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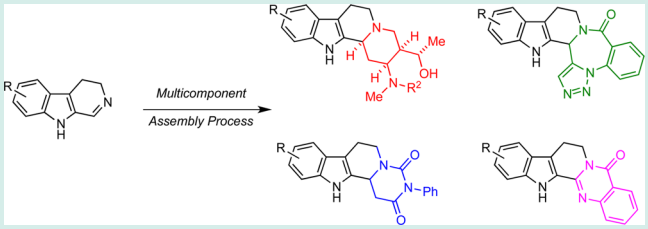
Multicomponent Assembly Processes for the Synthesis of Diverse *Yohimbine* and *Corynanthe* Alkaloid Analogues

Brett A. Granger, Zhiqian Wang, Kyosuke Kaneda, Zhenglai Fang, and Stephen F. Martin*

Department of Chemistry and Biochemistry, The Texas Institute for Drug and Diagnostic Development, The University of Texas at Austin, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: A strategy involving a Mannich-type multicomponent assembly process followed by a 1,3-dipolar cycloaddition has been developed for the rapid and efficient construction of parent heterocyclic scaffolds bearing indole and isoxazolidine rings. These key intermediates were then readily elaborated using well-established protocols for refunctionalization and cross-coupling to access a diverse 180-member library of novel pentacyclic and tetracyclic compounds related to the *Yohimbine* and *Corynanthe* alkaloids. Several other new multicomponent assembly processes were developed to access dihydro-β-carboline-fused benzodiazepines, pyrimidinediones, and rutaecarpine derivatives.



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

INTRODUCTION

The discovery of small molecules that potently and selectively modulate biological targets is a critical endeavor that enables fundamental studies of complex systems using temporal biological probes and that generates potential drug leads to treat medical abnormalities. Once a promising lead compound is identified, its physiochemical properties may be fine-tuned through selective modification of functional groups and substituents. In this context, others have developed useful strategies for the preparation of small molecule libraries toward the goal of identifying compounds that display potent activity toward known targets via high throughput screening (HTS).[1]

The *Yohimbine* and *Corynanthe* alkaloids, of which yohimbine (**1**), tetrahydroalstonine (**2**), and geissoschizine (**3**) are typical members (Figure 1), are well documented to elicit a wide array of useful biological effects.[2] Accordingly, analogues of these compounds are attractive targets for creating unique libraries for HTS. The related octahydroindolo[2,3-*a*]quinolizine-2-amine scaffold (**4**) is also present in compounds that exhibit various important biological activities as exemplified by compounds such as the derived amide **5** and the sulfonamide **6**, both of which are potent α_2-adrenoceptor antagonists.[3]

During the course of developing concise syntheses of **2** and **3**,[4] we discovered a novel Mannich-type multicomponent assembly process (MCAP) that inspired the subsequent development of a number of three- and four-component MCAPs that generate highly functionalized intermediates. The combination of these MCAPs in tandem with various ring closing reactions that are enabled by selective pairing of resident functional groups has led to a powerful strategy for the diversity oriented synthesis (DOS) of a broad array of unique heterocycles[5] comprising the benzodiazepine,[6] benzoxazocine,[7] benzazocine, isoindolinone,[8] tetrahydrobenzonaphtheridine, pyridazine, norbenzomorphan, 2-aryl piperidine, and tetrahydroisoquinoline scaffolds.[9,10] More recently we reported a useful extension of this general approach to DOS for the facile synthesis of compounds containing the octahydroindolo[2,3-*a*]-quinolizine-2-amine scaffold.[11] We herein report the application of this strategy to the rapid synthesis of a 180-member library of these compounds, many of which possess substitution patterns that were heretofore unknown.

RESULTS AND DISCUSSION

In close analogy with our syntheses of **2** and **3**,[4] the first step toward creating a novel library of compounds possessing the yohimboid and corynantheoid skeletons involved the reaction of the readily available dihydro-β-carbolines **7**−**9**[12] with *trans*-crotonyl chloride and silyl enol ether **10**[13] to form the aldehydes **11**−**13** (Scheme 1). When compounds **11**−**13** were condensed with *N*-methylhydroxylamine in toluene, the intermediate nitrone that was formed underwent an intramolecular 1,3-dipolar cycloaddition with the crotonamide moiety to furnish isoxazolidines **14**−**16** in 43−60% yield over the two steps. The relative stereochemistry resident in **14**−**16** was confirmed by single crystal X-ray analysis of a compound derived from **16** (vide infra). Reduction of the lactam moiety in **14** with lithium aluminum hydride provided amine **17** in 98% yield.

