HETEROCYCLES, Vol. 93, No. 1, 2016, pp. 114 - 126. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 23rd July, 2015, Accepted, 2nd September, 2015, Published online, 6th October, 2015
DOI: 10.3987/COM-15-S(T)7

ACCESS TO APOERYSOPINE AND PRATOSINE SKELETONS VIA INTRAMOLECULAR CARBOLITHIATION AND PALLADIUM-CATALYZED ALKENYLATION REACTIONS

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Abstract – (Pyrrolo[1,2-*a*]benzazepinyl)acetamides, obtained through carbolithiation reactions**,** have been used as intermediates in the access to Apoerysopine skeleton. Derivatization implies reduction to the correponding aldehyde using the Snieckus procedure for *in situ* generation of the Schwartz reagent, followed by Wittig reaction and intramolecular Pd(II)-catalyzed C-H alkenylation. The same sequence has been applied for the obtention of Pratosine from a pyrroloisoquinoline intermediate.

INTRODUCTION[a]

The pyrrolobenzazepine core is a structural motif present in some biologically active compounds, such as *Cephalotaxus* alkaloids,[1] which have been used in the treatment of myeloid leukaemia.[2] In addition to their muscle relaxant, antihypertensive or antipsychotic effects,[3] the use of some substituted pyrrolo[2,1-*b*][3]benzazepines as advanced intermediates for the synthesis of these alkaloids has attracted significant attention (Figure 1).[4] Nonetheless, the synthesis of medium-sized heterocycles remains a challenge. Successful approaches include Ring-Closing Metathesis (RCM),[5] intramolecular palladium-catalyzed reactions,[6] intramolecular α-amidoalkylation reactions,[7] and Parham cyclization.[8] We have also shown that intramolecular carbolithiation reaction[9] of 2-alkenyl substituted *N*-phenethylpyrroles allows the construction of seven membered rings, thus opening new routes to benzo-[*c*]pyrrolo[1,2-*a*]azepines functionalized at C-11.[10,11] This type of heterocycles could be employed as useful precursors for the construction of the tetracyclic core of *Cephalotaxus* alkaloids *via* Friedel-Crafts reaction. In fact, Li and co-workers[12] developed a facile total synthesis of Hainanensine and analogues *via*

[a] Dedicated to Prof. Dr. Lutz F. Tietze on the occasion of his birthday

an acid catalyzed ring expansion of a 10b-substituted tetrahydropyrroloisoquinoline that provided a tetrahydropyrrolobenzazepine, which underwent an intramolecular Friedel-Crafts reaction. The formation of a pyrrolobenzazepine intermediate was demonstrated by the clean transformation of a previously prepared derivative into the tetracyclic skeleton of Hainanensine (Figure 2).

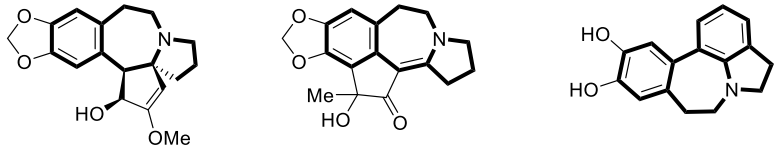


Figure 1

However, we reasoned that there would also be the possibility of a C-H activation reaction to take place on the C-3 pyrrole carbon of the dihydropyrrolobenzazepine to construct biaryl C-C bonds and give access to the benzazepinoindole nucleus, present in some alkaloids of the *Erythrina* family[13,14] as Apoerysopine.[15] In this context, we have previously demonstrated[16] that the competition between intramolecular Mizoroki-Heck reaction and direct arylation reactions on 2-alkenyl substituted iodinated *N*-(arylalkyl)pyrroles can be controlled by choosing the appropriate catalytic system, so the reaction can be switched from the alkene to the pyrrole nucleus. Therefore, we decided to investigate the possibility of carrying out an intramolecular C-H alkenylation of the pyrrole ring selectively, in the presence of a methoxylated aromatic ring, through an intramolecular Fujiwara-Moritani reaction[17] of the previously formed pyrrolobenzazepines. Thus, the pyrrolobenzazepines would be obtained through an intramolecular carbolithiation reaction, and further derivatization of the C-11 substituent into an allyl group would be required (Figure 2).

