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Intramolecular N-arylation in heterocyclization: synthesis of new pyrido-fused pyrrolo[1,2-*a*][1,4]diazepinones

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ABSTRACT

Alkylation of L-prolinamide with 3-(chloromethyl)-2-halopyridines, followed by cyclization through an intramolecular Pd-catalysed amidation, provided an entry to the pyrido[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10-one scaffold. Furthermore, a synthetic route towards diverse new pyrido[*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-ones has been developed by acylation of contiguously substituted (aminomethyl)halopyridines with Boc-L-proline followed by intramolecular amination.

[1,4]Benzodiazepines are a class of privileged templates showing selective activities against a diverse array of biological targets.[1] Well-known [1,4]benzodiazepines include the tricyclic pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (PBDs), exemplified by DC-81 (Fig. 1); these antibiotics are produced naturally by *Streptomyces* species, and have been extensively investigated as sequence-selective DNA-binding agents with significant antitumour properties.[2] Their easy-to-synthesize 11-one derivatives (PBD dilactams) have been used as their precursors,[3] and also have interesting biological profiles themselves.[4] By contrast, their 5-deoxy-11-oxo derivatives are little-explored,[5] although a recent report described them as a promising new class of potential anti-ischaemic agents.[6] Accordingly, our interest in pyridoazepines as bioisosters of pharmacologically relevant benzazepines[7] has led us to develop a short approach to previously unreported pyrido[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10-one (**1**),[8] which has a tricyclic skeleton analogous to that of DC-81. Also, since the pyrrolo[1,2-*a*][1,4]benzodiazepin-4-one scaffold (**2**, X = Y = Z = CH), which incorporates the bioactive 1,4-benzodiazepin-3-one core, has recently been explored,[9] we extended our study to its pyrido analogues **3a–c**.

For the preparation of the aza-PBD monolactam **1** we designed a synthetic strategy based on the sequential construction of two C–N bonds between a 2-halo-3-(chloromethyl)pyridine (**6**) and L-prolinamide: N-alkylation of the latter at the pyrrolidinic nitrogen with **6** would be followed by closure of the diazepinone ring by intramolecular N-arylation in haloamide **7** (Scheme 1).[10]

The 3-(chloromethyl)-2-halopyridines required for the alkylation step were prepared from the corresponding 2-halonicotinaldehydes **4a** (2-chloronicotinaldehyde is commercially available, and its bromo derivative was easily obtained by treatment of 2-bromopyridine with LDA followed by formylation with DMF[11]). Reduction of **4a** with $NaBH_4$ in MeOH at room temperature (yield 60% for Hal = Br, 69% for Hal = Cl) followed by treatment with $SOCl_2$ and pyridine in dichloromethane (yield 95% for Hal = Br, quantitative for Hal = Cl) gave the 3-(chloromethyl)-2-halopyridines **6**. L-Prolinamide was then N-alkylated with these halides in acetonitrile in the presence of Hünig's base (room temperature, 30 h; yield 67% for Hal = Cl, 55% for Hal = Br).

For the ring closure step, we first attempted an intramolecular copper-catalysed N-arylation[12] under Buchwald's conditions using a diamine as the ligand.[13] However, upon treatment with CuI, *N*,*N*′-dimethylethylenediamine and potassium carbonate in toluene at 110 °C, amides **7** underwent decomposition, and the same result was obtained when chiral (1*S*,2*S*)-cyclohexane-1,2-diamine was used as the ligand. Fortunately, no such problem prevented intramolecular palladium-catalysed amidation:[14] treatment of haloamides **7** with $Pd(OAc)_2$, K_2CO_3 and BINAP in dioxane at 120 °C gave pyrido[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10-one (**1**) in excellent yield (90% for both the chloride and the bromide).[15] We have thus prepared the new aza-PBD **1** from 2-bromopyridine in five steps and 26% overall yield, and from 2-chloronicotinaldehyde **4a** in four steps and 42% overall yield. The enantiomeric purity of

