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Libraries of 2,3,4,6,7,11*b*-Hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-amine Derivatives via a Multicomponent Assembly Process/1,3-Dipolar Cycloaddition Strategy

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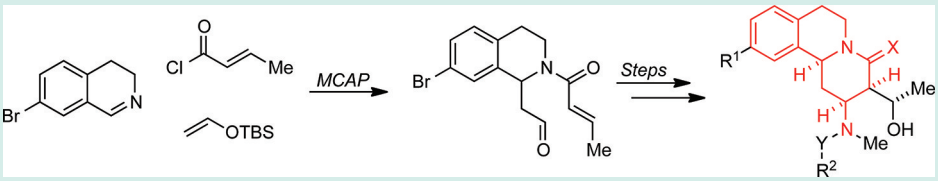
Supporting Information



ABSTRACT: A Mannich-type multicomponent assembly process/1,3-dipolar cycloaddition strategy has been developed for the rapid and efficient construction of a parent tetrahydroisoquinoline fused isoxazolidine scaffold, which was subsequently functionalized using well-established protocols to access a diverse 70-membered library of novel 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-2-amine derivatives.

KEYWORDS: *combinatorial chemistry, dipolar cycloaddition, heterocycles, Mannich, multicomponent reaction*

INTRODUCTION

Modern day drug discovery relies on the identification of potent and selective modulators of biological systems, either as probes for the functional and mechanistic study of these systems, or as drug leads. Once initial leads are identified, their properties can be fine-tuned through selective modification of functional groups and substituents to achieve the desired physiochemical attributes. According to Lipinski's rule of five, compounds with a molecular weight of 500 or less, a clogP of 5 or less, 5 or less hydrogen bond donors, and 10 or less hydrogen bond acceptors are more likely to be successful candidates than compounds violating more than one of these rules.[1] Although these criteria are certainly not absolute, they provide medicinal chemists with a reliable guideline for rational library design. In the context of lead compound identification, various strategies have been developed for generating small molecule libraries[2] that are then evaluated for their biological properties by high-throughput screening (HTS).

Some years ago we developed a novel approach to the total synthesis of (±)-tetrahydroalstonine. A pivotal step in this synthesis was a Mannich-type multicomponent assembly process (MCAP) that allowed facile access to a key aldehyde intermediate that was further elaborated via an intramolecular Diels–Alder reaction to a pentacyclic intermediate, refunctionalization of which delivered the natural product in a mere five chemical operations from tryptamine.[3] We have since developed this reaction into a four-component process[4,5] and have demonstrated its utility for the diversity oriented synthesis (DOS) of unique heterocycles comprising the benzodiazepine,[6] tetrahydropyridine,[7] 2-aryl piperidine,[8] and tetrahydroisoquinoline ring systems.[9,10]

The tetrahydroisoquinoline ring system is present in a variety of natural products and pharmaceutical agents that exhibit a wide array of biological properties including antihypertensive,[11] antitumor,[12] and antimalarial activities.[13] Moreover, compounds containing the 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-2-amine scaffold (**1**) are documented as α_2-adrenoceptor antagonists (**2**–**4**),[14] opioid receptor antagonists (**5**),[15] and dipeptidyl peptidase IV (DPP-IV) inhibitors (**6**)[16] (Figure 1). We have recently reported a method for the rapid and efficient assembly of the scaffold comprising **1** via an MCAP/1,3-dipolar cycloaddition strategy.[9] To demonstrate the utility of this chemistry in the synthesis of libraries of small molecules, we prepared a diverse 70-membered library of 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-2-amine (**1**) derivatives from a readily accessible scaffold by exploiting well-established palladium-catalyzed cross-coupling protocols, and simple N-functionalization reactions. We now report the details of these studies.

RESULTS AND DISCUSSION

The library synthesis commenced with the construction of the parent tetrahydroisoquinoline fused isoxazolidine scaffolds **10** and **11** from readily available 7-bromodihydroisoquinoline (**7**) (Scheme 1).[17] In the event, treatment of imine **7** with *trans*-crotonoyl chloride and silyl enol ether **8** in the presence of catalytic amounts of TMSOTf at room temperature furnished aldehyde **9**, which upon condensation with N-methylhydroxylamine gave an intermediate nitrone that underwent facile 1,3-