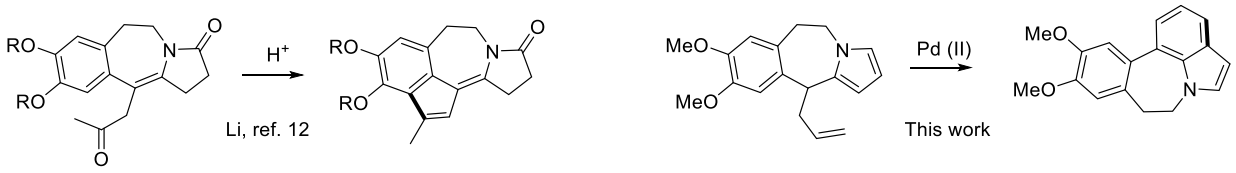
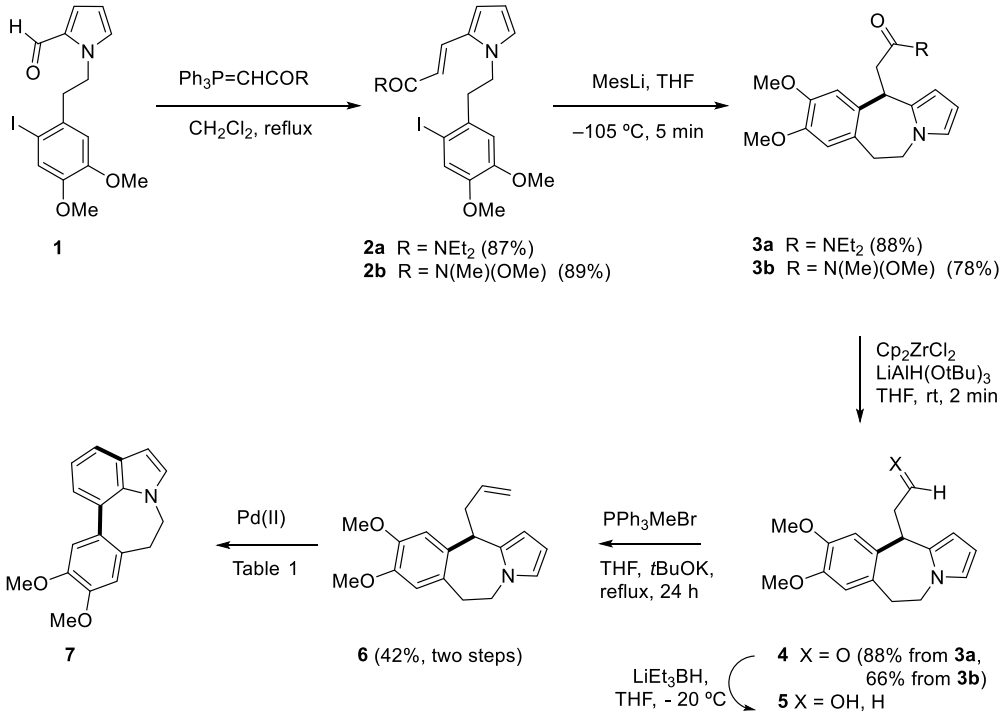


Figure 2

RESULTS AND DISCUSSION

We have recently shown that the intramolecular carbolithiation reactions of 2-alkenyl substituted *N*-benzylpyrroles constitutes an efficient route to pyrrolo[1,2-*b*]isoquinolines, benzazepines, and benzazocines when the internal alkene bears an electron-withdrawing group and a non-nucleophilic metalating agent, such as MesLi, is used.[10] Thus, the intramolecular carbolithiation reaction of **2a,** occurred efficiently in just 5 min using 2 equivalents of mesityllithium at –105 ºC to afford the pyrrolobenzazepine **3a** in high yield (88%) (Scheme 1).[10]



Scheme 1

Table 1. Pd(II)-Catalyzed cyclization of **6**

Entry	Pd (mol%)	Oxidant/Additive(eq.)	Solvent	T (°C)	t (h)	**7** [a]
1	$PdCl_2(MeCN)_2$ (5)	$PhCO_3tBu$ (1.2), *p*TsOH (1), $Cu(OAc)_2$ (0.05)	AcOH	rt	2	-[b]
2	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (1.8)	DMF/DMSO	70	5	99[c]
3	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (1.8)	MeCN	70	30	82[c]
4	$PdCl_2(MeCN)_2$ (10)	$Cu(OAc)_2$ (1.8)	DMF/DMSO	70	30	-[b]
5	$PdCl_2(MeCN)_2$ (2.5)	*p*BQ (1.15), H_2O (1)	*t*BuOH	85	30	59[c]

[a] Yield calculated by GC-MS. [b] A complex mixture of products was observed. [c] 10-12% isolated yield of **7** was obtained.