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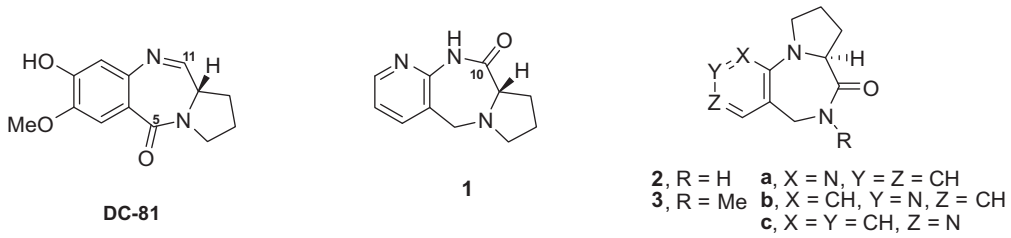
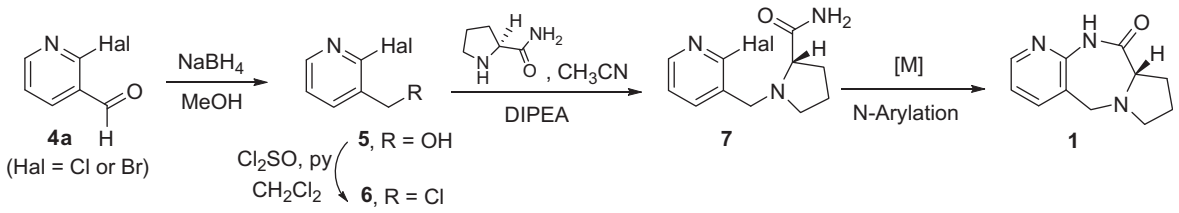


Figure 1. Compounds containing the pyrrolo[1,2-*a*][1,4]diazepinone scaffold.

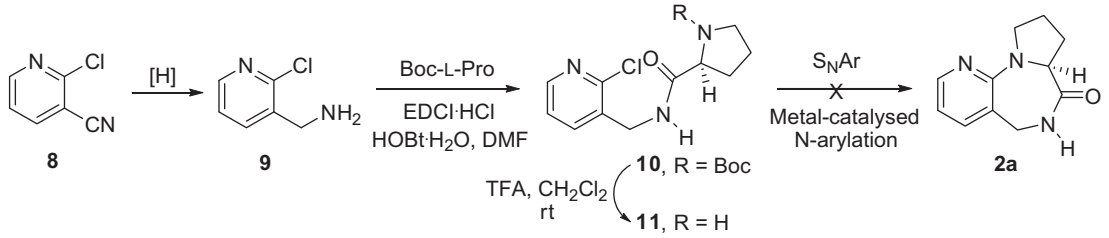


Scheme 1. Synthetic route to pyrido[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepinone **1**.

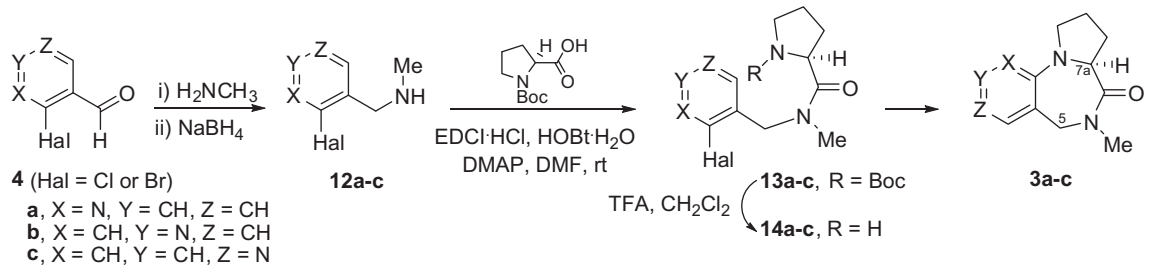
pyrrolodiazepine **1** was determined by chiral HPLC,[16] which showed a unique enantiomer with the configuration expected for the L-prolinamide used.