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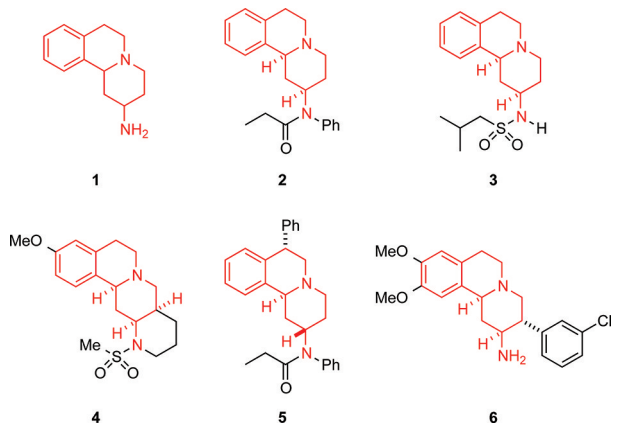
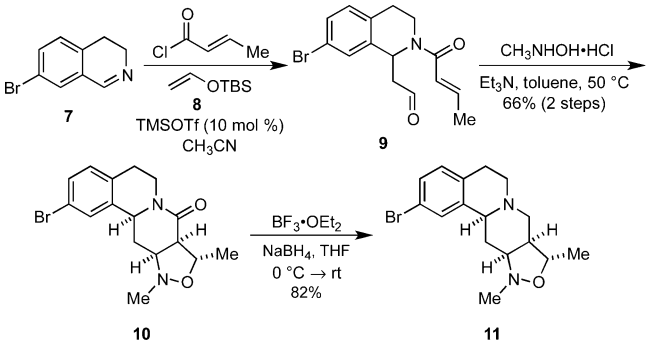


Figure 1. Biologically active compounds containing the 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-2-amine scaffold.

Scheme 1. Synthesis of Isoxazolidine Scaffolds 10 and 11

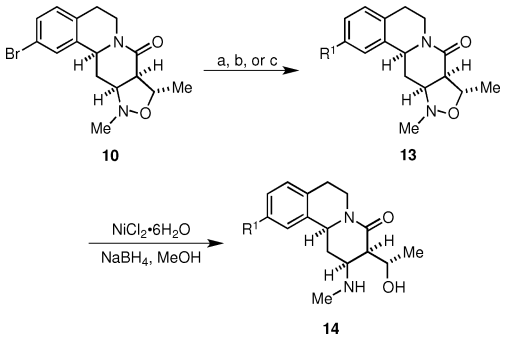


dipolar cycloaddition to provide the isoxazolidine **10** in 66% yield from **7**; no other stereoisomers were detected. The relative stereochemistry of **10** was determined unambiguously by single crystal X-ray analysis.[9d] Notably, **10** is easily prepared from **7** on a multigram scale, without the need for column chromatography. Reduction of the lactam moiety in **10** with freshly prepared borane gave tertiary amine **11** in 82% yield. It was necessary to use borane for this transformation, because reaction with lithium aluminum hydride was unselective and resulted in reductive cleavage of the N,O-bond of the isoxazolidine ring, as well as reduction of the lactam moiety.

With scaffolds **10** and **11** in hand, we prepared the corresponding libraries of lactams and amines, respectively. Accordingly, reaction of **10** under standard Suzuki[18] or Buchwald–Hartwig[19] cross-coupling conditions provided chemset **13** in moderate to excellent yields (Scheme 2, Figure 2, and Table 1). For Suzuki reactions, arylboronic acids were chosen such that electron neutral (**12**{*1*}), electron rich (**12**{*2*}), and electron deficient (**12**{*3*}) groups with varied substitution patterns were incorporated in the biaryl products in order to enable exploration of structure–activity relationships (SAR) during biological screening. Subsequent N,O-bond cleavage mediated by nickel(II) boride that was generated in situ proceeded smoothly to furnish chemset **14** in 81–92% yields.[20] This transformation could also be achieved with Zn/AcOH; however, this reductive method was typically lower yielding.

The secondary amine functionality resident in chemset **14** was an obvious embarkation point for derivatization, and as such, we sought to exploit it for rapid access to novel derivatives of **1**. Reaction of chemset **14** with the N-functionalizing

Scheme 2. Cross-Coupling Reactions of Lactam 10 and N,O-Bond Cleavage of Isoxazolidines 13[a]



[a]Conditions: (a) **12**{*1*–*3*}, Pd[P(*t*-Bu)$_3$]$_2$ (1 mol %), Cs_2CO_3, 1,4-dioxane, 100 °C; (b) **12**{*4*,*5*}, Pd(OAc)$_2$ (5 mol %), JohnPhos (5 mol %), NaO*t*-Bu, toluene, 100 °C; (c) **12**{*6*}, Pd(OAc)$_2$ (5 mol %), JohnPhos (5 mol %), K_3PO_4, toluene, 100 °C.

