Atom-Economical Construction of a Rare 6,7-Dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepine Scaffold

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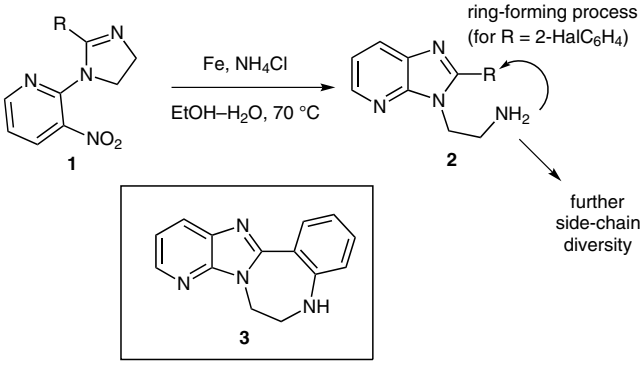
Abstract: We have developed a route towards novel 6,7-dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepines, in five straightforward steps from commercially available 2-bromobenzaldehydes and 3-(2-aminoethyl)imidazo[4,5-*b*]pyridines we have described previously, with full control over the three elements of diversity. The route appears to be suitable for systematic exploration of structure–activity relationships around this medicinally relevant tetracyclic scaffold.

Key words: scaffold-oriented synthesis, Buchwald arylation, Bechamp reduction

Recently, we described a facile transformation of *N*-(3-nitro-2-pyridyl)imidazolines **1** into 3-(2-aminoethyl)imidazo[4,5-*b*]pyridines **2** under Bechamp reduction conditions.[1] The 2-aminoethyl side chain in **2** (derived from the imidazoline bismethylene moiety in **1**) means that these compounds may be considered as analogues of tryptamine.[2] We reasoned that the primary amine functionality could be viewed not only as a site for introducing additional side-chain diversity (e.g., via reductive amination) but also as providing an opportunity for linking the imidazo[4,5-*b*]pyridine moiety to the 2-aryl substituent (via intramolecular aryl halide amination) and thus forming a tetracyclic scaffold **3** (Scheme 1).

A preliminary review of the literature related to **3** revealed its novelty. Indeed, only one compound (**4**) containing this scaffold in its entirety has been described in the literature (though no biological data have been reported).[3] At the same time, the two tricyclic moieties contained in **3** appear as cores for a range of pharmaceuticals (Scheme 2). The 6,7-dihydroimidazo[1,2-*d*][1,4]benzodiazepine portion (shown in the box) was featured in Hoffmann-La Roche's inverse agonists of $GABA_A$ α5 receptors **5**,[4] Leiden University's ligands for adenosine receptors **6**,[5] Acadia Pharmaceuticals' Mrg receptor agonists for pain management **7**[6] (also developed at Caltech[7]), Arqule's inhibitors of Akt1 kinase **8** with antiproliferative activity,[8] as well as inhibitors of *E. coli* RecA ATPase **9** described by University of North Carolina.[9] The latter, along with **7**, appear to stem from a closely related combinatorial library disclosed by Trega Biosciences.[10]



Scheme 1 Imidazo[4,5-*b*]pyridines **2** with a 2-aminoethyl side chain for building further scaffold complexity toward **3**

In contrast, the 7,8,9,10-tetrahydropyrido[3′,2′:4,5]imidazo[1,2-*a*]azepine moiety (shown in the circle) is far less common and only one report on inverse agonists and antagonists of histamine H3 receptors, exemplified by **10**, was found in the literature.[11]

Prompted by these observations and having access to compound **11** that we had prepared earlier[1] and which contained all necessary substitution, we proceeded to test out formation of the tetrahydroimidazo[1,2-*a*]azepine system under Buchwald conditions.[12] Although the formation of a seven-membered ring via intramolecular palladium-catalyzed amination of haloaromatics (to give benzazepines) is well documented in the literature,[13] there has been only one report of a similar reaction involving (benzo)imidazo-bridged amino side chains [realized under copper(I)-catalyzed conditions].[14] We were therefore gratified to observe that compound **11** was converted cleanly, although somewhat sluggishly, into the desired 6,7-dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepine (3, Scheme 3) under very similar conditions15 to those used in the preparation of precursor 11,1 thus alleviating a need to screen for alternative ligands and sources of palladium. Compound 3 turned out to be highly crystalline (which is consistent with its rigid tetracyclic structure) and we were able to obtain a single-crystal X-ray structure for it to confirm the connectivity within the tetracycle (Figure 1).16

