General and Easy Access to 11-Substituted 4-Hydroxy-2,3,4,5-tetrahydro[1,4]diazepino[1,2-*a*]indol-1-one Derivatives

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Abstract: An efficient route to prepare the 4-hydroxy-2,3,4,5-tetrahydro[1,4]diazepino[1,2-*a*]indol-1-one scaffold is described. The key reactions of the synthesis are an iodolactonisation followed by a lactone-to-lactam rearrangement. Various 11-substituted derivatives were obtained by palladium-mediated cross-coupling reactions.

Key words: diazepinoindole, seven-membered ring, iodolactonisation, palladium

Syntheses and reactivities of 1,4-diazepines fused with five- and six-membered heterocyclic rings are well investigated.[1] 2,3,4,5-Tetrahydro[1,4]diazepino[1,2-*a*]indol-1-one derivatives have received much less attention. One series of compounds **I** has been reported as precursor of serotonine antagonists (Figure 1).[2,3] The synthesis of **I** is achieved by ring closure of ethyl 1-(3-aminopropyl)-3-substituted-indole-2-carboxylates.[3]

As a part of an ongoing research work dedicated to the design of kinase inhibitors, we became interested in the design of new derivatives **II**. The retrosynthetic approach of this series was based on an iodolactonisation of 1-allylindole-2-carboxylic acids followed by a lactone-to-lactam rearrangement as shown in Scheme 1.

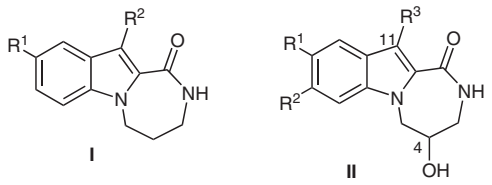
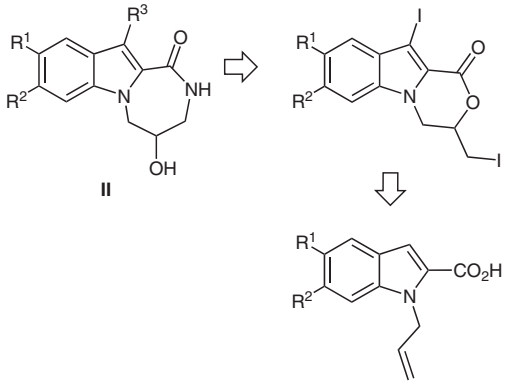


Figure 1 General formulae of **I** and **II**

We now report a direct and convenient procedure for the access of 4-hydroxy-11-iodo-2,3,4,5-tetrahydro[1,4]diazepino[1,2-*a*]indol-1-one skeleton (Scheme 2, Table 1) followed by the functionalisation of the position C-11 via palladium-mediated cross-coupling reactions.

The esters **1** were synthesised by adapting standard methods. Compounds **1a**[4] and **1b** were prepared from esterification of the commercially available acids in 92–98% yield. Treatment of commercially available *p*-anisaldehyde with ethyl azidoacetate in the presence of MeONa yielded the azidoacrylate, which was converted into indole **1c** by refluxing in xylene (overall yield 68%).[5] N-Allylation of indolic nitrogen **1** was carried out in the presence of allyl bromide and an appropriate base such as K_2CO_3 or NaH to afford **2** in good yield (**2a**: 94%, **2b**: 94% and **2c**: 88%). Saponification of esters **2** afforded acids **3** in 96–100% yield.



Scheme 1 Retrosynthetic scheme for the synthesis of **II**

The iodolactonisation was investigated on model compound **3a**. The first reaction conditions using iodine (2 equiv) in $CHCl_3$–H_2O at 0 °C for 90 minutes afforded compound **4a** in 66% yield.[6] Iodination of the position C-3 of the indole part occurred in the same time. Increase of the temperature reaction at 70 °C afforded **4a** in a better yield (84%). The second assay was performed on **3a** in the presence of *N*-iodosuccinimide (2.3 equiv) and 2,6-lutidine in CH_2Cl_2 at –20 °C.[7] Compound **4a** was again obtained in good yield (81%).[8] Iodolactonisation using *N*-iodosuccinimide was applied to **3b** and **3c** to afford **4b** and **4c**, respectively, in 94% and 67% yield. The treatment of **3c** with iodine at 0 °C afforded **4c** in a disappointing 15% yield. In this case, 1-allyl-2,3-diiodo-6-methoxyindole was isolated as the major product (41%).

