Organolithium or Heck-type cyclization of *N*-*ortho*-iodobenzyl-2-alkenylpyrrolidines to give indolizidines

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Dedicated to Professor Bill Bailey on the occasion of his 65th anniversary

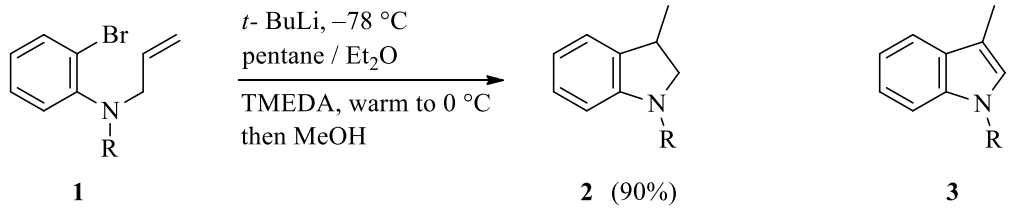
DOI: http://dx.doi.org/10.3998/ark.5550190.0012.507

Abstract
Carbolithiation reactions of 2-alkenyl-substituted pyrrolidines have been studied. An electron-withdrawing group in the alkene (R = $CONEt_2$) is required for the 6-*exo*-*trig* cyclization to afford hexahydropyrrolo[1,2-*b*]isoquinolines. Alternatively, the cyclization of the unactivated alkene can be performed under Heck conditions.

Keywords: Organolithium, carbanion, carbolithiation, palladium, Heck, heterocycles

Introduction

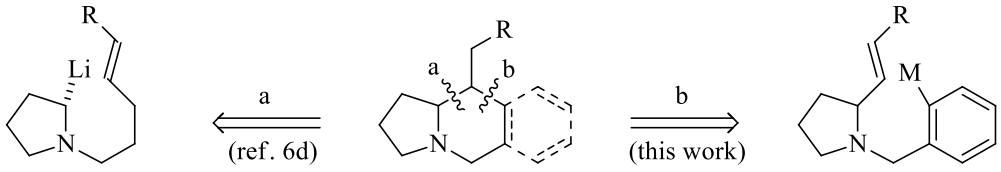
Cyclization of organometallic species onto alkenes plays a key role in organic synthesis. Perhaps most common is the use of organopalladium species, typically formed by insertion of palladium(0) into an aromatic halide.[1] Cyclization onto an alkene is normally followed by β-elimination (of a palladium hydride species) to regenerate an alkene. An alternative methodology, developed extensively by Bailey and co-workers, makes use of an organolithium species, often formed by halogen–lithium exchange.[2] For example, treatment of the bromide **1** (R = allyl) with two equivalents of *tert*-butyllithium promotes the formation of the aryllithium which cyclizes to give, after protonation, the indoline **2** (Scheme 1).[3] The same chemistry with bromide **1** (R = H), palladium acetate (3 mol%) and tris(2-tolyl)phosphine (6 mol%) is known to give (after heating for several days) the product **3** (R = H) in 60% yield (or 87% yield from the iodide).[4]



1 **2** (90%) **3**

Scheme 1

Our research groups have a long-standing interest in using organometallic species for cyclization onto π-systems to give nitrogen-containing heterocycles.[5,6] One target of interest is the preparation of 5-substituted indolizidines. Coldham and co-workers have shown that intramolecular carbolithiation of the organolithium **4** (R = H or SPh) provides a route for the preparation of the desired indolizidines **5** (Scheme 2, disconnection a).[6d] In this chemistry cyclization to give the six-membered ring is competitive with enantiomerization of the organolithium. On the other hand, Lete and co-workers have reported that pyrrolo[1,2-*b*]isoquinolines can be obtained by intramolecular carbolithiation starting from 2-alkenyl *N*-(*o*-iodobenzyl)pyrroles.[5c] We wondered whether we could approach such biologically important indolizidine targets[7] by disconnection b (Scheme 2, M = metal). There is precedent for carrying out such chemistry using an intramolecular Heck reaction with **6**, R = Me.[8] We decided to explore this reaction for a selection of R groups using either Heck or intramolecular carbolithiation chemistry.