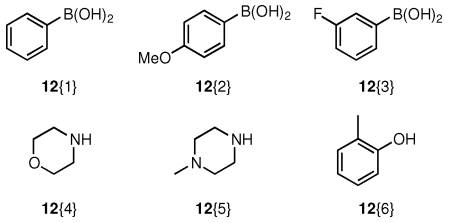


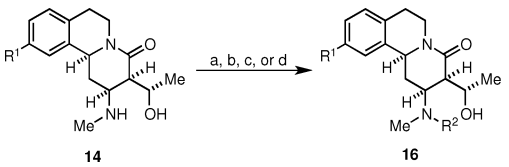
Figure 2. Reagents used for cross-coupling reactions of lactam **10**.

Table 1. Preparation of 13 via Palladium-Catalyzed Cross-Couplings and 14 via N,O-Bond Cleavage

entry	cross-coupling reagent	product	yield (%)	product	yield (%)
1	**12**{*1*}	**13**{*1*}	99	**14**{*1*}	87
2	**12**{*2*}	**13**{*2*}	94	**14**{*2*}	88
3	**12**{*3*}	**13**{*3*}	99	**14**{*3*}	83
4	**12**{*4*}	**13**{*4*}	99	**14**{*4*}	81
5	**12**{*5*}	**13**{*5*}	88	**14**{*5*}	90
6	**12**{*6*}	**13**{*6*}	57	**14**{*6*}	92

reagents **15** under standard conditions provided chemset **16** (Scheme 3, Figure 3, and Table 2) in moderate to excellent

Scheme 3. N-Functionalization of Secondary Amines 14[a]



[a]Conditions: (a) **15**{*1*–*5*}, Et_3N, CH_2Cl_2, 0 °C → rt; (b) **15**{*6*,*7*}, Et_3N, CH_2Cl_2; (c) **15**{*8*–*10*}, CH_2Cl_2; (d) **15**{*11*,*12*}, CH_2Cl_2.

yields. A wide array of N-functionalizing reagents was chosen including alkyl, heteroaryl, and aryl substituents with varied electronics and substitution patterns to gain useful SAR data. Notably, these reactions were selective for reaction on nitrogen, and products of O-functionalization were only seldom detected in trace quantities. Although the biological profiles of compounds related to **1** are well documented, lactam derivatives, such as those embodied in chemset **16**, have not been thoroughly studied.

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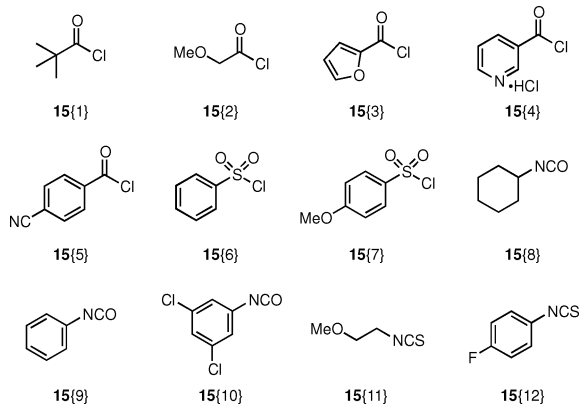


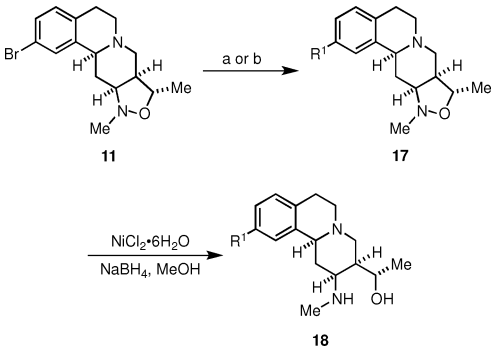
Figure 3. N-Functionalizing reagents.