We thus envisaged a series of analogues that could be derived from 2-bromobenzaldehydes **12** and 2-chloro-3-nit-

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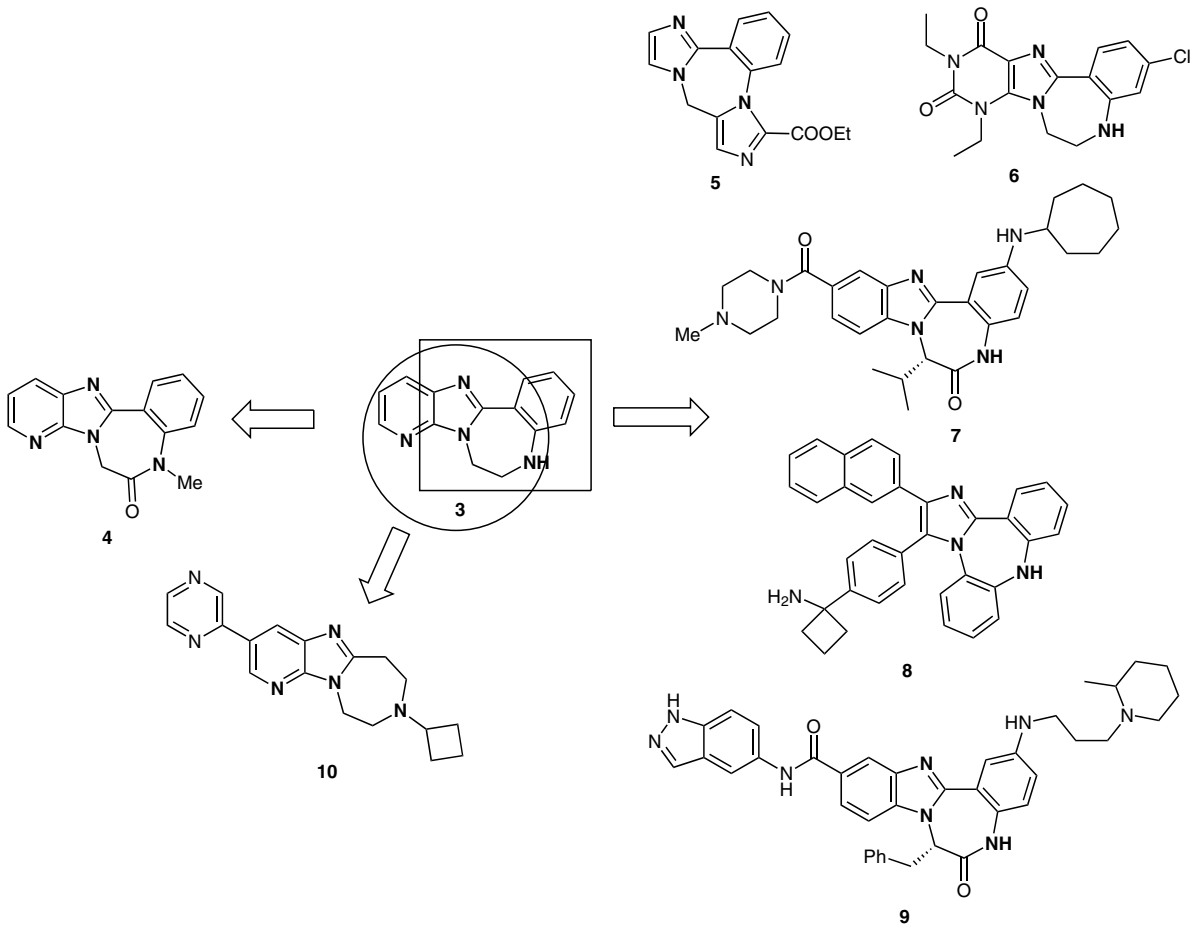
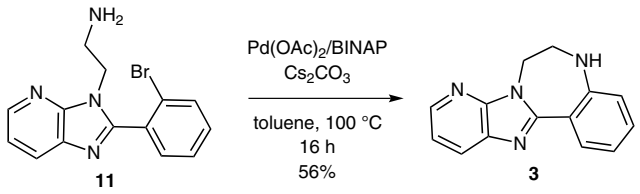