For the pyrido[*f*]fused tricyclic analogues **2** and **3** we planned to assemble the central diazepinone ring by condensation of a contiguously substituted (aminomethyl)chloropyridine with Boc-L-proline, followed by cyclization by intramolecular N-arylation,[17] as illustrated in Scheme 2 for pyrido[3,2-*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-one (**2a**). [(2-Chloropyridin-3-yl)methyl]amine (**9**) was prepared from commercially available 2-chloronicotinonitrile (**8**) by reduction at room temperature: although attempts at reduction with excess $LiAlH_4$ (250 mol %) or $NiCl_2/NaBH_4$ (100:300 mol %) led to complex mixtures of compounds, treatment for 1 h with $NaBH_4$ (50 mol %) and $CoCl_2$ (100 mol %) in dry methanol[18] provided the required amine in 49% yield, while treatment for 7 h with Raney nickel under 1 atm of hydrogen in ammonia-saturated methanol afforded a much improved 93% yield. Acylation with Boc-L-Pro in the presence of EDCI·HCl (1.2 equiv) and HOBt·H_2O (1.2 equiv) in DMF at room temperature then provided a 79% yield of amide **10**, which was deprotected in 77% yield by treatment for 30 min with TFA in dichloromethane at room temperature. However, failure was met in all attempts at closure of the diazepinone ring of amide **11**. We first tried intramolecular nucleophilic aromatic substitution, which we hoped would be promoted by the pyrrolidinic nitrogen;[19] but heating **11** in refluxing ^{i}PrOH for 24 h afforded no product, heating at a higher temperature in refluxing ^{n}BuOH gave a 50% yield of an imidazolidinone produced by formation of an aminal between the 1,2-diamine and *n*-butanal impurity, and heating for 12 h at 130 °C or 80 °C in the aprotic polar solvent DMF[20] caused decomposition. Attempts at closure of **11** by intramolecular transition-metal-catalysed N-arylation[21,22] fared no better. Thus treatment of **11** (94 mmol) with CuI (0.94 mmol, 0.01 equiv) under Ar for 11 h at 120 °C in 10 mL of DMSO containing L-proline (1.8 mmol, 0.02 equiv) and K_2CO_3 (281 mmol, 3 equiv)[23] led to decomposition; and the use of $Pd(OAc)_2$ or $PdCl_2$ with various ligands (dppm, tol-BINAP), bases ($NaHCO_3$, KO^{t}Bu, Cs_2CO_3) and solvents (^{i}PrOH, toluene, NMP) was similarly unproductive.[24]

This reluctance of compound **11** to cyclize was attributed to its predominant existence as the *Z*-rotamer,[25] in which the reactive partners are far apart; a similar situation prevents related systems from undergoing cyclodehydration, and also affects other cyclizations in which part of the ring being formed is an amide link.[5c] We accordingly proceeded to N-methylate the amide in order to favour the more propitious *E*-rotamer. The required tertiary amides **13** were prepared from readily available halopyridinecarbaldehydes **4** as indicated in Scheme 3. For **13a**, both nicotinaldehydes **4a** were converted to the corresponding *N*-methylmethanamines **12a** in yields higher than 90% by a reductive alkylation process involving reaction with methylamine (2 equiv) in refluxing toluene with removal of water with a Dean–Stark trap, followed by reduction of the resulting imine with $NaBH_4$ in methanol at room temperature. Condensation of the secondary amine **12a**^{Cl} with Boc-L-proline in DMF by means of the classical treatment with EDCI·HCl (1.2 equiv) and HOBt·H_2O (1.2 equiv) in DMF at room temperature provided a 65% yield of the corresponding amide **13a**^{Cl}; and when a catalytic amount of DMAP (0.1 equiv) was added, the yield rose to 78%. A similar yield of **13a**^{Br} was obtained in the same way from **12a**^{Br}. Deprotection of compounds **13a** with TFA then afforded prolinamides **14a** in quantitative yield. The ^{1}H NMR spectra of **14a**, unlike that of **11**, showed signal splitting indicative of the presence of two rotamers in approximately 70:30 ratio.



Scheme 2. Attempted preparation of pyridodiazepinone **2a**.



Scheme 3. Synthetic approach to pyridodiazepinones 3**a**–**c**.

Table 1
Cyclization conditions for amide **14a**

Entry	**14a** (Hal)	Conditions	*T* (°C)	Time (h)	Product (% yield)
1	Cl	^{i}PrOH	70	24	**14a**
2	Cl	KO^{t}Bu, PhMe	110	48	**3a** (16)
3	Cl	NaI, DMF	90	24	**3a** (20)
4	Cl	NaI, K_2CO_3, DMF	90	140	**3a** (18)
5	Cl	NaI, K_2CO_3, dioxane	90	60	**3a** (14)
6	Cl	NaI, K_2CO_3, DMSO	90	48	**3a** (36)
7	Cl	NaI, K_2CO_3, DMSO	110	24	**3a** (45)
8	Cl	NaI, Et_3N, DMSO	110	24	**3a** (57)
9	Cl	$Pd(OAc)_2$, KO^{t}Bu, tol-BINAP, PhMe	110	7	**3a** (38)
10	Br	KO^{t}Bu, PhMe	110	7	**3a** (29)
11	Br	NaI, K_2CO_3, DMSO	90	8	**3a** (45)