Lactones **4** were finally converted into the desired lactams **5**. Once again, optimisation studies were required for this rearrangement. Treatment of **4a** with ammonia in methanol failed due to the low solubility of the starting material.[6] Addition of DMF in the reaction mixture in order to increase the solubility, unfortunately led to a partial conversion even after three days and **5a**[9] was obtained in 46% yield. By using THF instead of DMF, the reaction pro-

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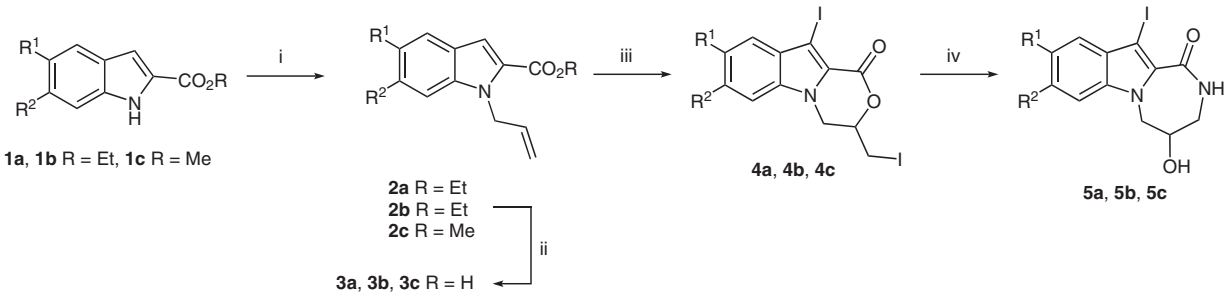
Table 1 Reaction Yields for Compounds **2–5**

Compd	R^1	R^2	Yield of **2** (%)	Yield of **3** (%)	Yield of **4** (%)		Yield of **5** (%)
					I_2	NIS	
1a	H	H	94	100	66	81	68
1b	OMe	H	94	96	–[a]	94	79
1c	H	OMe	88	98	15	67	81

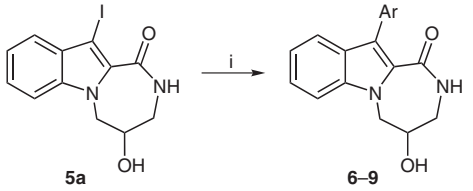
[a] Not tested.



Scheme 2 *Reagents and conditions*: i) allylbromide (2.0 equiv), K_2CO_3, MeCN, reflux, 60 h (**1a**) or NaH, DMF, 0 °C to r.t., 15 h (**1b**,**c**); ii) NaOH, EtOH–H_2O, reflux, 1 h (**2a**) or LiOH·H_2O, EtOH or MeOH, reflux, 18 h (**2b**,**c**); iii) I_2 (2 equiv), aq $NaHCO_3$, $CHCl_3$–H_2O, 0 °C, 90 min or NIS (2.3 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, –20 °C, 3 h 30; iv) NH_3 (g), MeOH–THF, r.t., 48 h for **5a** and 24 h for **5b** and **5c**.

ceeded in 48 hours affording **5a** in 68% yield. Following the same conditions, **4b** and **4c** gave **5b** and **5c** in 79–81% yield. Without methanol, no reaction occurred and starting material was recovered. According to the synthesis described above, the preparation of several grams of **5a** was easily performed for further biological and methodology studies.

Taking advantage of iodine on the indole ring, introduction of a substituent on the position C-11 by palladium coupling reactions could be expected.



Scheme 3 *Reagents and conditions*: i) Method A: $Pd(PPh_3)_4$ (10 mol%), $ArB(OH)_2$ (1.5 equiv), aq $NaHCO_3$, toluene–EtOH, reflux, 15 h; Method B: $Pd(PPh_3)_4$ (5 mol%), $ArB(OH)_2$ (1.1 equiv), Na_2CO_3, DME–H_2O, 85 °C, 3–5 h; Method C: 10% Pd/C, $ArB(OH)_2$ (2.0 equiv), Na_2CO_3, DME–H_2O, 85 °C, 4 h.