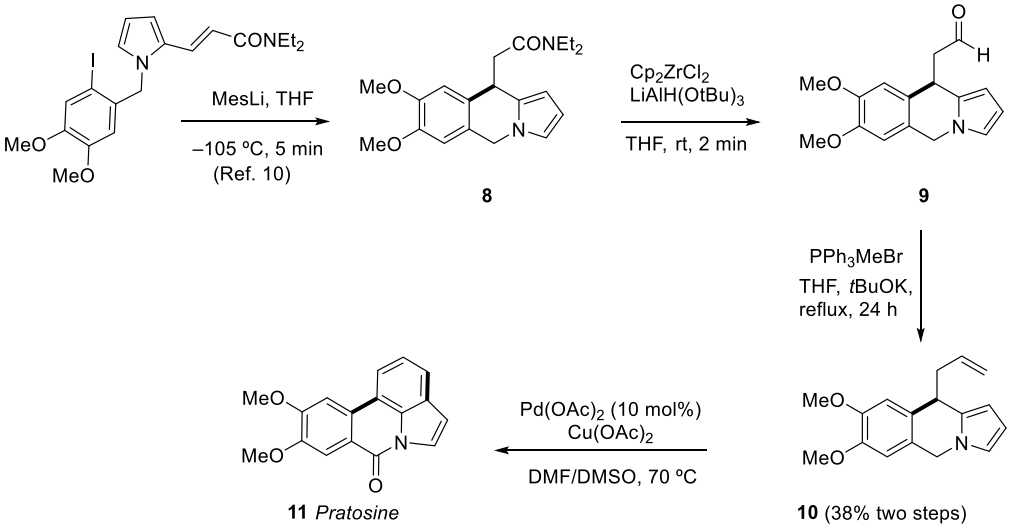
We have previously observed that the nature of the amide group had a strong influence on the carbolithiation reaction on related systems.[18] Thus, the Weinreb amide derivative had proved to be more efficient than the diethylamide. Thereby, we decided to test Weinreb amide **2b** (Scheme 1), obtained with excellent yield and as a single *E* diastereoisomer *via* Wittig reaction of **1**. Alkenylpyrrole **2b** was then submitted to an intramolecular carbolithiation reaction employing the best conditions found for the diethylamide **2a** leading to the desired pyrrolo[1,2-*a*]benzazepine **3b** with 78% yield (Scheme 1). In this case, the use of a Weinreb amide **2b** did not improve the results obtained with the diethylamide derivative **2a** (78 *vs.* 88%).

Then we derivatized the amides **3a,b** into the corresponding aldehyde. The reduction of *N,N*-disubstituted amides to aldehydes is not easy to achieve, due to the possibility of over-reduction to the corresponding alcohols. A mild, efficient and general method for the reduction of amides to aldehydes using the Schwartz reagent[19] was reported in 2000 by Georg,[20] but although this reagent is commercially available, it is expensive and it cannot be stored due to is sensitivity to air, light and moisture.[21] Thus, Snieckus[22] has developed a method for its generation *in situ* from Cp_2ZrCl_2 by reaction of lithium tri-*t*-butoxyaluminum hydride. Taking advantage of their excellent results, we decided to use their method for the reduction of the amides. Therefore, to a solution of the benzazepines **3a,b** and Cp_2ZrCl_2 in THF (10 mL) at room temperature was rapidly added $LiAlH(Ot\text{-}Bu)_3$ and the solution was stirred 2 min, leading the aldehyde **4** in good yield. It is noteworthy that not only the *N,N*-diethylamide **3a** is reduced in high yield (87%), but also the Weinreb amide **3b** (66%) (Scheme 1). The reaction was very fast and completely selective. However, the aldehyde **4** is not stable, and was further transformed immediately after its preparation. Thus, freshly prepared aldehyde **4,** without further purification, was treated with $LiEt_3BH$ at -20 °C obtaining the alcohol **5** in good yield (45% two steps), which was stable and could be fully characterized. In the same way, **4** was converted into the corresponding 11-allyl substituted pyrrolobenzazepine **6** by treatment with methyltriphenylphosphonium bromide and *t*-BuOK (42%, two steps) (Scheme 1). Then we studied the intramolecular Pd(II)-catalyzed alkenylation reaction **6**. We have recently reported the Pd(II)-mediated intramolecular C-H alkenylation reaction of substituted (*N*-aryl-*N*-methyl)acrylamides for the synthesis of 4-substituted quinolones.[23] Thus, we took the conditions optimized for that reaction as starting point (Table 1, entry 1), using $PdCl_2(MeCN)_2$ (5 mol%), and *t*-butyl perbenzoate in the presence of $Cu(OAc)_2$ (5 mol %) as oxidant (Table 1, entry 1), obtaining a complex mixture of products. We changed the reaction conditions, avoiding the use of acids. Thus, the use of $Pd(OAc)_2$ (10 mol%) and $Cu(OAc)_2$ in DMF/DMSO (9:1) at 70 °C, gave the expected compound. The conversion was complete, and the formation of **7** estimated by GC-MS was almost quantitative, but unfortunately the isolated yield was very low and it could not be improved although different work-up and purification procedures were applied. No formation of the product resulting from attack on the aromatic ring could be detected. The change of the solvent or the oxidant (entries 3-5) gave similar results.