For the cyclization step we tried the same types of reaction as in the case of secondary amide **11**. Heating **14a**^{Cl} at 70 °C in isopropanol to promote an S_NAr reaction caused no reaction within 24 h (Table 1, entry 1); and heating for 48 h at 110 °C in toluene in a sealed tube, in the presence of KO^{t}Bu as base, afforded **3a** only in very low yield (entry 2). In the polar solvent DMF, with an addition of NaI to promote exchange of the chlorine atom, yields were similar after warming for 24 h (entry 3) or after 140 h in the presence of potassium carbonate as the base (entry 4); and prolonged heating in dioxane under the same conditions had the same result (entry 5). However, in DMSO the combination of NaI and K_2CO_3 proved more efficient, giving a 36% yield of **3a** after warming at 90 °C for 48 h, and 45% in a shorter time at 110 °C (entries 6 and 7); finally, a 57% yield was obtained upon replacing the base by triethylamine (entry 8).[26]

The alternative Pd-catalysed N-arylation, implemented using the conditions of entry 9, gave a smaller yield of 38%. With **14a**^{Br} as the substrate, the S_NAr reaction afforded yields ranging from 29% in toluene to 45% under the optimized conditions in DMSO (entries 10 and 11). To sum up, we have prepared the new compound (7a*S*)-6-methyl-5,6,7a,8,9,10-hexahydro-7*H*-pyrido[3,2-*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-one (**3a**) from 2-chloropyridinecarbaldehyde (**4a**) in five steps and 36% overall yield, and from 2-bromopyridine in six steps and 25% overall yield. The optical purity of the final product was confirmed by chiral HPLC to be >98%,[27] thus showing that the stereogenicity provided by the L-proline unit is preserved throughout the synthesis.

For the preparation of pyrido[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-one **3b** we started from halopyridinecarbaldehydes **4b**,[28] which were converted to amines **12b** in good yields by reductive N-alkylation of methylamine. Amines **12b** were then N-acylated with Boc-L-proline in the presence of EDCI/HOBt/DMAP to obtain amides **13b** (69% for Hal = Cl, 88% for Hal = Br), which were deprotected with TFA in dichloromethane. Amides **14b** are not appropriate for direct N-arylation by aromatic nucleophilic substitution,[29] but on treatment with $Pd(OAc)_2$ (0.2 equiv), BINAP (0.4 equiv) and KO^{t}Bu (2 equiv) in toluene at 110 °C provided the desired new diazepinone **3b** in 40% and 44% yield from the chloro and bromo derivatives, respectively.[30]

Similarly, we prepared pyrido[3,4-*f*]pyrrolo[1,2-*a*][1,4]diazepin-7-one **3c** from 4-bromopyridine hydrochloride, which was successively transformed into carbaldehyde **4c**,[31] amine **12c** and tertiary amide **13c**. Treatment of **13c**^{Br} for 30 min with TFA in CH_2Cl_2 at rt gave only a low yield of the deprotected amide **14c**^{Br} due to partial decomposition, but lowering the reaction temperature to 0 °C afforded the desired amine in just 15 min in 93% yield. Although cyclization of **14c**^{Br} by nucleophilic aromatic substitution is possible in principle, treatment with NaI and K_2CO_3 in DMSO at 90 °C led only to recovery of the initial amide. Attempted Pd-catalysed N-arylation using $Pd(OAc)_2$ (0.2 equiv), KO^{t}Bu (2 equiv) and BINAP (0.4 equiv) in toluene in a sealed tube heated at 110 °C for 6.5 h provided pyridodiazepinone **3c** in only low yield, but the reaction for 24 h at 80 °C with $Pd_2(dba)_3$ (0.05 equiv), BINAP (0.2 equiv) and Cs_2CO_3 (4.2 equiv) in toluene in a sealed tube gave a 91% yield.[32]

In conclusion, the new pyrido[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepinone **1** has been efficiently synthesized by N-alkylation of L-prolinamide with a 2-halo-3-(chloromethyl)pyridine followed by internal Pd-catalysed N-amidation; and members of a new family, the pyrido[*f*]pyrrolo[1,2-*a*][1,4]diazepinones, have been obtained very efficiently from commercially available halopyridines by formylation, reductive condensation with methylamine, amidation with Boc-L-proline, deprotection and final cyclization by intramolecular N-arylation under basic conditions and/or by Pd-catalysed coupling.