Having prepared the nor-bromo scaffolds **14** and **17**, we envisioned that *N*,*O*-bond cleavage followed by nitrogen functionalization would lead to the generation of an initial collection of small molecules (Scheme 2). In the event, reaction

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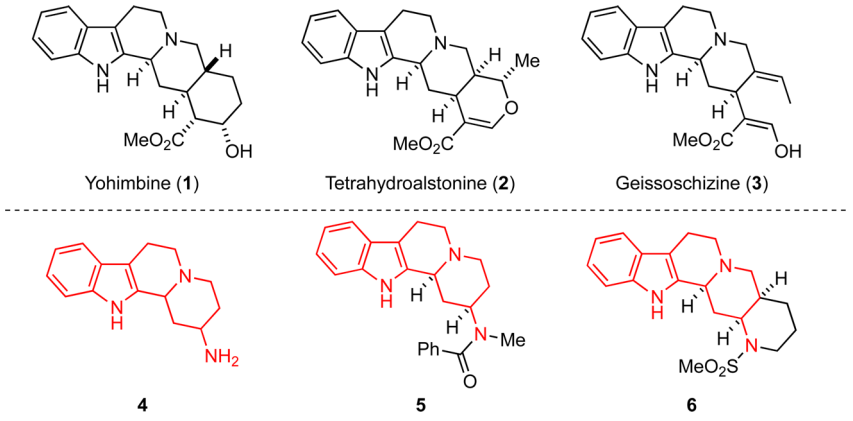
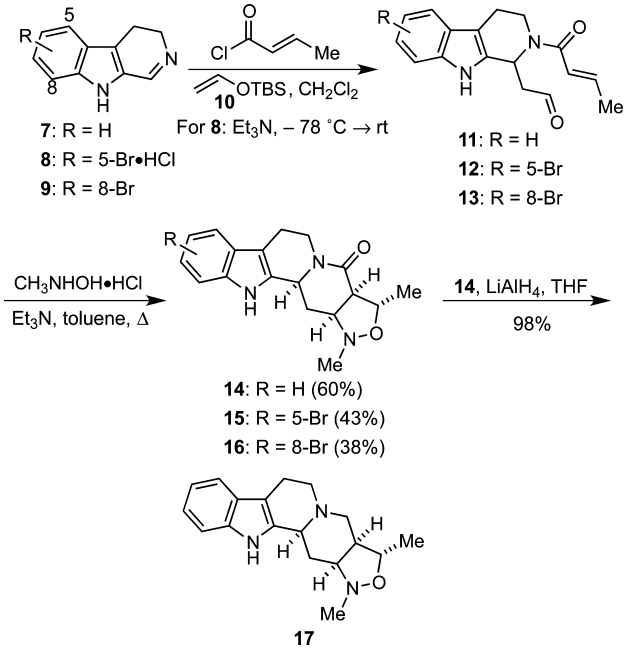
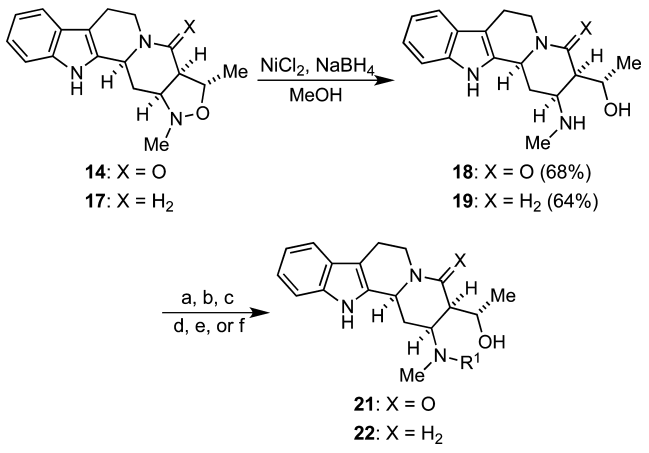


Figure 1. Natural products and compounds containing the octahydroindolo[2,3-*a*] quinolizine scaffold.

Scheme 1. Synthesis of Isoxazolidine Scaffolds 14−17



Scheme 2. *N,O*-Bond Cleavage and *N*-Functionalization



Conditions: (a) **20**{*1*−*11*}, Et_3N, CH_2Cl_2; (b) **20**{*12*−*14*}, Et_3N, CH_2Cl_2; (c) **20**{*15*−*24*}, CH_2Cl_2; (d) **20**{*25*−*28*}, CH_2Cl_2; (e) **20**{*29*−*31*}, MeCN, 82 °C; then $NaBH_3CN$, AcOH, rt; (f) **20**{*32*−*33*}, Na_2CO_3, THF/H_2O.