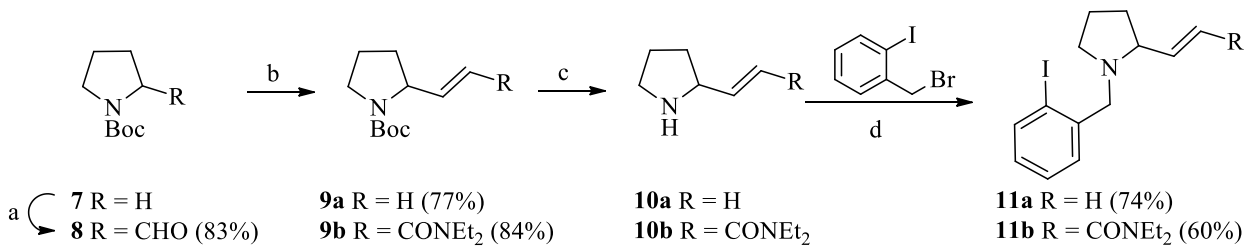


4 **5** **6**

Scheme 2

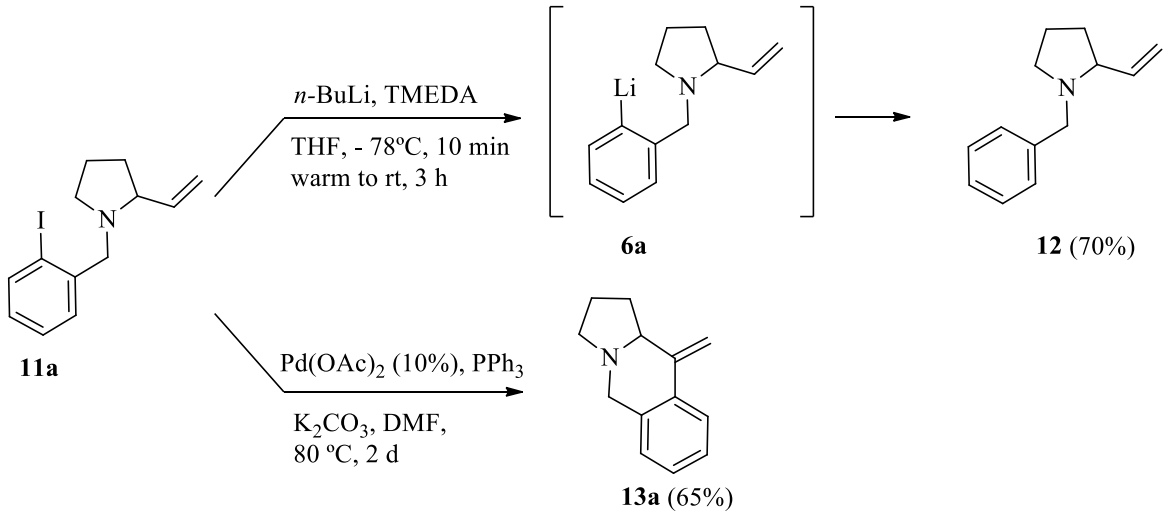
Results and Discussion

Our first task was the synthesis of the 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrrolidines **11a,b**, in which the alkene is unsubstituted or incorporates an electron-withdrawing group. As shown in Scheme 3, aldehyde **8** was obtained by deprotonation of *N*-Boc-pyrrolidine **7** followed by DMF quench.[9] Wittig reaction with the corresponding phosphorus ylides gave the alkenes **9a,b**. Nitrogen deprotection with trifluoroacetic acid (TFA) (quantitative) and alkylation with *ortho*-iodobenzylbromide gave **11a,b**.