Table 2. Data for Compounds 16 Synthesized via N-Functionalizations

entry	secondary amine	N-functionalizing reagent	product	yield (%)
1	**14**{*2*}	**15**{*1*}	**16**{*2,1*}	76
2	**14**{*3*}	**15**{*1*}	**16**{*3,1*}	65
3	**14**{*4*}	**15**{*1*}	**16**{*4,1*}	67
4	**14**{*1*}	**15**{*2*}	**16**{*1,2*}	64
5	**14**{*5*}	**15**{*2*}	**16**{*5,2*}	84
6	**14**{*6*}	**15**{*2*}	**16**{*6,2*}	79
7	**14**{*1*}	**15**{*3*}	**16**{*1,3*}	44
8	**14**{*5*}	**15**{*3*}	**16**{*5,3*}	69
9	**14**{*6*}	**15**{*3*}	**16**{*6,3*}	85
10	**14**{*1*}	**15**{*4*}	**16**{*1,4*}	81
11	**14**{*5*}	**15**{*4*}	**16**{*5,4*}	99
12	**14**{*6*}	**15**{*4*}	**16**{*6,4*}	80
13	**14**{*1*}	**15**{*5*}	**16**{*1,5*}	74
14	**14**{*5*}	**15**{*5*}	**16**{*5,5*}	89
15	**14**{*6*}	**15**{*5*}	**16**{*6,5*}	88
16	**14**{*2*}	**15**{*6*}	**16**{*2,6*}	64
17	**14**{*3*}	**15**{*6*}	**16**{*3,6*}	92
18	**14**{*4*}	**15**{*6*}	**16**{*4,6*}	61
19	**14**{*1*}	**15**{*7*}	**16**{*1,7*}	78
20	**14**{*5*}	**15**{*7*}	**16**{*5,7*}	55
21	**14**{*6*}	**15**{*7*}	**16**{*6,7*}	75
22	**14**{*1*}	**15**{*8*}	**16**{*1,8*}	72
23	**14**{*5*}	**15**{*8*}	**16**{*5,8*}	62
24	**14**{*6*}	**15**{*8*}	**16**{*6,8*}	78
25	**14**{*2*}	**15**{*9*}	**16**{*2,9*}	69
26	**14**{*3*}	**15**{*9*}	**16**{*3,9*}	86
27	**14**{*4*}	**15**{*9*}	**16**{*4,9*}	74
28	**14**{*1*}	**15**{*10*}	**16**{*1,10*}	73
29	**14**{*5*}	**15**{*10*}	**16**{*5,10*}	61
30	**14**{*6*}	**15**{*10*}	**16**{*6,10*}	48
31	**14**{*1*}	**15**{*11*}	**16**{*1,11*}	42
32	**14**{*5*}	**15**{*11*}	**16**{*5,11*}	65
33	**14**{*6*}	**15**{*11*}	**16**{*6,11*}	87
34	**14**{*1*}	**15**{*12*}	**16**{*1,12*}	75
35	**14**{*5*}	**15**{*12*}	**16**{*5,12*}	74
36	**14**{*6*}	**15**{*12*}	**16**{*6,12*}	68

Analogous to the chemistry outlined in Scheme 2, cross-coupling of amine **11** with the reagents in chemset **12** under Suzuki[21] or Buchwald–Hartwig[22] conditions provided chemset **17** in 81–95% yield (Scheme 4, Figure 4, Table 3). Perhaps because of the tertiary amine functionality present in **11**, we found that catalyst systems different from those used to promote the related cross-couplings of lactam **10** (Scheme 2) gave better yields of product. Subsequent N,O-bond cleavage proceeded without event to furnish chemset **18** in good yields.

Scheme 4. Cross-Coupling Reactions and N,O-Bond Cleavage of Amine 11[a]



[a]Conditions: (a) **12**{*7,8*}, $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (5 mol %), CsF, toluene, 110 °C; (b) **12**{*4*}, $Pd(OAc)_2$ (10 mol %), (±)-BINAP (12 mol %), Cs_2CO_3, toluene, 100 °C.

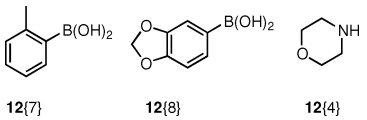


Figure 4. Reagents used for cross-coupling reactions.

Table 3. Preparation of 17 via Palladium-Catalyzed Cross-Couplings and 18 via N,O-Bond Cleavage

entry	cross-coupling reagent	product	yield (%)	product	yield (%)
1	**12**{*7*}	**17**{*7*}	95	**18**{*7*}	90
2	**12**{*8*}	**17**{*8*}	82	**18**{*8*}	84
3	**12**{*4*}	**17**{*4*}	81	**18**{*4*}	90

The secondary amine functionality present in chemset **18** was exploited to rapidly prepare derivatives of **1**. Chemset **19** was readily accessed through reaction of amines **18** with **15**{*3*}, **15**{*13*}, and **15**{*5*} under standard conditions (Scheme 5, Figure 5, and Table 4). Attempted reductive amination of amines **18** under standard conditions resulted in mixtures of N,O-acetals **20** and tertiary amines **21**. Because the N,O-acetals **20** proved markedly stable, a two-step procedure was employed to access tertiary amines **21**. Accordingly, amines **18** were condensed with cyclohexane carboxaldehyde (**15**{14}) to give *N,O*-acetals **20**, which underwent facile reduction with sodium cyanoborohydride in the presence of acetic acid to provide tertiary amines **21** in good overall yield.

