (2 H, t, $J$ 7.3, $=CCH_2$), 3.79–3.88 (2 H, m, $NCH_2$), 3.96 (2 H, q, $J$ 6.7, $CO_2CH_2$), 5.95 (1 H, s, =CH), 7.25–7.31 (5 H, m, $H_{arom}$); $\delta_C(CDCl_3)$ C, 137.8, 138.3, 153.6 (CO); CH, 110.6 (=CH), 125.8, 127.5, 127.8; $CH_2$, 21.4, 33.4, 49.4, 61.7; $CH_3$, 13.7.

### General procedure for the hydrogenation of ene carbamates 7a–d

A suspension of compounds **7a**–**d** (2 mmol) in methanol (30 ml) was vigorously stirred with Pd/C (10%, 20 mg) and subsequently treated with a solution of $HCO_2NH_4$ (640 mg, 10 mmol) in distilled water (5 ml). The reaction mixture was refluxed for 2 h, filtered on Celite, and water (30 ml) and $CH_2Cl_2$ (10 ml) were added. The organic layer was dried over $MgSO_4$. Concentration *in vacuo* left an oily product which was purified by column chromatography using ethyl acetate–hexanes (3:7) as eluent.

**2-[3,4-(Methylenedioxy)phenylmethyl]-1-ethoxycarbonylpyrrolidine 6a.** An oil (Found: C, 64.7; H, 7.0; N, 5.2. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.05%); $\nu_{max}$(KBr)/cm$^{-1}$ 1695 (CO); $\delta_H$($CDCl_3$: since this compound was a mixture of two rotational isomers some peaks were broadened) 1.07 (3 H, t, $J$ 6.9, $CH_3$), 1.48–1.62 (4 H, m, $2 \times CH_2$), 2.26 (1 H, dd, $J$ 13.3, 9.1, $CH_2Ar$), 2.73 (1 H, d, $J$ 13.3, $CH_2Ar$), 3.12–3.19 (2 H, m, $NCH_2$), 3.70–3.78 (1 H, NCH), 3.94 (2 H, q, $J$ 6.9, $CO_2CH_2$), 5.66 (2 H, s, $OCH_2O$), 6.38–6.61 (3 H, m, $H_{arom}$); $\delta_C$($CDCl_3$: this compound was a mixture of two rotational isomers, ratio 1:1) C, 132.5, 145.8, 147.5, 154.8 (CO); CH, 58.6 and 59.0, 107.8, 109.4, 122.0; $CH_2$, 22.4 and 23.3, 28.6 and 29.5, 38.9 and 40.0, 46.3 and 46.4, 60.5, 100.6 ($OCH_2O$); $CH_3$, 14.6; *m/z* 277 ($M^+$, 21%) and 142 (100).

**2-[(3,4-Dimethoxyphenyl)methyl]-1-ethoxycarbonylpyrrolidine 6b.** An oil (Found: C, 65.4; H, 8.0; N, 4.8. $C_{16}H_{23}NO_4$ requires C, 65.5; H, 7.9; N, 4.8%); $\nu_{max}$(KBr)/cm$^{-1}$ 1690 (CO); $\delta_H$($CDCl_3$: since this compound was a mixture of two rotational isomers some peaks were broadened) 1.21 (3 H, t, $J$ 7.1, $CH_3$), 1.56–1.69 (4 H, m, $2 \times CH_2$), 2.44 (1 H, dd, $J$ 13.2, 9.3, $CH_2Ar$), 2.95 (1 H, dd, $J$ 13.2, 2.0, $CH_2Ar$), 3.16–3.23 (2 H, m, $NCH_2$), 3.75 (3 H, s, $OCH_3$), 3.77 (3 H, s, $OCH_3$), 3.85–3.97 (1 H, m, NCH), 4.07 (2 H, q, $J$ 7.1, $CO_2CH_2$), 6.58–6.72 (3 H, m, $H_{arom}$); $\delta_C$($CDCl_3$: this compound was a mixture of two rotational isomers, ratio 1:1) C, 131.6, 147.5, 148.7, 155.1 (CO); CH, 59.1 and 58.6, 111.0, 112.5, 121.4; $CH_2$, 22.6 and 23.4, 28.8 and 29.6, 38.9 and 40.0, 46.4 and 46.6, 60.6; $CH_3$, 14.8, 55.7; *m/z* 293 ($M^+$, 12%) and 142 (100).