Scheme 3. *Reagents and conditions*: a: *s*-BuLi / TMEDA, Et_2O, –78 ºC, 2 h, then DMF, rt, 2 h. b: $Ph_3P(CH_3)Br$, *n*-BuLi, THF, –78 ºC, 30 min, then rt, overnight (for **9a**); $Ph_3P{=}CHCONEt_2$, CH_2Cl_2, rt overnight (for **9b**). c: TFA, CH_2Cl_2, rt, overnight. d: KOH, EtOH, rt, 15 h.

We first studied the carbolithiation reactions of *N*-(*o*-iodobenzyl)pyrrolidine **11a** with *n*-BuLi/TMEDA (Scheme 4). Although iodine–lithium exchange occurred efficiently, aryllithium **6a** failed to undergo the carbolithiation reaction onto the unsubstituted alkene, and only the dehalogenated pyrrolidine **12** was obtained after work-up.[10] However, when **11a** was treated with palladium acetate (10 mol%) and triphenylphosphine (20 mol%) in the presence of potassium carbonate, under classical Heck reaction conditions, the hexahydropyrrolo[1,2-*b*]isoquinoline **13a** was obtained in good yield.

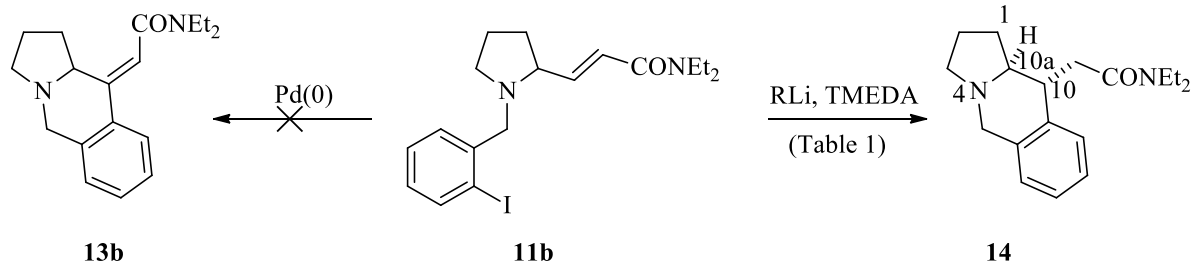


Scheme 4

Then, we studied the intramolecular carbolithiation of **11b** (Scheme 5). As shown in Table 1, the introduction of the electron-withdrawing group on the alkene moiety favours the 6-*exo*-cyclization of the intermediate aryllithium, and the hexahydropyrrolo[1,2-*b*]isoquinoline **14** was obtained in excellent yield. Cyclization took place at low temperature, although the best results were obtained when the reaction mixture was allowed to warm to room temperature. It is noteworthy that both *n*-BuLi and *t*-BuLi effected efficient iodine–lithium exchange (in the presence of TMEDA). No products from direct addition of these reagents to the α,β-unsaturated amide group were detected (as reported for related systems).[5c] The cyclization took place with

complete stereoselectivity, affording in all cases product **14** as a single diastereomer.[11] Attack of the intermediate aryllithium could occur as shown in Figure 1, leading to **14** with a relative 10,10a-*trans* configuration. This model allows possible nitrogen–lithium chelation and subsequent intramolecular carbolithiation. NOESY and COSY experiments confirmed the stereochemistry of **14**. The most significant NOESY results obtained are shown in Figure 1. In particular, 2D NOESY experiments showed an enhancement between the protons H-10 and H-1, and between H-10a and the methylenic protons of the substituent at C-10. These data are consistent with a *trans* stereochemistry in the indolizidine system.