In a similar fashion, the application of this synthetic sequence to a pyrrolo[1,2-*b*]isoquinoline would lead to the formation of the tetracyclic framework of Lycorine class of *Amaryllidaceae* alkaloids,[24] which exhibit a broad spectrum of pharmacological activity.[25] In this context, we have recently shown that the enantioselective palladium-catalyzed polyene cyclization can be successfully applied to the construction of this type of alkaloids.[26]

Thus, we next applied this synthetic sequence to pyrrolo[1,2-*b*]isoquinoline **8,** previously synthesized in our research group *via* MesLi mediated carbolithiation reaction.[10] Thus, the reduction with *in situ* Schwartz

reagent, gave aldehyde **9,** which was not stable and was used without further purification. Thereby, the 10b-allylpyrroloisoquinoline **10** was obtained with 38% yield (two steps) *via* Wittig reaction. Finally, the intramolecular alkenylation reaction was tested. In this case, after several attempts, only small amounts of **11** could be isolated. As can be seen, oxidation of the benzylic position had also occurred, obtaining the naturally occurring pyrrolo[3,2,1-*de*]phenanthridinone alkaloid *Pratosine* (**11**)[27] in low isolated yield (10%) (Scheme 2).



Scheme 2

In conclusion, pyrrolo[1,2-*a*]benzazepinyl acetamides **3a,b,** obtained through carbolithiation reactions, can be efficiently reduced to the correponding aldehyde **4** using the Snieckus procedure for *in situ* generation of the Schwartz reagent. After transformation into the 11-allyl pyrrolobenzazepine, the intramolecular Pd(II)-catlyzed C-H alkenylation reaction leads to the tetracyclic benzazepinoindole skeleton of the methoxylated derivative of Apoerysopine **7**, although the isolated yields are low under the conditions tested. Similarly, when this sequence is applied to a pyrroloisoquinoline, such as **8**, the natural product Pratosine is obtained, although in low yield.

EXPERIMENTAL

General experimental methods: IR spectra were obtained in film over NaCl pellets, or using an ATR. NMR spectra were recorded at 20-25 ˚C, at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C or at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C in $CDCl_3$ solutions, unless otherwise stated. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Mass spectra were recorded under chemical ionization (CI) at 230 eV. Exact mass was obtained using a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was performed on silica gel (230-400 mesh) or on alumina (70-230 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[28]

t-Butyllithium was 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.

Starting Materials. Aldehyde **1** and pyrroloisoquinoline **8** were prepared by the appropriate reported procedure.[10] All other chemicals used in this study were commercially available.

(*E*)-3-(1-(2-Iodo-4,5-dimethoxyphenethyl)-1*H*-pyrrol-2-yl)-*N*-methoxy-*N*-methylacrylamide (2b). *N*-methoxy-*N*-methyl-2-(triphenylphosphanylidene)acetamide (4.56 g, 12.8 mmol) was added in portions to a refluxing solution of *N*-phenethylpyrrole **1** (2.41 g, 6.25 mmol) in CH_2Cl_2 (40 mL) over 3 d (2 eq. each day). The crude reaction mixture was washed with H_2O (3 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc 6:4) afforded **2b** as an oil (2.61 g, 89%): IR (film) 1645, 1600 cm^{-1}; ^1H NMR δ 3.03 (t, J = 6.9 Hz, 2H, CH_2Ar), 3.27 (s, 3H, NCH_3), 3.68 (s, 3H, $NOCH_3$), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.18 (t, J = 6.9 Hz, 1H, CH_2N), 6.06-6.13 (m, 1H, Pyrrole H_4), 6.25 (s, 1H, Ar H_6), 6.51-6.59 (m, 1H, Pyrrole H_3), 6.61-6.67 (m, 1H, Pyrrole H_5), 6.71 (d, J = 15.4 Hz, 1H, OC*H*C=H), 7.18 (s, 1H, Ar H_3), 7.62 (d, J = 15.4 Hz, 1H, OCHC=C*H*); ^{13}C NMR δ32.4 (NCH_3), 32.6 (CH_2Ar), 47.0 (CH_2N), 55.8 (OCH_3), 56.1 (OCH_3), 61.8 (N OCH_3), 87.7 (Ar C_2), 109.2 (Pyrrole C_4), 110.7 (Pyrrole C_3), 110.8 (Ar C_6), 121.5 (Ar C_3), 125.6 (OCH*C*=CH), 129.4 (Pyrrole C_5), 130.9 (OCHC=*C*H), 132.7 (Ar C_1), 148.4, 149.2 (Ar C_4, C_5), 167.7 (CO); MS (CI) *m/z* (rel intensity) 471 (57) $[MH]^+$, 441 (21), 411 (19), 410 (100), 343 (32), 313 (29), 284 (11). HRMS (CI): calcd. for $C_{19}H_{24}IN_2O_4$ $[MH]^+$ 471.0781; found: 471.0762.