**2-[(3,4,5-Trimethoxyphenyl)methyl]-1-ethoxycarbonylpyrrolidine 6c.** An oil (Found: C, 63.05; H, 7.8; N, 4.5. $C_{17}H_{25}NO_5$ requires C, 63.15; H, 7.8; N, 4.3%); $\nu_{max}$(KBr)/cm$^{-1}$ 1695 (CO); $\delta_H$($CDCl_3$: since this compound was a mixture of two rotational isomers some peaks were broadened) 1.17 (3 H, t, $J$ 7.0, $CH_3$), 1.56–1.78 (4 H, m, $2 \times CH_2$), 2.33 (1 H, dd, $J$ 12.9, 9.6, $CH_2Ar$), 2.92 (1 H, d, $J$ 12.9, $CH_2Ar$), 3.17–3.33 (2 H, m, $NCH_2$), 3.68 (6 H, s, $2 \times OCH_3$), 3.74 (3 H, s, $OCH_3$), 3.87–3.96 (1 H, m, NCH), 4.04 (2 H, q, $J$ 7.0, $CO_2CH_2$), 6.29 (2 H, s, $H_{arom}$); $\delta_C$($CDCl_3$: this compound was a mixture of two rotational isomers, ratio 1:1) C, 134.7, 150.6, 153.0, 155.0 (CO); CH, 58.6 and 59.1, 106.2; $CH_2$, 22.6 and 23.4, 28.9 and 29.9, 39.7 and 40.9, 46.3 and 46.4, 60.2; $CH_3$, 14.7, 55.9, 60.6; *m/z* 323 ($M^+$, 21%), 187 (17) and 142 (100).

**2-Phenylmethyl-1-ethoxycarbonylpyrrolidine 6d.** An oil (Found: C, 72.0; H, 8.2; N, 6.1. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%); $\nu_{max}$(KBr)/cm$^{-1}$ 1693 (CO); $\delta_H$($CDCl_3$: since this compound was a mixture of two rotational isomers some peaks were broadened) 1.27 (3 H, t, $J$ 7.1, $CH_3$), 1.62–1.83 (4 H, m, $2 \times CH_2$), 2.54 (1 H, dd, $J$ 13.0, 9.4, $CH_2Ar$), 2.92–3.36 (3 H, m, $NCH_2$ + 1 H $CH_2Ar$), 3.92–4.06 (1 H, m, NCH), 4.12 (2 H, q, $J$ 7.1, $CO_2CH_2$), 7.15–7.46 (5 H, m, $H_{arom}$); $\delta_C$($CDCl_3$: this compound was a mixture of two rotational isomers, ratio 1:1) C, 139.0, 155.2 (CO); CH, 58.7 and 59.2, 126.2, 128.3, 129.4, 129.5; $CH_2$, 22.6 and 23.5, 28.9 and 29.7, 39.5 and 40.5, 46.5 and 46.6, 60.8; $CH_3$, 14.8; *m/z* 233 ($M^+$, 12%) and 91 (100).

### General procedure for the photoisomerization process

A solution of the ene carbamate (*E*)-**7a**–**d** (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* 1:1) was obtained after 4 h. The solvent was evaporated under vacuum and the residue purified by flash column chromatography with ethyl acetate–hexanes (3:7) as eluent. Compounds (*Z*)-**7a**–**d** and (*E*)-**7a**–**d** were isolated and the photochemical protocol was repeated twice with the *E*-isomer. Yields are reported in Table 1.

**General procedure for asymmetric hydrogenation**

$\{[(S)\text{-BINAP}]RuCl_2\}_2\cdot NEt_3$ and $[(S)\text{-BINAP}](p\text{-Cymene})$-RuCl are commercially available. $[(S)\text{-TolBINAP}]RuBr_2$ and $[(S)\text{-MeOBIPHEP}]RuBr_2$,[13] $[(R)\text{-BINAP}]Ru(OAc)_2$ and $[(R)\text{-BINAP}]Ru(TFA)_2$ (ref. 14) were prepared as previously described. All the reactions were performed under anaerobic conditions using standard Schlenk techniques. In a typical experiment, a solution of the (*Z*)-ene carbamate **7a**–**d** (1 mmol) in methanol (10 ml) and $CH_2Cl_2$ (2 ml) was degassed by two freeze–thaw cycles and then transferred on the solid catalyst precursor ($5 \times 10^{-3}$ mmol). The resulting solution was transferred in a 100 ml stainless steel autoclave, hydrogen (99%, Air Liquide) was introduced (5–25 atm) and the reaction mixture was magnetically stirred at 30 °C. After the desired reaction time (18–48 h) the hydrogen was removed and the solution was concentrated *in vacuo*.

For the determination of the enantiomeric excesses the carbamates **6a**–**d** were converted into their *N*-1-naphthoyl analogs in the following manner. A solution of the carbamate **6a**–**d** (1.3 mmol) and KOH (100 mg, 1.8 mmol) in isopropanol (10 ml) was refluxed for 12 h. The solvent was removed under vacuum, the residue was dissolved in $CH_2Cl_2$ (20 ml) and then washed with water ($2 \times 10$ ml). The organic layer was dried ($MgSO_4$), concentrated under vacuum and the residue was dissolved in toluene (10 ml). $NEt_3$ (55 mg, 0.54 mmol) was added and a solution of 1-naphthoyl chloride (75 mg, 0.4 mmol) in toluene (2 ml) was added dropwise with stirring under Ar at 0 °C. The reaction mixture was stirred for an additional 2 h, filtered, washed with water ($2 \times 10$ ml) and dried ($MgSO_4$). Concentration *in vacuo* left a residue which was directly analyzed by HPLC [Supelcosil (*R*)-DNBPG column] with hexane–isopropanol (**6a**–**c**, 95:5; **6d**, 98:2) as eluent. Flow rate 1.0 ml $min^{-1}$. UV detection at 254 nm; $t_R$ of the naphthoyl derivatives (−) and (+) of **6a** (46.7 min; 50.7 min), **6b** (51.0 min; 54.5 min), **6c** (142.6 min; 148.5 min), **6d** (64.3 min; 68.2 min).