We first performed the Suzuki coupling reaction (Scheme 3) between phenylboronic acid and our model compound **5a** in the presence of freshly prepared tetrakis(triphenylphosphine)palladium (10 mol%), aqueous $NaHCO_3$ in toluene–ethanol at reflux (Method A).[10] Compound **6**[11] was isolated in 43% yield but the reaction was not completed. We noticed that the substitution of phenylboronic acid by 2-furanylboronic acid or 2-thienylboronic acid afforded products **7** and **8**, respectively, in 56% and 58% yield. We observed that the starting material **5a** was not totally soluble in the solvent system (toluene–ethanol) used. Therefore, we decided to replace it by a mixture of DME–H_2O.[12] In this case, we performed the coupling reaction with tetrakis(triphenylphosphine)palladium (5 mol%), arylboronic acid (1.1 equiv) and Na_2CO_3 in DME–H_2O at 85 °C in 3–5 hours (Method B) leading to 11-aryl derivatives **6–9** in high yield (Scheme 3 and Table 2).

We replaced $Pd(PPh_3)_4$ by 10% Pd/C described as a suitable alternative to the 'classical' homogeneous condi-

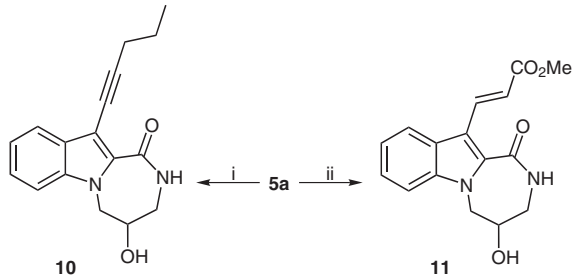
Table 2 Suzuki Coupling Yields of Compounds **6–9**

Method	Compd	Ar	Yield (%)[a]
A	**6**	Ph	43
B	**6**	Ph	86
C	**6**	Ph	88
A	**7**	2-Furanyl	56
B	**7**	2-Furanyl	82
C	**7**	2-Furanyl	20
A	**8**	2-Thienyl	58
B	**8**	2-Thienyl	75
B	**9**	4-$MeOC_6H_4$	81

[a] Isolated yield.

tions.[13] In this case, ligands and additives are generally not required for efficient transformations, and catalyst removal is easily performed by simple filtration. Just changing the Pd system, we carried out the reaction between **5a** and phenylboronic acid (Method C). The result was very encouraging because compound **6** was isolated in 88% yield. Unfortunately, when we applied the same conditions to 2-furanylboronic acid, the yield decreased from 82% to only 20% yield.

In a last part, other 'classical' palladium coupling reactions were performed on **5a** in order to obtain a large range of functionalised derivatives (Scheme 4). Thus, Sonogashira coupling reaction on **5a** was carried out with 1-pentyne to produce **10** in 63% yield.[14] Heck reaction of **5a** with an excess of methyl acrylate led to **11** in 87% yield.[15] In spite of multiple attempts, the Stille reaction of **5a** with allyltributyltin failed.[16]



Scheme 4 *Reagents and conditions*: i) $PdCl_2(PPh_3)_2$ (10 mol%), CuI (10 mol%), 1-pentyne (7 equiv), Et_3N, DMF, 45 °C, 4 h, 63%; ii) $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), methyl acrylate (10 equiv), Et_3N, DMF, 90 °C, 5 h, 87%.

In summary, we developed an efficient and straightforward route to original 4-hydroxy-11-iodo-2,3,4,5-tetrahydro[1,4]diazepino[1,2-*a*]indol-1-one derivatives. Several substituents on position C-11 were introduced by Suzuki, Sonogashira and Heck reactions. The compounds described here are currently under evaluation for their kinase-inhibitory activities and the biological results will be reported in due course.