2-(8,9-Dimethoxy-6,11-dihydro-5*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11-yl)-*N*-methoxy-*N*-methylacetamide (3b). To a solution of mesityl bromide (0.3 mL, 1.87 mmol) in dry THF (10 mL) was added *t*-BuLi (4.2 mL of a solution 0.9 M in hexane, 3.76 mmol) at -78 °C, and the resulting mixture was stirred at -20 °C for 1 h. The reaction mixture was cooled to -105 °C, and a solution of *N*-phenethylpyrrole **2b** (442 mg, 0.93 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred for 5 min. The reaction was quenched by the addition of saturated NH_4Cl solution (10 mL), and then Et_2O (15 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc 6:4) afforded **3b** as a colourless oil (248 mg, 78%): IR (film) 1650 cm^{-1}; ^1H NMR δ 3.09-3.17 (m, 5H, CH_2CO, CH_3), 3.23-3.29 (m, 2H, H_6), 3.53 (s, 3H, $NOCH_3$), 3.86 (s, 3H,OCH_3), 3.87 (s, 3H, OCH_3), 4.15-4.34 (m, 2H, H_5), 4.84 (t, J = 7.6 Hz, 1H, H_{11}), 5.89-5.98 (m, 1H, H_1), 6.01 (t, J = 3.1 Hz, 1H, H_2), 6.53-6.45 (m, 1H, H_3), 6.65 (s, 1H, H_7), 6.80 (s, 1H, H_{10}); ^{13}C NMR δ32.0 (NCH_3), 32.8 (C_6), 37.9 (*C*H_2CO), 39.2 (C_{11}), 48.3 (C_5), 56.0 (OCH_3), 56.1 (OCH_3), 61.3 ($NOCH_3$), 106.5 (C_1), 106.9 (C_2), 111.9 (C_{10}), 113.3 (C_7), 121.9 (C_3), 130.0 (C_{10a}), 132.7 (C_{11a}), 133.0 (C_{6a}), 147.4 (C_8), 147.5 (C_9), 172.3

(CO); MS (CI) *m/z* (rel intensity) 345 (8) $[MH]^+$, 344 (22) $[M]^+$, 313 (23), 270 (8), 243 (16), 242 (100). HRMS (CI): calcd. for $C_{19}H_{25}N_2O_4$ $[MH]^+$ 345.1814; found: 345.1797.

2-(8,9-Dimethoxy-6,11-dihydro-5*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11-yl)acetaldehyde (4). To a solution of amide **3a** (105 mg, 0.29 mmol) and Cp_2ZrCl_2 (193 mg, 0.64 mmol) in THF (10 mL) at rt was rapidly added LiAlH(O*t*-Bu)$_3$ (0.65 mL of a solution 1 M in THF) and the solution was stirred 2 min. The reaction was quenched by the addition of H_2O. HCl 5M was added until the pH was < 7. Then, EtOAc was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexane/EtOAc 6:4) gave **4** as a yellow solid (73 mg, 88%): mp (Hexane/EtOAc) 97-100 ºC; IR (ATR) 1635 cm^{-1}; ^{1}H NMR δ 3.06-3.41 (m, 4H, CH_2CHO, H_6), 3.85 (s, 6H, OCH_3), 4.20-4.26 (m, 2H, H_5), 4.86 (t, J = 7.6 Hz, 1H, H_{11}), 5.88 (dd, J = 3.0, 1.8 Hz, 1H, H_1), 6.04 (t, J = 3.0 Hz, 1H, H_2), 6.50-6.55 (m, 1H, H_3), 6.68 (s, 1H, H_7) 6.71 (s, 1H, H_{10}), 9.78 (s, 1H, CHO); ^{13}C NMR δ 32.5 (C_6), 36.3 (C_{11}), 48.3 (C_5), 48.4 (*C*H_2CHO) 56.0 (2 × OCH_3), 106.2 (C_1), 107.1 (C_2), 110.9 (C_{10}), 113.3 (C_7), 122.4 (C_3), 129.9 (C_{6a}), 132.0 (C_{10a}), 132.5 (C_{11a}), 147.7 (C_8, C_9), 200.9 (CHO); MS (CI) *m/z* (rel intensity) 286 (9) $[MH]^+$, 285 (11) $[M]^+$, 270 (15), 269 (21), 268 (79), 267 (100), 253 (19), 252 (15), 244 (19), 243 (30), 242 (96). HRMS (CI): calcd. for $C_{17}H_{20}NO_3$ $[MH]^+$ 286.1443; found: 286.1456.