**General procedure for the synthesis of the annulated products 5a–c**

A solution of the arylmethylpyrrolidine **6a**–**c** (2 mmol) and phosphorous oxychloride (5 ml, 53.6 mmol) was refluxed in toluene (20 ml) for 2 h. The solvent was removed *in vacuo*, $CH_2Cl_2$ (30 ml) was added and the organic solution was washed twice with aqueous NaOH (10%, $2 \times 20$ ml) then with water (20 ml) and dried. The solvent was removed under vacuum and the product was purified by flash column chromatography with ethyl acetate–hexanes (2:3) as eluent and finally recrystallized from $Et_2O$–hexane.

**5,7,8,9,9a,10-Hexahydro-[1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]-isoquinolin-5-one 5a.** Mp 157–158 °C (Found: C, 67.3; H, 5.9; N, 6.2. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.7; N, 6.05%); $\nu_{max}$(KBr)/$cm^{-1}$ 1643 (CO); $\delta_H$($CDCl_3$) 1.58–1.73 (1 H, m, $CH_2$), 1.76–1.88 (1 H, m, $CH_2$), 1.98–2.07 (1 H, m, $CH_2$), 2.17–2.28 (1 H, m, $CH_2$), 2.71 (1 H, d, *J* 14.3, $CH_2Ar$), 2.86 (1 H, dd, *J* 14.3, 4.1, $CH_2Ar$), 3.49–3.75 (3 H, m, NCH + $NCH_2$), 5.95 (2 H, s, $OCH_2O$), 6.58 (1 H, s, $H_{arom}$), 7.46 (1 H, s, $H_{arom}$); $\delta_C$($CDCl_3$) C, 124.4, 132.8, 146.8, 150.1, 162.8 (CO); CH, 56.9, 107.1, 107.7; $CH_2$, 23.1, 33.5, 35.0, 44.7, 101.4 ($OCH_2O$); *m*/*z* 231 ($M^+$, 100%) and 71 (91).

**7,8-Dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one 5b.** Mp 169–170 °C (Found: C, 68.2; H, 6.7; N, 5.5. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.95; N, 5.65%); $\nu_{max}$(KBr)/$cm^{-1}$ 1637 (CO); $\delta_H$($CDCl_3$) 1.63–1.96 (2 H, m, $CH_2$), 2.01–2.13 (1 H, m, $CH_2$), 2.18–2.27 (1 H, m, $CH_2$), 2.75 (1 H, d, *J* 14.5, $CH_2Ar$), 2.88 (1 H, dd, *J* 14.5, 4.2, $CH_2Ar$), 3.50–3.61 (1 H, m, $NCH_2$), 3.66–3.83 (2 H, m, 1 H $NCH_2$ + NCH), 3.87 (3 H, s, $OCH_3$), 3.89 (3 H, s, $OCH_3$), 6.60 (1 H, s, $H_{arom}$), 7.52 (1 H, s, $H_{arom}$); $\delta_C$($CDCl_3$) C, 122.8, 130.9, 147.9, 151.4, 163.2 (CO); CH, 57.1, 109.6, 109.9; $CH_2$, 23.0, 33.6, 34.6, 44.7; $CH_3$, 56.0, 56.1; *m*/*z* 247 ($M^+$, 100%) and 164 (88).

**6,7,8-Trimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one 5c.** Mp 127–128 °C (Found: C, 64.9; H, 7.0; N, 5.2. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.05%); $\nu_{max}$(KBr)/$cm^{-1}$ 1645 (CO); $\delta_H$($CDCl_3$) 1.64–1.96 (2 H, m, $CH_2$), 2.01–2.10 (1 H, m, $CH_2$), 2.22–2.36 (1 H, m, $CH_2$), 2.75 (1 H, d, *J* 14.9, $CH_2Ar$), 2.90 (1 H, dd, *J* 14.9, 4.2, $CH_2Ar$), 3.61–3.83 (3 H, m, $NCH_2$ + NCH), 3.90 (3 H, s, $OCH_3$), 3.92 (3 H, s, $OCH_3$), 4.02 (3 H, s, $OCH_3$), 6.51 (1 H, s, $H_{arom}$); $\delta_C$($CDCl_3$) C, 117.3, 135.3, 143.1, 154.8, 155.6, 163.6 (CO); CH, 61.9, 106.0; $CH_2$, 23.3, 29.7, 36.5, 44.9; $CH_3$, 55.9, 56.2, 61.0; *m*/*z* 277 ($M^+$, 100%) and 194 (97).

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