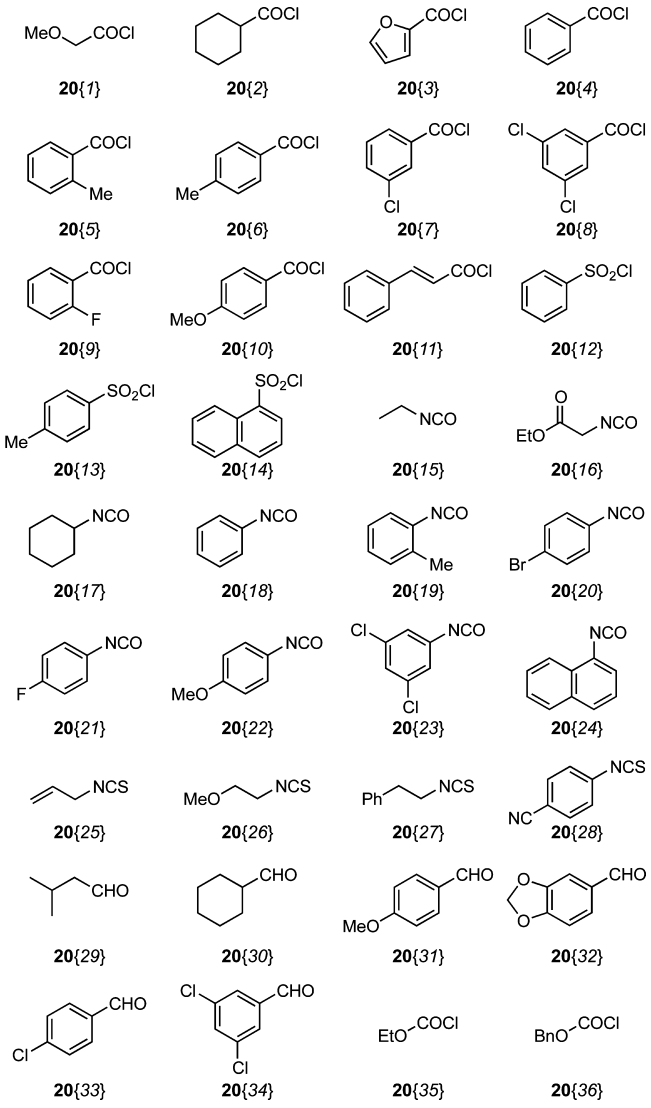


Figure 2. *N*-Functionalizing reagents.

of isoxazolidines **14** and **17** with nickel boride in methanol[14] delivered amines **18** and **19** in 68% and 64% yields, respectively. The secondary amine functionality resident in **18** and **19** was an obvious point for diversification, and the reaction of these intermediates with a series of *N*-functionalizing reagents **20** under standard conditions gave chemsets **21** and

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Table 1. Preparation of 21 and 22 via *N*-Functionalization

entry	*N*-functionalizing reagent	product	yield (%)
1	20{*1*}	21{*1*}	53
2	20{*3*}	21{*3*}	89
3	20{*5*}	21{*5*}	99
4	20{*8*}	21{*8*}	87
5	20{*12*}	21{*12*}	57
6	20{*16*}	21{*16*}	82
7	20{*17*}	21{*17*}	77
8	20{*18*}	21{*18*}	85
9	20{*20*}	21{*20*}	58
10	20{*21*}	21{*21*}	92
11	20{*23*}	21{*23*}	75
12	20{*24*}	21{*24*}	94
13	20{*26*}	21{*26*}	49
14	20{*32*}	21{*32*}	89
15	20{*33*}	21{*33*}	59
16	20{*35*}	21{*35*}	57
17	20{*36*}	21{*36*}	64
18	20{*3*}	22{*3*}	53
19	20{*5*}	22{*5*}	81
20	20{*10*}	22{*10*}	83
21	20{*13*}	22{*13*}	57
22	20{*14*}	22{*14*}	56
23	20{*15*}	22{*15*}	98
24	20{*16*}	22{*16*}	92
25	20{*17*}	22{*17*}	93
26	20{*18*}	22{*18*}	91
27	20{*20*}	22{*20*}	65
28	20{*21*}	22{*21*}	57
29	20{*22*}	22{*22*}	60
30	20{*23*}	22{*23*}	75
31	20{*24*}	22{*24*}	82
32	20{*26*}	22{*26*}	89
33	20{*27*}	22{*27*}	88
34	20{*28*}	22{*28*}	99
35	20{*29*}	22{*29*}	90
36	20{*31*}	22{*31*}	73
37	20{*34*}	22{*34*}	57
38	20{*35*}	22{*35*}	81
39	20{*36*}	22{*36*}	72