Finally, Heck reaction of **11b** was studied. However, when **11b** was treated with $Pd(OAc)_2$, PPh_3 and K_2CO_3 under the same conditions as used for **11a**, no cyclization product could be detected, and a mixture of products was obtained. Other reaction conditions, that have been used successfully in related substrates,[5a] were tested. Thus, **11b** was treated with $Pd(PPh_3)_4$ (5%), $^nBu_4NCl$ (1.5 eq), $NaHCO_3$ (2.5 eq), in refluxing CH_3CN or with $Pd(PPh_3)_4$ (30%), Et_3N (2.2 eq) in toluene. In these cases a cyclized product could be detected by ^1H NMR spectroscopy of the crude reaction mixtures, but it could not be isolated or characterized, possibly due to instability.

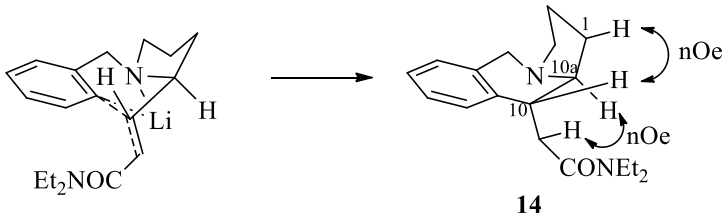


13b **11b** **14**

Scheme 5

Table 1. Carbolithiation reactions of **11b**

RLi	Conditions	14 Yield (%)
n-BuLi	–78 ºC, 10 min	70
n-BuLi	–78 ºC, 10 min; rt, 3 h	90
t-BuLi	–78 ºC, 10 min	63
t-BuLi	–78 ºC, 10 min; rt, 3 h	79



14

Figure 1. Possible transition state and selected NOE enhancements for **14**.

Conclusions

Intramolecular carbolithiation reaction of a 2-alkenyl-substituted pyrrolidine leads to a hexahydropyrrolo[1,2-*b*]isoquinoline *via* a 6-*exo* cyclization process, though the alkene needs to be substituted with an electron-withdrawing group (R = $CONEt_2$). Halogen–lithium exchange takes place efficiently with *n*-BuLi or *t*-BuLi, in the presence of the enamide moiety. The Heck reaction constitutes an efficient alternative to these reactions with the unsubstituted alkene.

Experimental Section

General. Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or in $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25 ºC, running at 300 or 500 MHz for ^1H and 75.5 or 125.7 MHz for ^{13}C in $CDCl_3$ solutions. Assignment of individual ^{13}C and ^1H resonances is supported by DEPT experiments and 2D experiments (COSY, HMBC, HSQC, NOESY) when necessary. Mass spectra were recorded under electron impact at 70 eV. Exact mass was obtained using a TOF detector. GC-MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m × 0.25 mm × 0.25 μm). TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography[12] on silica gel was performed with Kiesegel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[13] Organolithium reagents were titrated with diphenylacetic acid or *N*-benzylbenzamide periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 ˚C) and purged with argon.

***tert*-Butyl 2-formylpyrrolidine-1-carboxylate (8).** A 0.5 M solution of *N*-Boc pyrrolidine **7** (0.315 g, 1.83 mmol) in Et_2O (4 mL) at - 78 ºC was treated with TMEDA (0.27 mL, 1.83 mmol) and *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol). After 2 h at –78 ºC, the resulting solution was added dropwise via syringe over a solution of DMF (0.28 mL, 3.66 mmol) in Et_2O (2 mL). The reaction mixture was warmed up to room temperature for 2 h and quenched by the addition of sat. NH_4Cl solution(10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 20%) to give **8** as an oil (0.323 g, 83%), whose spectroscopic data were identical to those reported:[8] ^1H NMR ($CDCl_3$, ratio of rotamers 2:1) 1.42 (s, 9H, major rotamer), 1.50 (s, 9H, minor rotamer), 1.79–2.27 (m, 4H major rotamer, 4H minor rotamer), 3.36–3.68 (m, 2H major rotamer, 2H minor rotamer), 3.98–4.30 (m, 1H major rotamer, 1H minor rotamer), 9.46 (s, 1H, major rotamer), 9.52 (s, 1H, minor rotamer). ^{13}C NMR ($CDCl_3$), 24.0, 26.7, 28.3, 46.7, 65.0, 80.6, 158.2, 200.4.