SUMMARY

We have prepared a 70-membered library of derivatives of the pyrido[2,1-*a*]isoquinoline **1** utilizing a sequential MCAP/1,3-dipolar cycloaddition process to generate functionalized scaffolds that were readily diversified. It is noteworthy that only three members of this library violate Lipinski's rule of five. Thus, the vast majority of the members of this novel library are worthy lead candidates having favorable physiochemical properties (see table in Supporting Information). These compounds have been submitted to the NIH Molecular Libraries Small Molecule Repository (MLSMR) for distribution

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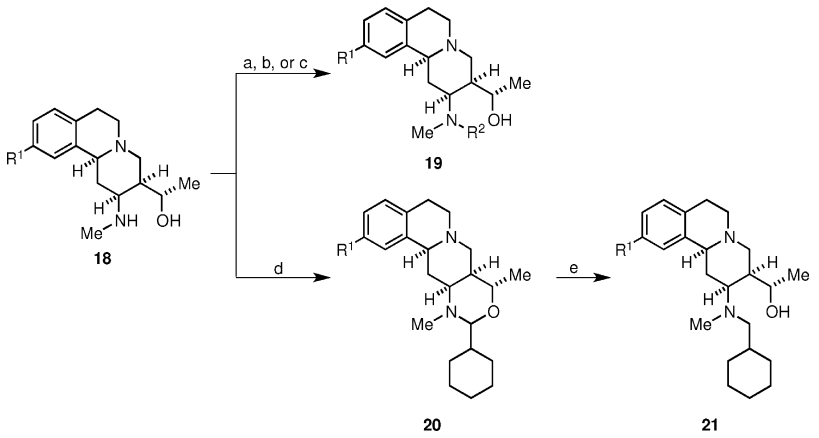
Scheme 5. N-Functionalization of Secondary Amines 18[a]



[a]Conditions: (a) **15**{*3*}, Et_3N, CH_2Cl_2; (b) **15**{*13*}, Et_3N, CH_2Cl_2; (c) **15**{*5*}, CH_2Cl_2; (d) **15**{*14*}, DCE, 84 °C; (e) $NaCNBH_3$, AcOH, DCE.

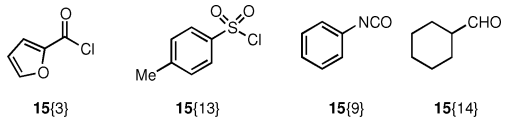


Figure 5. N-Functionalizing reagents.

Table 4. Data for Compounds 19−21 Synthesized via N-Functionalizations

entry	secondary amine	N-functionalizing reagent	product	yield (%)
1	**18**{*7*}	**15**{*3*}	**19**{*7,3*}	77
2	**18**{*8*}	**15**{*3*}	**19**{*8,3*}	67
3	**18**{*4*}	**15**{*3*}	**19**{*4,3*}	99
4	**18**{*7*}	**15**{*13*}	**19**{*7,13*}	62
5	**18**{*8*}	**15**{*13*}	**19**{*8,13*}	55
6	**18**{*4*}	**15**{*13*}	**19**{*4,13*}	73
7	**18**{*7*}	**15**{*9*}	**19**{*7,9*}	55
8	**18**{*8*}	**15**{*9*}	**19**{*8,9*}	70
9	**18**{*4*}	**15**{*9*}	**19**{*4,9*}	99
10	**18**{*7*}	**15**{*14*}	**20**{*7,14*}	99
11	**18**{*8*}	**15**{*14*}	**20**{*8,14*}	84
12	**18**{*4*}	**15**{*14*}	**20**{*4,14*}	81
13			**21**{*7,14*}	83
14			**21**{*8,14*}	70
15			**21**{*4,14*}	64

to HTS centers within the Molecular Libraries Probe Production Centers Network (MLPCN) and subsequent evaluation of their biological properties. Moreover, selected compounds have been sent to the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH PDSP). Further applications of this and related approaches to the synthesis of compound libraries are in progress, and the results of these investigations and the biological activities of representative members will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectral data for all new compounds, full characterization data for representative compounds, LCMS data for representative compounds, and tabulated Lipinski's rule parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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