Scheme 2 Pharmaceutical relevance of 6,7-dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepines **3**



Scheme 3 Preparation of compound **3** from precursor **11** described earlier[1]

ropyridines **14**, but we also aimed to introduce a third point of diversity by performing reductive alkylation of the 3-(2-aminoethyl)imidazo[4,5-*b*]pyridines prior to the Buchwald-type cyclization step. Thus, we sought to achieve full control over three elements of diversity that would make our protocol particularly attractive for library synthesis.

Preparation of 2-imidazolines **13** from the respective benzaldehydes **12**, with subsequent palladium-catalyzed N-arylation of the former using **14**, was achieved in a straightforward fashion as described previously.[17] The reductive rearrangement of the intermediate *N*-pyridyl imidazolines **15** under Bechamp conditions[1] turned out to be high-yielding, tolerating a range of substituents on the

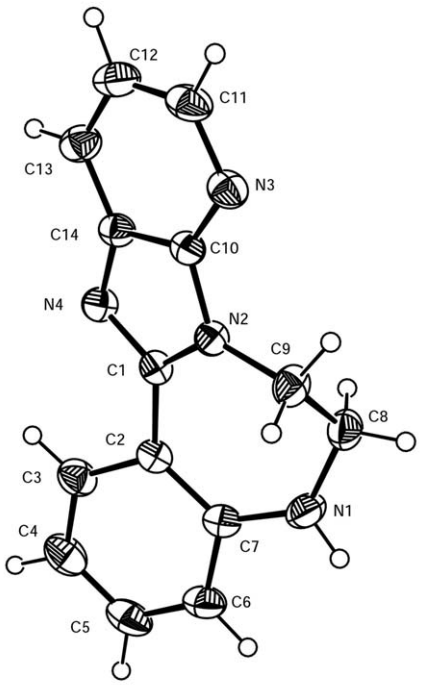


Figure 1 X-ray crystallographic structure of compound **3**

Table 1 Diversely Substituted 6,7-Dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepines **18a**–**m** Prepared in this Work

Entry	Product **18**	X	Y	R	Yield of **16** (%)	Yield of **18** (%)
1	**18a**	4-F	H	Ph	65	44
2	**18b**	5-F	H	Ph	73	63
3	**18c**	5-MeO	H	*c*-Pr	81	23
4	**18d**	H	H	4-$MeOC_6H_4$	711	58
5	**18e**	H	6-Me	Ph	48	61
6	**18f**	H	5-Cl	Ph	59	61
7	**18g**	H	H	4-ClC_6H_4	711	59
8	**18h**	H	5-Cl	*c*-Pr	59	82
9	**18i**	5-Cl	H	Ph	77	77
10	**18j**	5-Cl	5-Cl	Ph	78	69
11	**18k**	5-Cl	6-Me	*c*-Hex	58	33
12	**18l**	H	H	*c*-Hex	711	41
13	**18m**	H	H	4-ClC_6H_4	711	64

pyridine and the phenyl rings. 3-(2-Aminoethyl)imidazo[4,5-*b*]pyridines **16** were subjected to a stepwise reductive alkylation procedure[18] with a range of aromatic as well as aliphatic aldehydes. The resultant secondary amines **17** were found to be at least 85% pure by ^1H NMR spectroscopy and, without further purification, were subjected to the same Buchwald arylation conditions as were used to prepare **3**.[15] The secondary amines **17** turned out to be markedly more reactive compared to their primary amine counterpart **11**, the complete conversion was achieved within 16 hours, providing the target tetracycles **18a**–**m** (Table 1) in good to excellent yields over two steps from **16** (Scheme 4).[19]

In summary, we have developed a concise, streamlined, and atom-economical[20] route toward novel 6,7-dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepines, in five steps from commercially available 2-bromobenzaldehydes, making use of the primary amine functionality of the 3-(2-aminoethyl)imidazo[4,5-*b*]pyridines we have described previously, with full control over the three elements of diversity. The route appears to be distinctly suitable for systematic library generation within this tetracyclic scaffold.