***N*-(*tert*-Butoxylcarbonyl)-2-vinylpyrrolidine (9a).** *n*-BuLi (5.32 mL of a 1.3 M solution in hexanes, 6.96 mmol) was added to a solution of methyltriphenylphosphine bromide (1.92 g, 5.28 mmol) in THF (15 mL) at 0 ºC, and the reaction was stirred for 30 min. The mixture was

recooled at –78 ºC and a solution of *N*-Boc- prolinal **8** (1.05 g, 5.28 mmol) in THF (10 mL) was added. After 30 min. at –78 ºC, the reaction mixture was warmed up to room temperature overnight and quenched by the addition of sat. NH_4Cl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 10%) to give **9a** as an oil (0.763 g, 77%) whose spectroscopic data were identical to those reported:[14] ^{1}H NMR ($CDCl_3$): 1.46 (s, 9H), 1.67–1.76 (m, 1H), 1.77–1.93 (m, 2H), 1.95–2.10 (m, 1H), 3.32–3.49 (m, 2H), 4.21–4.42 (m, 1H), 4.96–5.17 (m, 2H), 5.68–5.84 (m, 1H). ^{13}C NMR ($CDCl_3$): 23.0, 28.5, 31.8, 46.3, 59.1, 79.1, 113.7, 138.9, 154.6.

(*E*)-*N*,*N*-Diethyl-3-[(1-*tert*-butoxycarbonyl)pyrrolidin-2-yl]acrylamide (9b). *N*,*N*-diethyl-2-(triphenylphosphoranylidene)acetamide[15] (4 g, 10.8 mmol) was added in portions to a solution of *N*-Boc prolinal **8** (0.237 g, 1.191 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at room temperature overnight. The reaction crude mixture was washed with H_2O (2 x 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with H_2O (2 x 10 mL) and sat. NaCl solution (2 x 10 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (neutral alumina, hexane/AcOEt 50%) to give **9b** as an oil (0.297 g, 84%), IR ($CHCl_3$): 1609, 1685 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.10–1.21 (m, 6H), 1.43 (s, 9H), 1.74–1.90 (m, 3H), 1.96–2.10 (m, 1H), 3.30–3.49 (m, 6H), 4.35–4.55 (m, 1H), 6.10–6.30 (m, 1H), 6.60–6.84 (m, 1H). ^{13}C NMR ($CDCl_3$, rotamers): 13.1, 14.9, 22.7, 23.6, 28.5, 31.0, 31.7, 40.8, 42.2, 46.2, 46.5, 57.9, 58.1, 79.5, 119.3, 120.6, 143.9, 145.6, 154.5, 165.7. MS (EI) *m/z* (rel intensity) 297 ([M+H]$^+$, 7), 241 (100), 223 (6), 196 (10), 195 (5), 124 (13), 96 (6). HRMS Calcd for $C_{16}H_{29}N_2O_3$: 297.2178. Found: 297.2172.

2-Vinylpyrrolidine (10a) (trifluoroacetate salt). A solution of *N*-Boc-2-vinylpyrrolidine **9a** (0.327 g, 1.66 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (1.3 mL, 16.60 mmol) and the mixture was stirred overnight at room temperature. Evaporation of the solvent under reduced pressure afforded 2-vinyl pyrrolidine **10a** trifluoroacetate as an oil (0.555 g, quantitative). Data of the free pyrrolidine have been reported:[16] ^{1}H NMR ($CDCl_3$): 1.78–2.48 (m, 4H), 3.25–3.65 (m, 2H), 4.00–4.30 (m, 1H), 5.30–5.62 (m, 1H), 5.72–6.14 (m, 2H), 7.69–8.34 (bs, 1H), 8.51–9.16 (bs, 1H). ^{13}C NMR ($CDCl_3$): 23.5, 30.4, 45.2, 62.6, 116.9, 122.0, 131.4, 161.4.