22 (Figure 2, Table 1). A wide array of *N*-functionalizing reagents was selected that included alkyl, aryl, and heteroaryl acid chlorides, sulfonyl chlorides, isocyanates, isothiocyanates, aldehydes, and chloroformates with varying electronic properties to generate a set of compounds that would enable an exploration of structure−activity relationships (SAR) for any actives that were identified during screening. Notably, these transformations were highly selective for reaction at the amino group. On the rare occasions that the undesired *O*-functionalized products were detected, they were formed in only trace

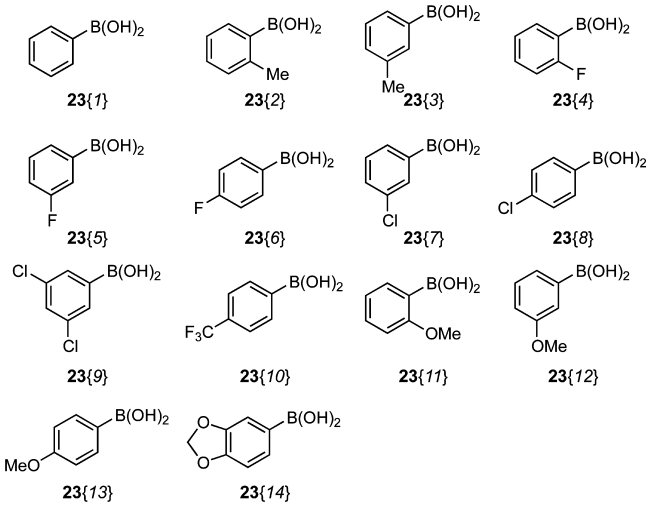


Figure 3. Boronic acids.

Table 2. Preparation of Chemset 24

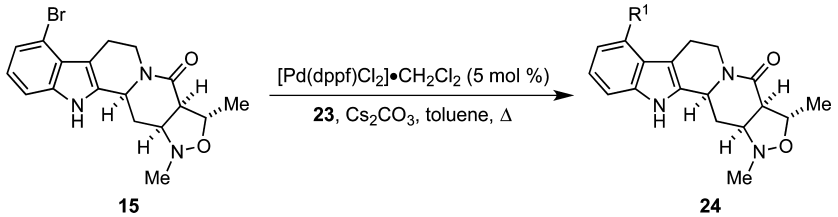
entry	boronic acid	product	yield (%)
1	23{*1*}	24{*1*}	90
2	23{*2*}	24{*2*}	92
3	23{*3*}	24{*3*}	71
4	23{*4*}	24{*4*}	44
5	23{*5*}	24{*5*}	85
6	23{*6*}	24{*6*}	66
7	23{*11*}	24{*11*}	58
8	23{*13*}	24{*13*}	56
9	23{*14*}	24{*14*}	91

quantities. When **18** and **19** were treated with aldehydes, the initially formed cyclic *N,O*-acetals, which were sufficiently stable for isolation, underwent reduction by the action of sodium cyanoborohydride in refluxing acetonitrile to furnish *N*-alkylated amino derivatives.

The aryl bromide moiety in the halogenated scaffolds **15** and **16** could be exploited in Suzuki[15] cross-coupling reactions, allowing for the creation of novel products possessing substitution patterns at the 5- and 8-positions that were not otherwise accessible. Accordingly, coupling of **15** with boronic acids **23** provided biaryl chemset **24** (Scheme 3, Figure 3, Table 2). To generate compounds that could be used to explore SAR, electron neutral **23**{*1*−*3*}, electron deficient **23**{*4*−*10*}, and electron rich **23**{*11*−*14*} boronic acids with varying substitution patterns were used as inputs.

Scission of the *N,O*-bond in **24**{*1*} and **24**{*5*}, followed by reaction of the intermediate amino alcohol moiety with *N*-functionalizing agents **20** led to the formation of chemset **26** (Scheme 4, Figure 2, Table 3). In analogous fashion, chemset **29** was prepared after reduction of the lactam moiety of **24**{*1*}