Preliminary evaluation of the biological properties of aza compounds **1** and **3a** has begun in the Department of Pharmacology of the Faculty of Pharmacy of our institution. The tests being performed include assays of in vitro binding to diverse neurotransmitters of the CNS, and in vivo assays. The results will be published in due course.

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15. *Experimental procedure for the Pd-catalysed amidation leading to (9aS)-5,7,8,9,9a,11-hexahydro-10H-pyrido[2,3-e]pyrrolo[1,2-a][1,4]diazepin-10-one* (**1**): A mixture of chloroamide **7** (75 mg, 0.313 mmol), K_2CO_3 (133 mg, 2 equiv), $Pd(OAc)_2$ (6 mg, 0.08 equiv) and BINAP (390 mg, 2 equiv) in dioxane (4 mL) was stirred under argon in a sealed tube at 120 °C. After 24 h the resulting mixture was filtered through Celite (finally washed with 10 mL of CH_2Cl_2), and the pooled filtrate and washings were concentrated under reduced pressure and purified by flash chromatography (SiO_2, 93:7 CH_2Cl_2/MeOH), affording diazepinone **1** (64 mg, 90% yield) as a white solid: mp 129–131 °C; $[\alpha]_D^{20}$ +208.4 (*c* 1, CH_2Cl_2), >98% ee. IR (KBr) 3066, 2924, 1665 (C=O), 1592, 1383 cm^{-1}. ^1H NMR δ: 9.65 (br s, 1H, NH), 8.43 (dd, *J* = 4.9 and 1.5 Hz, 1H, H_2), 7.59 (dd, *J* = 7.5 and 1.5 Hz, 1H, H_4), 7.05 (dd, *J* = 7.5 and 4.9 Hz, 1H, H_3), 3.97 (d, *J* = 13.2 Hz, 1H, H_5), 3.76 (d, *J* = 13.2 Hz, 1H, H_5), 3.61 (dd, *J* = 7.9 and 3.5 Hz, 1H, H_{9a}), 2.97–2.90 (m, 1H), 2.86–2.79 (m, 1H), 2.57–2.47 (m, 1H), 2.06–1.86 (m, 3H). ^{13}C NMR/DEPT δ: 173.02 (CO), 151.10 (C), 147.60 (CH), 138.47 (CH), 123.79 (C), 119.50 (CH), 64.13 (CH), 55.02 (CH_2), 54.56 (CH_2), 25.97 (CH_2), 23.58 (CH_2). MS (CI) (*m*/*z*): 204 ($[M+H]^+$, 100), 188 (10). HRMS (CI) calcd for $C_{11}H_{14}N_3O$ [$(M+H)^+$]: 204.1137, found: 204.1133.
16. HPLC was performed on a Chiralcel OD-H column eluted with an *n*-hexane/2-propanol gradient (from 80:20 to 50:50) at 0.5 mL/min, with UV detection at 254 nm. These conditions had been optimized for dibenzazepinones using a mixture of (5*R*,11a*S*)- and (5*S*,11a*S*)-5-phenyl-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones, which were prepared in racemic form from 2-aminobenzophenone and DL-proline following our previously described procedure (Ref. 5b). Under these conditions other racemic pyrrolodibenzazepinones have also been resolved successfully (Ref. 5c).
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25. In fact compound **11** exists exclusively in *Z* conformation with respect to the amide bond, that is, with the largest groups *anti* to each other, since there was no splitting of any signals in its ^1H NMR spectrum.