2-(8,9-Dimethoxy-6,11-dihydro-5*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11-yl)ethanol (5) (Two step procedure from amide **3a**)**.** To a solution of amide **3a** (128 mg, 0.36 mmol) and Cp_2ZrCl_2 (247 mg, 0.79 mmol) in THF (10 mL) at rt was rapidly added LiAlH(O*t*-Bu)$_3$ (0.8 mL of a solution 1 M in THF) and the solution was stirred 2 min. The reaction was quenched by the addition H_2O. HCl 5M was added until the pH was < 7. Then EtOAc was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. To a solution of the so-obtained aldehyde **4** (0.36 mmol) in THF (10 mL) was slowly added Li BEt_3HG (1.8 mL, 1M, 1.75 mmol) at -20 °C under argon atmosphere. After 30 min, the reaction mixture was quenched with saturated aqueous ammonium chloride (20 mL). After separation, the aqueous phase was extracted with EtOAc (3 × 15 mL), and the organic extracts were evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc 8:2) to give **5** as an oil (46 mg**,** 45%, two steps): IR (ATR) 3440 cm^{-1}; ^{1}H NMR δ 2.13-2.31 (m, 2H, C$H_2$$CH_2$OH), 3.06-3.31 (m, 2H, H_6), 3.56-3.78 (m, 2H, CH_2CH_2OH), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.05-4.40 (m, 3H, H_{11}, H_5), 5.97-5.99 (m, 1H, H_1), 6.02-6.06 (m, 1H, H_2), 6.53-6.57 (m, 1H, H_3), 6.64 (s, 1H, H_7), 6.73 (s, 1H, H_{10}); ^{13}C NMR δ 33.6 (C_6), 39.9 (*C*$H_2$$CH_2$OH), 41.5 ($C_{11}$), 48.1 ($C_5$), 56.0 (2 x OCH_3), 61.3 (CH_2*C*H_2OH), 106.9 (C_1), 107.2 (C_2), 112.8 (C_{10}), 113.7 (C_7), 122.0 (C_3), 129.6 (C_{10a}), 132.9 (C_{11a}), 133.4 (C_{6a}), 147.3 (C_8), 147.5 (C_9); MS (CI)

m/z (rel intensity) 288 (100) $[MH]^+$, 287 $[M]^+$, 270 (25), 243 (18), 242 (99). HRMS (CI): calcd. for $C_{17}H_{22}NO_3$ $[MH]^+$ 288.1600; found: 288.1590.

11-Allyl-8,9-dimethoxy-6,11-dihydro-5*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine (6) (Two step procedure from amide **3a**). To a solution of amide **3a** (274 mg, 0.76 mmol) and Cp_2ZrCl_2 (505 mg, 1.69 mmol) in THF (10 mL) at rt was rapidly added $LiAlH(O\textit{t}\text{-}Bu)_3$ (1.7 mL of a solution 1 M in THF) and the solution was stirred 2 min. The reaction was quenched by the addition distilled H_2O. HCl 5M was added until the pH was < 7. Then EtOAc was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *via* evaporation under reduced pressure. Potassium *tert*-butoxide (175 mg, 1.53 mmol) was added to a solution of methyltriphenylphosphonium bromide (560 mg, 1.53 mmol) in dry THF (10 mL) at 0 °C. The reaction mixture was stirred at room temperature under argon 30 min and then was cooled at 0 °C. Then, a solution of the so-obtained aldehyde **4** (0.76 mmol) in THF (10 mL) was added over 5 min, with stirring, and was heated under reflux 24 h. Then the reaction mixture was allowed to cool down to rt and it was filtered under vacuum. The filtrate was diluted with Et_2O (15 mL) and washed with $NaHSO_3$ sat. (15 mL), Na_2CO_3 sat. (15 mL) and brine (15 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc 98:2) afforded **6** as an oil (91 mg, 42%, two steps): IR (ATR) 1520 cm^{-1}; ^1H NMR δ 2.74-2.89 (m, 2H, CH_2CH_2=CH_2), 3.18 (ddd, *J* = 15.0, 6.5, 3.5 Hz, 1H, H_{6a}), 3.26 (ddd, *J* = 15.0, 10.0, 3.5 Hz, 1H, H_{6b}), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.22-4.13 (m, 2H, H_{11}, H_{5a}), 4.28 (ddd, *J* = 13.3, 10.0, 3.5 Hz, 1H, H_{5b}), 5.06-5.10 (m, 2H, =CH_2), 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.94 (dd, *J* = 3.1, 1.9 Hz, 1H, H_1), 6.05 (t, *J* = 3.1 Hz, 1H, H_2), 6.54-6.50 (m, 1H, H_3), 6.67 (s, 1H, H_7), 6.72 (s, 1H, H_{10}); ^{13}C NMR δ 32.7 (C_6), 39.6 (*C*H=CH_2), 43.2 (C_{11}), 48.0 (C_5), 55.8 (2 × OCH_3), 106.3 (C_1), 106.6 (C_2), 111.9 (C_7), 113.1 (C_{10}), 115.9 (=CH_2), 121.6 (C_3), 129.7 (C_{6a}), 133.2 (C_{10a}), 133, 3 (C_{11a}), 136.9 (*C*H=CH_2), 147.0 , 147.1 (C_8, C_9); MS (CI) *m/z* (rel intensity) 284 (54) $[MH]^+$, 243 (34), 242 (100). HRMS (CI): calcd. for $C_{18}H_{22}NO_2$ $[MH]^+$ 284.1651; found 284.1641.