(*E*)-*N*,*N*-Diethyl-3-(pyrrolidin-2-yl)acrylamide (10b) (trifluoroacetate salt). According to the procedure described for **10a**, *N*,*N*-diethyl-3-(1-Boc-2- pyrrolidin yl)acrylamide **9b** (0.287 g, 0.97 mmol) and TFA (0.4 mL, 4.85 mmol) gave the product **10b** as an oil (0.305 g, quantitative). ^{1}H NMR ($CDCl_3$) 0.96 – 1.19 (m, 6H), 1.64 – 2.16 (m, 4H), 3.09 – 3.41 (m, 6H), 4.05 (q, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 15 Hz, 1H), 6.76 (dd, *J* = 7.5, 15 Hz, 1H), 8.24 (bs, 2H). When the product was purified by flash column chromatography (neutral alumina, MeOH/AcOEt 50%) **10b** was obtained as a free amine (0.124 g, 65%), IR (CH_2Cl_2) 1609, 1656, 3448 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.11 (t, *J* = 7 Hz, 3H), 1.16 (t, *J* = 7 Hz, 3H), 1.61–1.74 (m, 1H), 1.86–1.94 (m, 2H), 1.94–2.04 (m, 1H), 2.91–2.99 (m, 1H), 3.03–3.11 (m, 1H), 3.22 (s, 1H), 3.32–3.42 (m, 4H), 3.77 (q, *J* = 6.5 Hz, 1H), 6.38 (dd, *J* = 15, 1, Hz, 1H), 6.83 (dd, *J* = 15, 6.5, Hz, 1H). ^{13}C NMR ($CDCl_3$): 13.0, 14.8, 25.0, 31.9, 40.8, 42.1, 46.3, 59.7, 120.3, 145.8, 165.5. MS (CI) *m/z* (rel intensity) 197

(MH^+, 56), 195 (18), 124 (100), 96 (25). HRMS Calcd for $C_{11}H_{21}N_2O$: 197.1654. Found: 197.1659.

***N*-(*o*-Iodobenzyl)-2-vinylpyrrolidine (11a).** A solution of 2-vinylpyrrolidine trifluoroacetate **10a** (0.555 g, 3.07 mmol) in EtOH (10 mL) was treated with KOH (0.344 g, 6.13 mmol) and the mixture was stirred at room temperature for 30 min followed by addition of *o*-iodobenzyl bromide (0.948 g, 3.07 mmol). The resulting solution was stirred at room temperature for 15 h. The reaction was quenched by the addition of water (10 mL), the organic layer was separated and the aqueous phase was extracted with AcOEt (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 10%) to give **11a** as an oil (0.712 g, 74%), IR (CH_2Cl_2): 1654 cm^{-1}. ^1H NMR ($CDCl_3$): 1.60–1.90 (m, 3H), 1.93–2.07 (m, 1H), 2.21 (q, *J* = 8.5 Hz, 1H), 2.96 (q, *J* = 8.5 Hz, 1H), 3.03 (dt, *J* = 8.5, 2.5 Hz , 1H), 3.30 (d, *J* = 14 Hz, 1H), 3.98 (d, *J* = 14 Hz, 1H), 5.13 (dd, *J* = 1.5, 10 Hz, 1H), 5.24 (dd, *J* = 1.5, 17 Hz, 1H), 5.74–5.93 (m, 1H), 6.94 (td, *J* = 7.5, 1 Hz, 1H), 7.33 (td, *J* = 7.5, 1 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.83 (dd, *J* = 7.5, 1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 22.3, 31.6, 53.5, 62.1, 68.8, 100.0, 116.5, 128.0, 128.4, 130.2, 139.2, 140.9, 142.0. MS (CI) *m/z* (rel intensity) 314 (MH^+, 41), 313 (M^+, 100), 186 (40). HRMS Calcd for $C_{13}H_{17}IN$ (MH^+): 314.0406. Found: 314.0403.