Acknowledgment

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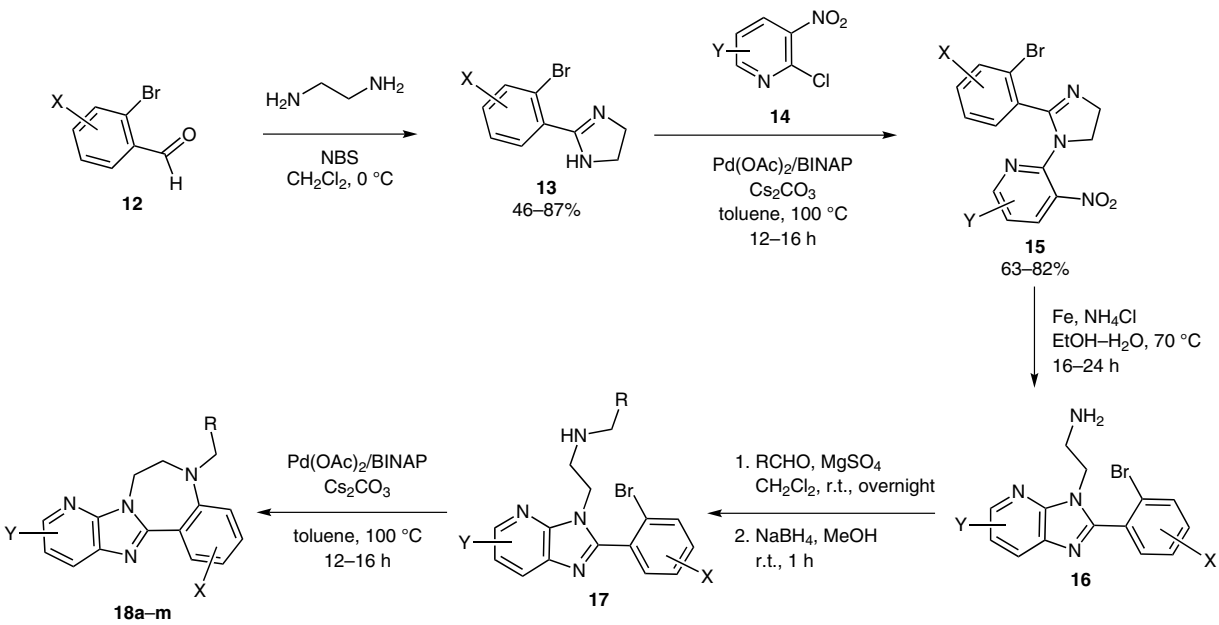

Scheme 4 Synthesis of tetracyclic 6,7-dihydropyrido[3′,2′:4,5]imidazo[1,2-*d*][1,4]benzodiazepines **18a**–**m** with three elements of diversity