7,8-Dimethoxy-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole (7). A mixture of **6** (122 mg, 0.43 mmol), $Pd(OAc)_2$ (9.9 mg, 0.04 mmol) and $Cu(OAc)_2$ (142.5 mg, 0.78 mmol) in 9:1 DMF/DMSO 0.4 M was stirred for 5 h at 70 °C. The reaction mixture was cooled to room temperature, filtered through a Celite pad and concentrated under reduced pressure. Flash column chromatography (silica gel, hexane/EtOAc 8:2) of the resulting residue afforded **7** as a colorless oil (14 mg, 12%): IR (ATR) 1515 cm^{-1}; ^1H NMR δ 3.18-3.24 (m, 2H, H_5), 3.94 (s, 3H OCH_3), 3.96 (s, 3H, CH_3), 4.36-4.48 (m, 2H, H_4), 6.52 (d, *J* = 3.0 Hz, 1H, H_1), 6.73 (s, 1H, H_6), 7.06 (d, *J* = 3.0 Hz, 1H, H_2), 7.19 (t, *J* = 7.5 Hz, 1H, H_{11}), 7.31 (s, 1H, H_9), 7.46 (d, *J* = 7.5 Hz, 1H, H_{12}), 7.59 (d, *J* = 7.5 Hz, 1H, H_{10}); ^{13}C NMR δ 36.4 (C_5), 51.9 (C_4), 56.1 (2 × OCH_3), 100.9 (C_1), 112.8 (C_9), 112.9 (C_6), 119.9 (C_{10}), 120.1 (C_{11}), 121.5 (C_{12}), 124.1 (C_{9b}), 129.1 (C_2), 130.0 (C_{12a}), 130.1 (C_{5a}),

132.4 (C_{9a}), 132.6 (C_{9c}), 148.0 (C_7, C_8); MS (CI) *m/z* (rel intensity) 280 (91) $[MH]^+$, 279 (100) $[M]^+$, 265 (19), 250 (17), 249 (16). HRMS (CI): calcd. for $C_{18}H_{18}NO_2$ $[MH]^+$ 280.1338; found: 280.1346.

2-(7,8-Dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetaldehyde (9) To a solution of amide **8** (264 mg, 0.77 mmol) and Cp_2ZrCl_2 (507 g, 0.70 mmol) in THF (10 mL) at rt was rapidly added $LiAlH(O\textit{t}\text{-}Bu)_3$ (1.70 mL of a solution 1 M in THF) and the solution was stirred 2 min. The reaction was quenched by the addition of H_2O. HCl 5M was added until the pH was < 7. Then EtOAc was added and aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, Hexane/EtOAc 6:4) gave **9** as a colourless oil (20 mg, 10%). **9** was unstable and was purified and isolated only for its characterization. In subsequent reactions was immediately used without further purification: IR (ATR) 1700 cm^{-1}; ^1H NMR δ 2.77-2.97 (m, 2H, CH_2CHO), 3.89 (s, 6H, 2 × OCH_3), 4.64 (t, *J* = 6.4 Hz, 1H, H_{10}), 4.99 (d, *J* = 15.5 Hz, 1H, H_{5a}), 5.02 (d, *J* = 15.5 Hz, 1H, H_{5b}), 6.01 (dd, *J* = 3.3, 1.4 Hz, 1H, H_1), 6.15-6.29 (m, 1H, H_2), 6.72 (broad s, 2H, H_3, H_9), 6.81 (s, 1H, H_6), 9.73 (s, 1H, CHO); ^{13}C NMR δ 33.1 (C_{10}), 47.2 (C_5), 51.6 (*C*H_2CHO), 56.0 (2 × OCH_3), 104.1 (C_1), 108.4 (C_2), 109.2 (C_9), 110.7 (C_6), 118.5 (C_3), 124.1 (C_{5a}), 128.3 (C_{9a}), 129.9 (C_{10a}), 147.8, 148.4 (C_7, C_8), 201.1 (CHO); MS (CI) *m/z* (rel intensity) 272 (7) $[MH]^+$, 271 (14) $[M]^+$, 230 (35), 228 (100). HRMS (CI): calcd. for $C_{16}H_{18}NO_3$ $[MH]^+$ 272.1287; found: 272.1295.