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(8) **Typical Procedure for Iodolactonisation.**
Under a N_2 atmosphere, to a solution of 1-allyl-1*H*-indole-2-carboxylic acid (**3a**, 1.49 g, 7.4 mmol) in anhyd CH_2Cl_2 (90 mL), was added at –20 °C, 2,6-lutidine (1.30 mL, 11.1 mmol, 1.5 equiv) and NIS (3.83 g, 17.0 mmol, 2.3 equiv). The solution was stirred at –20 °C for 3.5 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was washed with 1 M HCl solution (10 mL), sat. aq solution of $Na_2S_2O_3$ (2 × 30 mL), brine solution (2 × 30 mL), and sat. aq solution of $NaHCO_3$. The organic phases were combined, dried over Na_2SO_4 and evaporated in vacuo. The crude solid was purified by recrystallisation from CH_2Cl_2 to afford **4a** (2.73 g, 81%) as a white solid; mp 169 °C (dec., CH_2Cl_2). IR (KBr): 3020, 2950, 1710, 1100, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.42 (dd, 1 H, *J* = 8.7, 10.6 Hz, CH_2I), 3.59 (dd, 1 H, *J* = 4.4, 10.6 Hz, CH_2I), 4.27 (dd, 1 H, *J* = 9.0, 12.8 Hz, NCH_2), 4.74 (dd, 1 H, *J* = 3.3, 12.8 Hz, NCH_2), 4.80–4.89 (m, 1 H, CH), 7.31 (t, 1 H, *J* = 8.0 Hz, H_{ar}), 7.36 (d, 1 H, *J* = 8.0 Hz, H_{ar}), 7.50 (t, 1 H, *J* = 8.0 Hz, H_{ar}), 7.62 (d, 1 H, *J* = 8.0 Hz, H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.1 (CH_2I), 44.9 (NCH_2), 68.9 (C), 76.2 (CH), 110.4 (CH), 121.9 (C), 122.7 (CH), 124.2 (CH), 127.8 (CH), 131.1 (C), 136.8 (C), 157.4 (CO). ESI-MS: *m/z* = 454 $[M + H]^+$. Anal. Calcd for $C_{12}H_9I_2NO_2$: C, 31.82; H, 2.00; N, 3.09. Found: C, 32.11; H, 2.13; N, 2.95.
(9) **Typical Procedure for Lactam Formation.**
A solution of iodolactone **4a** (3.60 g, 7.95 mmol) in anhyd MeOH (60 mL) and anhyd THF (30 mL) was added dropwise over a period of 20 min to an ice-cold sat. NH_3 in MeOH solution (30 mL). The reaction mixture was allowed to warm up to r.t. for 48 h. The solvents were then removed by evaporation and the crude residue was purified by recrystallisation from EtOAc–EtOH to afford **5a** (1.75 g, 64%) as a white solid. The filtrate was then purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 94:6) to give 0.11 g of **5a** (overall yield 68%) as a white solid; mp 199 °C (dec., EtOAc–EtOH). IR (KBr): 3410, 3320–3200, 3060, 2920, 1635, 1515, 1090, 745 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 2.73–2.80 (m, 1 H, CH_2NH), 3.15–3.21 (m, 1 H, CH_2NH), 4.18–4.29 (m, 2 H, NCH_2 and CH), 4.43–4.49 (m, 1 H, NCH_2), 5.38 (d, 1 H, *J* = 3.4 Hz, OH), 7.19 (t, 1 H, *J* = 7.9 Hz, H_{ar}), 7.35 (t, 1 H, *J* = 7.9 Hz, H_{ar}), 7.39 (d, 1 H, *J* = 7.9 Hz, H_{ar}), 7.58 (d, 1 H, *J* = 7.9 Hz, H_{ar}), 8.30 (t, 1 H, *J* = 5.5 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.3 (CH_2), 48.7 (CH_2), 61.3 (CI), 69.5 (CH), 111.0 (CH), 120.8 (CH), 121.7 (CH), 124.6 (CH), 129.2 (C), 133.4 (C), 137.2 (C), 164.0 (CO). ESI-MS: *m/z* = 343 $[M + H]^+$. Anal. Calcd for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; N, 8.19. Found: C, 41.87; H, 3.12; N, 8.05.
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(11) **Physical Data of Compound 6.**
Mp >210 °C (washing EtOAc). IR (KBr): 3420, 3310–3250, 3070, 2980, 1640, 1550, 1490, 1085, 750, 700 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 2.82–2.91 (m, 1 H, CH_2NH), 3.20–3.30 (m, 1 H, CH_2NH), 4.25–4.30 (m, 2 H, NCH_2 and CH), 4.42–4.48 (m, 1 H, NCH_2), 5.38 (d, 1 H, *J* = 3.4 Hz, OH), 7.12 (t, 1 H, *J* = 7.5 Hz, H_{ar}), 7.29–7.64 (m, 8 H, H_{ar}), 8.25 (t, 1 H, *J* = 5.9 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.3 (CH_2), 47.9 (CH_2), 69.6 (CH), 110.5 (CH), 118.4 (C), 119.9 (CH), 120.3 (CH), 123.8 (CH), 125.4 (C), 126.4 (CH), 128.1 (2 CH), 129.7 (2 CH), 129.9 (C),

133.7 (C), 136.3 (C), 164.8 (CO). ESI-MS: *m/z* = 293 [M + H]$^+$. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.33; H, 5.67; N, 9.63.

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