(*E*)-*N*,*N*-Diethyl-3-[1-(*o*-iodobenzyl)pyrrolidin-2-yl]acrylamide (11b). According to the procedure described for **11a,** the pyrrolidine **10b** trifluoroacetate (0.150 g, 0.484 mmol), KOH (0.054 g, 0.968 mmol) and *o*-iodobenzyl bromide (0.150 g, 0.484 mmol) gave, after flash column chromatography (neutral alumina, hexane/AcOEt 20%) the product **11b** as an oil (0.120 g, 60%): ^1H NMR ($CDCl_3$): 1.11 (t, *J* = 7 Hz, 6H), 1.60–1.90 (m, 3H), 1.98–2.09 (m, 1H), 2.27 (q, *J* = 8.5 Hz, 1H), 3.01–3.12 (m, 1H), 3.16–3.46 (m, 6H), 3.85 (d, *J* = 14.5 Hz, 1H), 6.36 (d, *J* = 15 Hz, 1H), 6.85 (dd, *J* = 15, 7.5 Hz, 1H), 6.89 (td, *J* = 8, 1.5 Hz, 1H), 7.29 (td, *J* = 8, 1.5 Hz, 1H), 7.48 (dd, *J* = 8, 1.5 Hz, 1H), 7.77 (dd, *J* = 8, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): 13.2, 14.9, 22.8, 31.6, 40.8, 42.2, 53.8, 62.6, 66.4, 99.6, 121.0, 128.1, 128.4, 130.0, 139.1, 141.7, 147.1, 165.5. IR (CH_2Cl_2): 1661, 1615 cm^{-1}. MS (EI) *m/z* (rel intensity) 412 (M^+, 4), 312 (72), 286 (55), 217 (100), 195 (100), 122 (79), 90 (31). HRMS Calcd for $C_{18}H_{26}IN_2O$ (MH^+): 413.1090. Found: 413.1096.

***N*-benzyl-2-vinylpyrrolidine (12).** A solution of *N*-benzyl-2-vinylpyrrolidine **11a** (0.145g, 0.46 mmol) in THF (10 mL) was treated with *n*-BuLi (0.41 mL of a 1.3M solution in hexanes, 1.02 mmol) and TMEDA (0.15 mL, 1.02 mmol) at –78 ºC. After 10 min, the mixture was allowed to warm to room temperature, and stirred for 3 h. The reaction was quenched by the addition of sat. NH_4Cl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 20%) to give **12** as an oil (0.060 g, 70%), data identical to those reported:[17] ^1H NMR ($CDCl_3$): 1.55–1.91 (m, 3H), 1.92 – 2.07 (m, 1H), 2.14 (q, *J* = 8.5 Hz, 1H), 2.83 (q, *J* = 8.5 Hz, 1H), 2.96 (td, *J* = 10, 3 Hz, 1H), 3.11 (d, *J* = 13 Hz, 1H), 4.07 (d, *J* = 13 Hz, 1H), 5.19 (dd, *J* = 10, 1.5 Hz, 1H), 5.24 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.66–6.01 (m, 1H), 7.19 – 7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.1, 31.6, 53.3, 58.1, 68.4, 116.5, 126.7, 128.1, 129.0, 139.5, 141.0.