26. *Typical procedure for S_NAr leading to (7aS)-6-methyl-5,6,7a,8,9,10-hexahydro-7H-pyrido[3,2-f]pyrrolo[1,2-a][1,4]diazepin-7-one* (**3a**): A solution of chloroamide **14a** (85 mg, 0.33 mmol) in DMSO (4 mL) was treated with dehydrated NaI (50 mg, 0.33 mmol) and Et_3N (0.047 mL, 0.33 mmol) and stirred at 110 °C for 24 h. The resulting mixture was cooled, treated with NaCl (10 mL) and extracted with AcOEt (5 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (SiO_2, 94:6 CH_2Cl_2/MeOH) afforded diazepinone **3a** (41 mg, 57%) as oil. $[\alpha]_D^{20}$ −35.8 (*c* 1, CH_2Cl_2), >98% ee. IR ($CHCl_3$) 2926, 1690 (C=O), 1410, 1163 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 8.06 (dd, *J* = 4.8 and 1.6 Hz, 1H, H_2), 7.11 (dd, *J* = 7.1 y 1.6 Hz, 1H, H_4), 6.45 (dd, *J* = 7.1 y 4.8 Hz, 1H, H_3), 5.38 (d, *J* = 16.4 Hz, 1H, H_5), 5.03 (dd, *J* = 6.8 y 4.6 Hz, 1H, H_{7a}), 3.70–3.57 (m, 2H, CH_2), 3.62 (d, *J* = 16.4 Hz, 1H, H_5), 3.07 (s, 3H, NMe), 2.70–2.62 (m, 1H), 2.08–1.97 (m, 2H, CH_2), 1.95–1.86 (m, 1H). ^{13}C NMR/DEPT ($CDCl_3$), δ: 169.37 (CO), 155.98 (C_{11a}), 147.99 (C_2), 136.11 (C_4), 114.47 (C_{4a}), 111.29 (C_3), 57.56 (C_{7a}), 52.96 (C_5), 48.82 (C_{10}), 34.24 (NMe), 28.35 (C_8), 23.08 (C_9). MS (CI) (*m*/*z*): 218 ($[M+H]^+$, 100), MS (EI) (*m*/*z*): 217 (23). HRMS (CI) calcd for $C_{12}H_{16}N_3O$ ($[M+H]^+$): 218.1293, found: 218.1297. HRMS (EI) calcd for $C_{12}H_{15}N_3O$ [M^+]: 217.1215, found: 217.1214.
27. Enantiomeric separation was carried out by chiral HPLC using a Chiralcel OD-H column eluted with *n*-hexane/2-propanol (gradient from 70:30 to 60:40) and UV detection at 254 nm.
28. For preparation of **4b** (Hal = Br): Robichaud, J.; Bayly, Ch. I.; Black, W. C.; Desmarais, S.; Léger, S.; Massé, F.; McKay, D. J.; Oballa, R. M.; Pâquet, J.; Percival, M. D.; Truchon, J.-F.; Wesolowski, G.; Crane, Sh. N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3146–3151; For preparation of **4b** (Hal = Cl): Bertini, V.; Luccesini, F.; Pocci, M.; De Munno, A. *Heterocycles* **1995**, *41*, 675–688.
29. For a general discussion of the reactivity of halopyridines in the S_NAr reaction, see: (a) Boulton, A. J.; McKillop, A. Reactivity of Six-membered Rings. In *Comprehensive Heterocyclic Chemistry*; Katritsky, A., Rees, Ch. W., Eds.; Pergamon Press, 1984; Vol. 2, pp 59–62; (b) Toshikazu, I.; Matsumoto, K. In *Organic Synthesis at High Pressures*; Matsumoto, K., Acheson, R. M., Eds.; Wiley: New York, 1991; pp 201–212.
30. *Procedure for Pd-catalysed N-arylation leading to (7aS)-6-methyl-5,6,7a,8,9,10-hexahydro-7H-pyrido[4,3-f]pyrrolo[1,2-a][1,4]diazepin-7-one* (**3b**): A solution of bromoamide **14b** (79 mg, 0.26 mmol) in toluene (6 mL) was added to a mixture of $Pd(OAc)_2$ (12 mg, 0.05 mmol), KO^{t}Bu (65 mg, 0.53 mmol) and BINAP (65 mg, 0.10 mmol), and the mixture was stirred under argon in a sealed tube at 110 °C. After 5 h it was cooled, and the reaction was quenched with H_2O (10 mL). After extraction with CH_2Cl_2 (3 × 10 mL), the combined organic layers were washed with brine (3 × 10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated. Purification by flash chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) afforded diazepinone **3b** (25 mg, 44%) as oil. $[\alpha]_D^{20}$ −111 (*c* 0.2, CH_2Cl_2). IR ($CHCl_3$) 2926, 1663 (C=O), 1426, 1085 cm^{-1}. ^1H NMR δ: 7.86 (br