10-Allyl-7,8-dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (10). To a solution of amide **8** (611 mg, 1.78 mmol) and Cp_2ZrCl_2 (1.17 g, 4.00 mmol) in THF (10 mL) at rt was rapidly added $LiAlH(O\textit{t}\text{-}Bu)_3$ (3.93 mL of a solution 1 M in THF) and the solution was stirred 2 min. The reaction was quenched by the addition of H_2O. HCl 5M was added until the pH was < 7. Then EtOAc was added and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Potassium *tert*-butoxide (408 mg, 3.57 mmol) was added to a solution of methyltriphenylphosphine bromide (1.12 g, 3.57 mmol) in dry THF (10 mL) at 0 °C. The reaction mixture was stirred at room temperature under argon 30 min and then was cooled at 0 °C. A solution of the so-obtained aldehyde **9** (1.78 mmol) in THF (10 mL) was added over 5 min, with stirring, and the mixture was heated under reflux 24 h. Then the reaction mixture was allowed to cool to rt and it was filtered under vacuum. The filtrate was diluted with Et_2O (15 mL) and washed with $NaHSO_3$ sat. (15 mL), Na_2CO_3 sat. (15 mL) and brine (15 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc 98:2) afforded **10** as an oil (183 mg, 38%, two steps): IR (ATR) 1700 cm^{-1}; ^1H NMR δ 2.46-2.56 (m, 2H, CH_2CH=CH_2), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.09 (t, *J* = 6.3 Hz, 1H, H_{10}), 4.86-5.12 (m, 4H, H_5, =CH_2), 5.69-5.73 (m, 1H, CH_2C*H*=CH_2), 5.99-6.03 (m, H_1), 6.18-6.21 (m, 1H, H_2), 6.65-6.73 (m, 2H, H_3, H_9), 6.80 (s, 1H, H_6); ^{13}C NMR δ 39.1 (C_{10}), 43.3

($CH_2CH=CH_2$), 47.3 (C_5), 56.0 (2 × OCH_3), 103.8 (C_1), 108.1 (C_2), 108.9 (C_9), 111.3 (C_6), 117.0 ($=CH_2$), 118.0 (C_3), 124.1 (C_{5a}), 129.4 (C_{9a}), 130.9 (C_{10a}), 135.7 ($CH=CH_2$), 147.4 (C_7), 148.0 (C_8); MS (CI) *m/z* (rel intensity) 270 (46) $[MH]^+$, 229 (29), 228 (100). HRMS (CI): calcd. for $C_{17}H_{20}NO_2$ $[MH]^+$ 270.1494; found: 270.1499.

9,10-Dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (11) (Pratosine). A mixture of **10** (92 mg, 0.34 mmol), $Pd(OAc)_2$ (8 mg, 0.034 mmol) and $Cu(OAc)_2$ (113 mg, 0.62 mmol) in 9:1 DMF/DMSO 0.4 M was stirred for 24 h at 70 °C. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (silica gel, hexane/EtOAc 8:2) of the resulting residue afforded **11** whose data are coincidental to those reported[29] (9 mg, 10%): IR (ATR) 1700 cm^{-1}; ^1H NMR δ 4.10 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.93 (d, J = 3.5 Hz, 1H, H_4), 7.52 (t, J = 7.7 Hz, 1H, H_2), 7.70 (s, 1H, H_{11}), 7.79 (d, J = 7.7 Hz, 1H, H_3), 8.02 (d, J = 7.7 Hz, 1H, H_1), 8.05 (s, 1H, H_8), 8.10 (d, J = 3.5 Hz, 1H, H_5); ^{13}C NMR δ 56.3 (2 × OCH_3), 103.7 (C_4), 110.1 (C_{11}), 110.7 (C_8), 116.7 (C_{10b}), 118.0 (C_1), 120.6 (C_{10c}), 122.4 (C_2), 123.6 (C_3), 123.9 (C_5), 128.5 (C_{10a}), 129.5 (C_{3a}), 130.9 (C_{6a}), 149.8 (C_9), 153.7 (C_{10}), 158.3 (C_7); MS (CI) *m/z* (rel intensity) 280 (100) $[MH]^+$, 279 (59) $[M]^+$, 258 (51), 257 (19). HRMS (CI): calcd. for $C_{17}H_{14}NO_3$ $[MH]^+$ 280.0974; found: 280.0990.

ACKNOWLEDGEMENTS

We thank Prof. V. Snieckus and Dr. Y. Zhao for helpful discussion regarding the Schwartz reduction. Ministerio de Economía y Competitividad (CTQ2013-41229-P), Gobierno Vasco (IT-623-13) and Universidad del País Vasco / Euskal Herriko Unibertsitatea UPV/EHU (UFI11/22, PPM12/03) are gratefully acknowledged for their financial support. We also thank Gobierno Vasco for a grant (E.C.). Technical and human support provided by Servicios Generales de Investigación SGIker (UPV/EHU, MINECO, GV/EJ, ERDF and ESF) is also acknowledged.

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