Scheme 3. Preparation of Biaryl Chemset 24 via Suzuki Coupling



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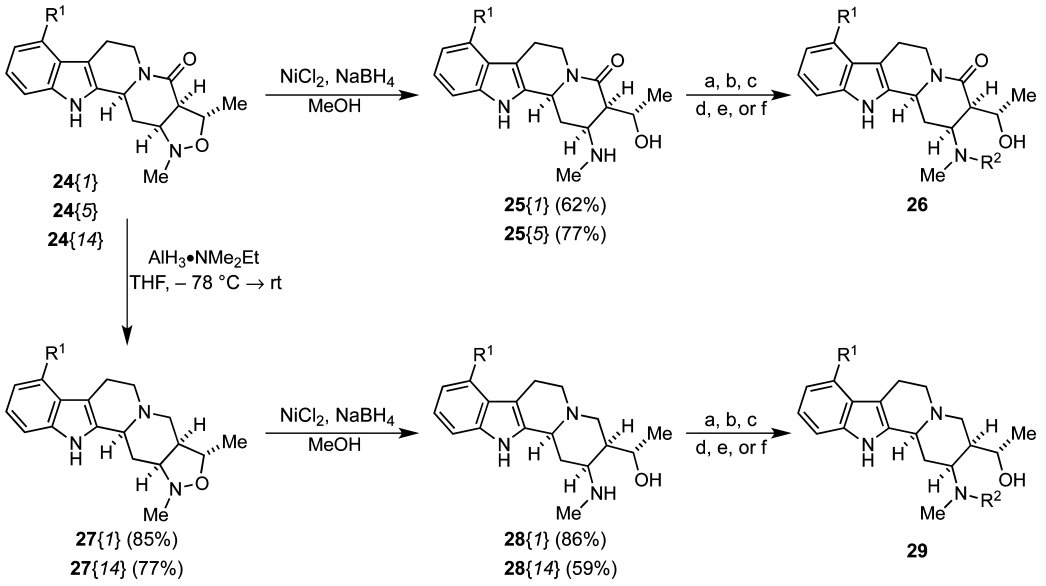
Scheme 4. Preparation of the 5-Substituted Library via Lactam Reduction, *N,O*-Bond Cleavage, and *N*-Functionalization



Conditions: (a) **20**{*1*–*11*}, Et_3N, CH_2Cl_2; (b) **20**{*12*–*14*}, Et_3N, CH_2Cl_2; (c) **20**{*15*–*24*}, CH_2Cl_2; (d) **20**{*25*–*28*}, CH_2Cl_2; (e) **20**{*29*–*31*}, MeCN, 82 °C; then $NaBH_3CN$, AcOH, rt; (f) **20**{*32*–*33*}, Na_2CO_3, THF/H_2O.

Table 3. Preparation of Chemsets 26 and 29

entry	amino alcohol	*N*-functionalizing reagent	product	yield (%)
1	25{*1*}	20{*2*}	26{*1,2*}	98
2	25{*1*}	20{*3*}	26{*1,3*}	93
3	25{*1*}	20{*4*}	26{*1,4*}	58
4	25{*1*}	20{*13*}	26{*1,13*}	57
5	25{*1*}	20{*17*}	26{*1,17*}	93
6	25{*1*}	20{*18*}	26{*1,18*}	77
7	25{*1*}	20{*26*}	26{*1,26*}	48
8	25{*1*}	20{*30*}	26{*1,30*}	68
9	25{*1*}	20{*36*}	26{*1,36*}	51
10	25{*5*}	20{*1*}	26{*5,1*}	85
11	25{*5*}	20{*15*}	26{*5,15*}	99
12	25{*5*}	20{*25*}	26{*5,25*}	99
13	25{*5*}	20{*35*}	26{*5,35*}	83
14	28{*1*}	20{*2*}	29{*1,2*}	78
15	28{*1*}	20{*3*}	29{*1,3*}	85
16	28{*1*}	20{*10*}	29{*1,10*}	74
17	28{*1*}	20{*18*}	29{*1,18*}	41
18	28{*1*}	20{*30*}	29{*1,30*}	72
19	28{*14*}	20{*3*}	29{*14,3*}	55
20	28{*14*}	20{*15*}	29{*14,15*}	72

and **24**{*13*} with the complex of alane with *N,N*-dimethylethylamine.

The 8-bromo scaffold **16** was also readily diversified via Suzuki reactions to provide chemset **30** (Scheme 5, Figure 3, Table 4). We determined the structure for compound **30**{*12*} by X-ray crystallography, thereby confirming our initial assignment of relative stereochemistry.

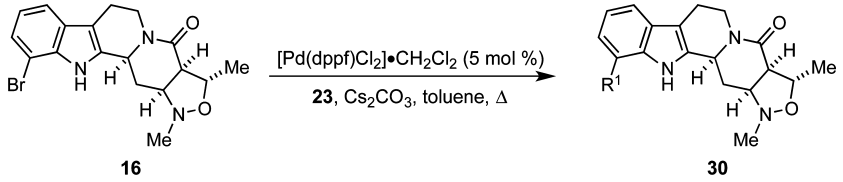
Table 4. Preparation of Chemset 30

entry	boronic acid	product	yield (%)
1	23{*1*}	30{*1*}	68
2	23{*2*}	30{*2*}	99
3	23{*3*}	30{*3*}	64
4	23{*4*}	30{*4*}	98
5	23{*5*}	30{*5*}	81
6	23{*6*}	30{*6*}	76
7	23{*7*}	30{*7*}	62
8	23{*8*}	30{*8*}	77
9	23{*9*}	30{*9*}	67
10	23{*10*}	30{*10*}	83
11	23{*12*}	30{*12*}	98
12	23{*13*}	30{*13*}	83
13	23{*14*}	30{*14*}	87