d, J = 4.8 Hz, 1H, H_3), 7.85 (br s, 1H, H_1), 6.79 (br d, J = 4.8 Hz, 1H, H_4), 5.46 (d, J = 16.6 Hz, 1H, H_5), 4.99 (dd, J = 6.9 and 3.9 Hz, 1H, H_{7a}), 3.67 (d, J = 16.6 Hz, 1H, H_5), 3.41–3.33 (m, 2H, CH_2), 3.07 (s, 3H, NMe), 2.66–2.61 (m, 1H), 2.12–2.05 (m, 1H), 2.01–1.94 (m, 2H, CH_2). ^{13}C NMR/DEPT δ: 169.56 (CO), 142.13 (C_{11a}), 137.66 (C_3), 135.3 (C_1), 125.57 (C_{4a}), 123.03 (C_4), 58.82 (C_{7a}), 53.35 (C_5), 49.08 (C_{10}), 34.67 (NMe), 27.61 (C_8), 23.76 (C_9). MS (EI) (m/z): 217 (M^+, 82). HRMS (EI): calcd for $C_{12}H_{15}N_3O$ [M^+], 217.1215; found, 217.1219.

31. For preparation of **4c** (Hal = Br): Knutsen, L. J. S.; Hobbs, Ch. J.; Earnshaw, Ch. G.; Fiumana, A.; Gilbert, J.; Mellor, S. L.; Radford, F.; Smith, N. J.; Birch, P. J.; Burley, J. R.; Ward, S. D. C.; James, I. F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 662–667; For preparation of **4c** (Hal = Cl): Thrasher, K. J.; Hembre, E. J.; Gardinier, K. M.; Savin, K. A.; Hong, J. E.; Jungheim, L. N. *Heterocycles* **2006**, *67*, 543–547.
32. *Typical procedure for Pd-catalysed N-arylation leading to (7aS)-6-methyl-5,6,7a,8,9,10-hexahydro-7H-pyrido[3,4-f]pyrrolo[1,2-a][1,4]diazepin-7-one* (**3c**): A solution of amide **14c** (48 mg, 0.16 mmol) in toluene (4 mL) was added to a mixture of $Pd_2(dba)_3$ (7 mg, 0.008 mmol), Cs_2CO_3 (220 mg, 0.67 mmol) and BINAP (13 mg, 0.02 mmol) in a sealed tube and was stirred at 80 °C. After 24 h, the resulting mixture was cooled, treated with NH_4OH (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 5 mL) and brine (2 × 5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated. Purification by flash chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) afforded diazepinone **3c** (32 mg, 92%) as oil. $[\alpha]_D^{20}$ −57.8 (*c* 1, CH_2Cl_2), >98% ee. IR (KBr) 2925, 1663 (C=O), 1593, 1507, 1195 cm^{-1}. ^{1}H NMR δ: 8.13 (d, J = 5.8 Hz, 1H, H_2), 7.94 (s, 1H, H_4), 6.30 (d, J = 5.8 Hz, 1H, H_1), 5.39 (d, J = 16.5 Hz, 1H, H_5), 5.10 (dd, J = 7.0 y 4.5 Hz, 1H, H_{7a}), 3.70 (d, J = 16.6 Hz, 1H, H_5), 3.35–3.32 (m, 2H, CH_2), 3.08 (s, 3H, NMe), 2.69–2.64 (m, 1H), 2.11–1.95 (m, 3H). ^{13}C NMR/DEPT δ: 168 (CO), 151.13 (C_{11a}), 149.93 (C_4), 147.89 (C_2), 147.89 (CH), 114.50 (C_{4a}), 107.88 (C_1), 58.68 (C_{7a}), 51.10 (C_5), 49.24 (C_{10}), 34.12 (NMe), 27.92 (C_8), 23.33 (C_9). MS (CI) (m/z): 218 ([M+H]$^+$, 100). MS (EI) (m/z): 217 (M^+, 100). HRMS (EI) calcd for $C_{12}H_{15}N_3O$ [M^+]: 217.1215, found: 217.1216.