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(15) **General Procedure for the Intramolecular Buchwald Arylation (0.1–0.4 mmol Scale)**
A thick-glassed, screw-capped pressure tube (50 mL) was charged with a suspension of the requisite 2-aminoethyl-substituted imidazo[4,5-*b*]pyridine intermediate **17** (1.0 equiv) and Cs_2CO_3 (1.1 equiv) in toluene (3 mL/mmol), along with a stir bar. Meanwhile, $Pd(OAc)_2$ (0.05 equiv) and BINAP (0.1 equiv) were weighed into a vial, suspended in toluene (2–3 mL), and shaken while immersed in a 100 °C oil bath for 2 min. The resulting clear, purple, or light-brown catalyst solution was added in one portion to the vigorously stirred reaction mixture. The tube was filled with argon, capped and stirred at 100 °C for 16 h (48 h for **3**). The mixture was allowed to cool to ambient temperature, filtered through a plug of Celite, and the latter was additionally washed with EtOAc. The filtrate was concentrated under reduced pressure, and the crude material was purified by column chromatography on silica gel using a 0–5% gradient of MeOH in CH_2Cl_2 to furnish target compounds **3** and **18a**–**m**.
(16) Crystallographic data (excluding structure factors) for compound **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1004050. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].
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(18) **General Procedure for the Reductive Alkylation of 16 (0.5 mmol Scale)**
Equimolar amounts of **16** and the requisite aldehyde were combined in CH_2Cl_2 (5 mL). Anhydrous $MgSO_4$ (500 mg) was added, and the mixture was stirred at r.t. overnight. The $MgSO_4$ was filtered off, washed with CH_2Cl_2 (50 mL), and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in MeOH (5 mL), treated with $NaBH_4$ (0.3 mmol), and the mixture stirred at r.t. for 1 h, at which point the reaction was complete according to TLC analysis. The mixture was partitioned between EtOAc (50 mL) and sat. aq $NaHCO_3$ (25 mL), the organic layer separated, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy and used in the next step without further purification.
(19) **Characterization Data for Selected Compounds**
Compound **18d**: white solid; mp 131–133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (dd, *J* = 7.9, 1.45 Hz, 1 H), 8.34 (dd, *J* = 4.75, 1.25 Hz, 1 H), 8.11 (dd, *J* = 7.95, 1.25 Hz, 1 H), 7.34–7.37 (m, 1 H), 7.26 (dd, *J* = 7.95, 4.75 Hz, 1 H), 7.21 (d, *J* = 8.55 Hz, 2 H), 7.06 (t, *J* = 7.85 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.58 (s, 2 H), 4.43–4.45 (m, 2 H), 3.80 (s, 3 H), 3.64–3.66 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 153.3, 149.8, 148.7, 143.4, 134.2, 132.1, 131.9, 129.3, 129.0, 126.4, 120.7, 119.1, 118.0, 117.9, 114.4, 56.9, 55.5, 51.7, 45.5. LC–MS (ESI): *m/z* = 357.40 $[M + H]^+$. Anal. Calcd for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, 73.98; H, 5.57; N, 15.84.
Compound **18g**: white solid; mp 170–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 8.05, 1.5 Hz, 1 H), 8.34 (dd, *J* = 4.8, 1.25 Hz, 1 H), 8.11 (dd, *J* = 7.75, 1.4 Hz, 1 H), 7.26–7.36 (m, 4 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 7.07 (t, *J* = 7.9 Hz, 1 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 4.60 (s, 2 H), 4.47–4.49 (m, 2 H), 3.65–3.67 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.2, 149.2, 148.6, 143.6, 136.1, 134.3, 133.5, 132.1, 132.0, 129.2, 129.0, 126.6, 121.1, 119.2, 118.5, 118.1, 57.1, 52.5, 45.0. LC–MS (ESI): *m/z* = 361.31 $[M + H]^+$. Anal. Calcd for $C_{21}H_{17}ClN_4$: C, 69.90; H, 4.75; N, 15.53. Found: C, 70.02; H, 4.67; N, 15.64.
Compound **18k**: beige solid, mp 134–136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83–7.99 (m, 2 H), 7.77 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 1 H), 7.46 (d, *J* = 1.7 Hz, 1 H), 4.33–4.38 (m, 2 H), 3.85–3.33 (m, 2 H), 3.33–3.47 (m, 2 H), 2.83 (s, 3 H), 1.38–1.53 (m, 9 H), 1.12–1.28 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8, 149.6, 147.7, 143.1, 132.3, 130.1, 128.6, 128.5, 126.3, 119.2, 118.7, 114.3, 60.1, 53.4, 40.5, 40.4, 30.1, 27.1, 26.5, 22.8. LC–MS (ESI): *m/z* = 381.92 $[M + H]^+$. Anal. Calcd for $C_{22}H_{25}ClN_4$: C, 69.16; H, 6.86; N, 14.64. Found: C, 69.07; H, 6.79; N, 14.72.
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