Nickel boride mediated *N,O*-bond cleavage of **30**{*1*}, **30**{*3*}, and **30**{*14*} provided the corresponding amino alcohols, which were subjected to *N*-functionalization by reagents **20** to afford chemset **32** (Scheme 6, Figure 2, Table 5). After reduction of lactams **30** with lithium aluminum hydride, analogous chemistry allowed for the preparation of chemset **35** from amines **33**.

We have previously reported the development of several novel MCAPs for the synthesis of fused-tetrahydroisoquinoline scaffolds,[9] and it occurred to us that we might apply this

Scheme 5. Preparation of Biaryl Chemset 30 via Suzuki Coupling



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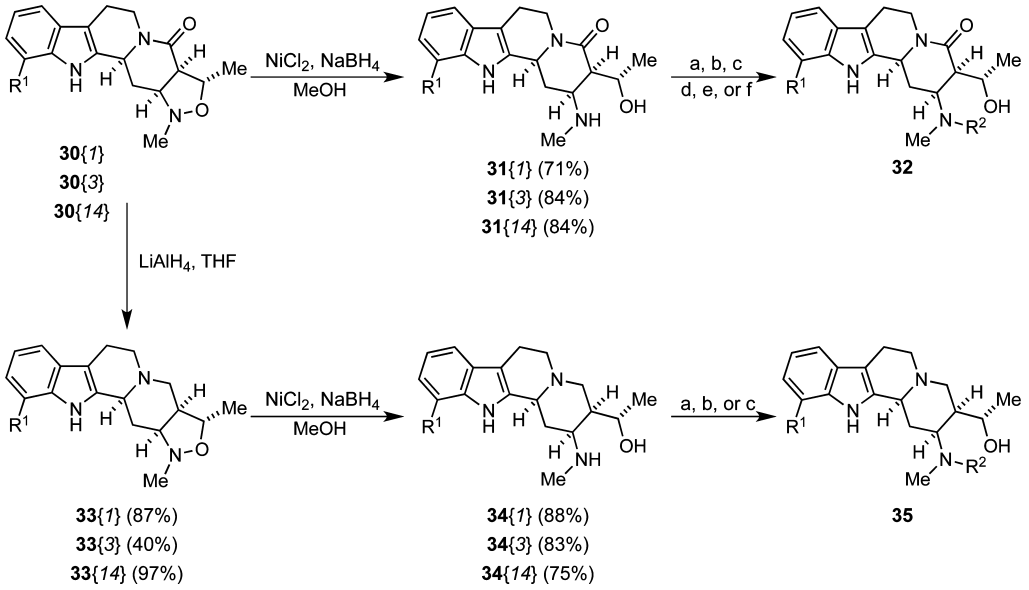
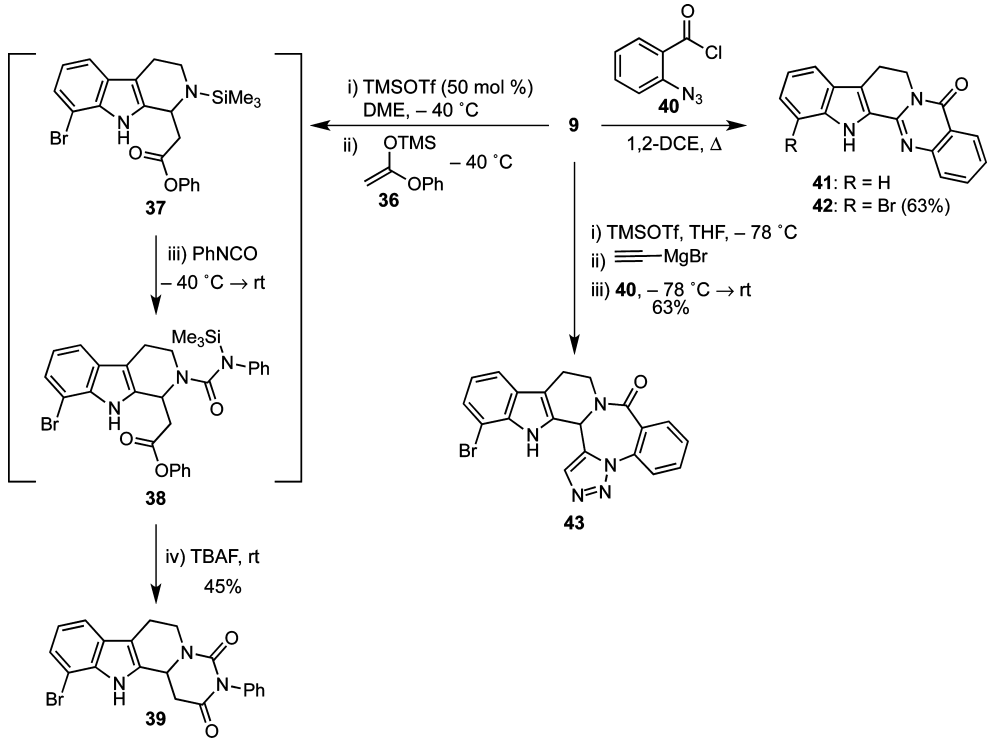
Scheme 6. Preparation of the 8-Substituted Library via Lactam Reduction, *N,O*-Bond Cleavage, and *N*-Functionalization