10-Methylidene-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (13a). A solution of pyrrolidine **11a** (0.157 g, 0.50 mmol) in DMF (2 mL) was treated with $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.10 mmol) and K_2CO_3 (0.104 g, 0.75 mmol). The resulting mixture was heated at 80 ºC for 2 days. The reaction was quenched by the addition of water (10 mL), the organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried with K_2CO_3 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 50%) to give **13a** as an oil (0.060 g, 65%): IR (CH_2Cl_2): 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 1.82–2.05 (m, 3H), 2.12–2.43 (m, 2H), 2.81–2.97 (m, 1H), 3.22–3.40 (m, 1H), 3.53 (d, *J* = 14.5 Hz, 1H), 4.15 (d, *J* = 14.5 Hz, 1H), 5.03 (d, *J* = 2 Hz, 1H), 5.69 (d, *J* = 2 Hz, 1H), 7.08–7.14 (m, 1H), 7.19–7.25 (m, 2H), 7.69–7.76 (m, 1H). ^{13}C NMR ($CDCl_3$): 21.4, 28.6, 54.8, 56.2, 64.7, 106.3, 123.9, 126.6, 126.9, 127.6, 132.5, 135.0, 144.0. MS (CI) *m/z* (rel intensity) 186 (MH^+, 92),185 (M^+, 100), 184 (54). HRMS Calcd for $C_{13}H_{16}IN$ (MH^+): 186.1283. Found: 186.1292.

***N,N*-Diethyl-2-((10*RS*,10a*SR*)-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetamide (14).** A solution of **11b** (0.064 g, 0.15 mmol) in THF (10 mL) was treated with *n*-BuLi (0.3 mL of a 1.3M solution in hexanes, 0.34 mmol) and TMEDA (0.15 mL, 1.02 mmol) at –78 ºC. After 10 min, the mixture was allowed to warm to room temperature, and stirred for 3 h. The reaction was quenched by the addition of sat. NH_4Cl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/AcOEt 80%) to give the product as an oil (0.039 g, 90%), IR (CH_2Cl_2): 1639 cm^{-1}. ^1H NMR ($CDCl_3$): 1.16 (t, *J* = 7.1 *Hz*, 6H, 2 x CH_3), 1.62–1.69 (m, 1H. H-1), 1.71–1.78 (m, 1H, H-2), 1.80–1.93 (m, 1H, H-2), 2.03–2.14 (m, 1H, H-1), 2.17–2.29 (m, 2H, H-3 and H-10a), 2.53 (dd, *J* = 15.5, 6 Hz, 1H, C*H*HCONEt$_2$), 2.73 (dd, *J* = 15.5, 6 Hz, 1H, CH*H*CONEt$_2$), 3.24 (t, *J* = 9 Hz, 1H H-3), 3.33 (q, *J* = 7 Hz, 2H, NCH_2CH$_3$), 3.37–3.48 (m, 3H, NCH_2CH$_3$ and H-5), 3.50–3.57 (m, 1H, H-10), 4.05 (d, *J* = 14.5 Hz, 1H, H-5), 7.00–7.23 (m, 4H, H-arom). ^{13}C NMR ($CDCl_3$): 13.0 (CH_3), 14.5 (CH_3), 21.5 (C-2), 30.4 (C-1), 37.9 (CH_2), 40.6 (*C*H_2CH$_3$), 41.4 (C-10), 42.1 (*C*H_2CH$_3$), 54.9 (C-3), 56.2 (C-5), 67.1 (C-10a), 125.7 (C-7), 126.5, 126.6 (C-9, C-8), 127.1 (C-6), 135.1 (C-9a), 138.8 (C-5a), 171.0 (C=O). MS (CI) *m/z* (rel intensity) 287 (MH^+, 100), 286 (M^+, 5), 214 (3), 186 (2), 172 (11). HRMS Calcd for $C_{18}H_{27}N_2O$ (MH^+): 287.2123. Found: 287.2135.

Acknowledgements

We thank the Ministerio de Ciencia e Innovación (CTQ2009-07733), Departamento de Educación, Universidades e Investigación (Gobierno Vasco), the University of Sheffield and Universidad del País Vasco for their financial support.

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