Conditions: (a) **20**{*1*–*11*}, Et_3N, CH_2Cl_2; (b) **20**{*12*–*14*}, Et_3N, CH_2Cl_2; (c) **20**{*15*–*24*}, CH_2Cl_2; (d) **20**{*25*–*28*}, CH_2Cl_2; (e) **20**{*29*–*31*}, MeCN, 82 °C; then $NaBH_3CN$, AcOH, rt; (f) **20**{*32*–*33*}, Na_2CO_3, THF/H_2O.

Scheme 7. Preparation of Scaffolds via Novel MCAP Chemistry



chemistry to the synthesis of unique scaffolds derived from **9**. Compounds containing the pyrimidinedione ring exemplified in **39** are known to exhibit hypotensive, diuretic, and antianoxic effects.[16] In initial experiments toward accessing this heterocyclic systems, **9** was allowed to react with the silyl ketene acetal **36**[17] in the presence of a substoichiometric amount of TMSOTf. The putative intermediate amino ester **37** was then treated with phenylisocyanate to give the pyrimidinedione **39**, presumably by cyclization of **38** (Scheme 7).[9a] However, when we recently returned to this reaction to prepare a compound library derived from this scaffold, only small amounts of **39** were isolated, and varying amounts of the amino ester and urea ester derived from protodesilylation of **37** and **38**, respectively, were observed instead. After some experimentation, we found that adding TBAF to the reaction mixture was necessary to effect complete cyclization, and **39** was then reproducibly obtained in 45% overall yield from **9**. This useful procedure provides convenient access to pyrimidinediones from **9** in one-

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Table 5. Preparation of Chemsets 32 and 35

entry	amino alcohol	*N*-functionalizing reagent	product	yield (%)
1	31{*1*}	20{*1*}	32{*1,1*}	99
2	31{*1*}	20{*3*}	32{*1,3*}	87
3	31{*1*}	20{*5*}	32{*1,5*}	98
4	31{*1*}	20{*6*}	32{*1,6*}	99
5	31{*1*}	20{*8*}	32{*1,8*}	98
6	31{*1*}	20{*9*}	32{*1,9*}	99
7	31{*1*}	20{*10*}	32{*1,10*}	92
8	31{*1*}	20{*11*}	32{*1,11*}	98
9	31{*1*}	20{*13*}	32{*1,13*}	99
10	31{*1*}	20{*15*}	32{*1,15*}	97
11	31{*1*}	20{*16*}	32{*1,16*}	89
12	31{*1*}	20{*17*}	32{*1,17*}	94
13	31{*1*}	20{*18*}	32{*1,18*}	97
14	31{*1*}	20{*19*}	32{*1,19*}	98
15	31{*1*}	20{*22*}	32{*1,22*}	99
16	31{*1*}	20{*24*}	32{*1,24*}	92
17	31{*1*}	20{*25*}	32{*1,25*}	89
18	31{*1*}	20{*26*}	32{*1,26*}	94
19	31{*1*}	20{*27*}	32{*1,27*}	99
20	31{*1*}	20{*28*}	32{*1,28*}	95
21	31{*1*}	20{*30*}	32{*1,30*}	87
22	31{*1*}	20{*35*}	32{*1,35*}	85
23	31{*1*}	20{*36*}	32{*1,36*}	91
24	31{*3*}	20{*3*}	32{*3,3*}	81
25	31{*3*}	20{*5*}	32{*3,5*}	78
26	31{*3*}	20{*15*}	32{*3,15*}	72
27	31{*3*}	20{*16*}	32{*3,16*}	85
28	31{*3*}	20{*17*}	32{*3,17*}	80
29	31{*3*}	20{*18*}	32{*3,18*}	81
30	31{*3*}	20{*19*}	32{*3,19*}	87
31	31{*3*}	20{*22*}	32{*3,22*}	79
32	31{*14*}	20{*1*}	32{*14,1*}	99
33	31{*14*}	20{*3*}	32{*14,3*}	85
34	31{*14*}	20{*5*}	32{*14,5*}	89
35	31{*14*}	20{*9*}	32{*14,9*}	95
36	31{*14*}	20{*15*}	32{*14,15*}	89
37	31{*14*}	20{*16*}	32{*14,16*}	89
38	31{*14*}	20{*17*}	32{*14,17*}	83
39	31{*14*}	20{*18*}	32{*14,18*}	72
40	31{*14*}	20{*19*}	32{*14,19*}	85
41	31{*14*}	20{*26*}	32{*14,26*}	89
42	31{*14*}	20{*35*}	32{*14,35*}	82
43	31{*14*}	20{*36*}	32{*14,36*}	70
44	34{*1*}	20{*3*}	35{*1,3*}	90
45	34{*1*}	20{*5*}	35{*1,5*}	63
46	34{*1*}	20{*17*}	35{*1,17*}	76
47	34{*1*}	20{*18*}	35{*1,18*}	78
48	34{*1*}	20{*26*}	35{*1,26*}	70
49	34{*1*}	20{*27*}	35{*1,27*}	76
50	34{*1*}	20{*28*}	35{*1,28*}	79
51	34{*1*}	20{*30*}	35{*1,30*}	65
52	34{*3*}	20{*2*}	35{*3,2*}	78
53	34{*3*}	20{*3*}	35{*3,3*}	79
54	34{*3*}	20{*5*}	35{*3,5*}	78
55	34{*3*}	20{*6*}	35{*3,6*}	95
56	34{*3*}	20{*7*}	35{*3,7*}	59
57	34{*3*}	20{*9*}	35{*3,9*}	79
58	34{*3*}	20{*15*}	35{*3,15*}	77
59	34{*3*}	20{*17*}	35{*3,17*}	82
60	34{*3*}	20{*18*}	35{*3,18*}	86
61	34{*3*}	20{*19*}	35{*3,19*}	87
62	34{*3*}	20{*26*}	35{*3,26*}	86
63	34{*3*}	20{*27*}	35{*3,27*}	74
64	34{*3*}	20{*28*}	35{*3,28*}	87
65	34{*3*}	20{*35*}	35{*3,35*}	68
66	34{*3*}	20{*36*}	35{*3,36*}	72
67	34{*14*}	20{*3*}	35{*14,3*}	91
68	34{*14*}	20{*5*}	35{*14,5*}	61
69	34{*14*}	20{*6*}	35{*14,6*}	78
70	34{*14*}	20{*9*}	35{*14,9*}	60
71	34{*14*}	20{*17*}	35{*14,17*}	46
72	34{*14*}	20{*18*}	35{*14,18*}	93
73	34{*14*}	20{*19*}	35{*14,19*}	85
74	34{*14*}	20{*26*}	35{*14,26*}	85
75	34{*14*}	20{*27*}	35{*14,27*}	80

pot procedure that represents a marked improvement upon known methods to such compounds.[18]

The quinazolinocarboline alkaloid rutaecarpine (**41**) was isolated from *Evodia Rutaecarpa* in 1915,[19] and this compound together with a number of its derivatives displays a wide array of biological activities.[20] We thus envisioned that compounds related to **41** having substituents on the indole ring might be attractive compounds for screening. In previous work, we discovered that reaction of the hydrochloride salt of **7** with *o*-azidobenzoyl chloride (**40**) provided a novel entry to **41**,[9a] so we queried whether this chemistry might also be applied to bromo-substituted analogues of **41**. To establish the underlying feasibility of this approach to rutaecarpine derivatives, imine **9** and *o*-azidobenzoyl chloride (**40**) were heated in refluxing 1,2-dichloroethane to furnish **42**, which is known as a selective COX-2 inhibitor,[21] in 63% yield. Derivatives prepared from **42** via cross-coupling chemistry may exhibit novel biological activities.

The 1,5-benzodiazepin-2-one scaffold present in **43** is found in compounds that bind to various targets including the interleukin-1β converting enzyme (ICE)[22] and voltage-gated potassium channels.[23] Moreover, triazolo-fused benzodiazepine scaffolds are present in compounds that have been reported to inhibit serine protease[24] and to bind to the benzodiazepine receptor.[25] We thus decided to fuse this scaffold to the 8-bromo-3,4-dihydro-β-carboline scaffold (**9**) to provide a novel set of compounds that might be screened. In the event, sequential treatment of **9** with TMSOTf, ethynylmagnesium bromide, and the acid chloride **40** afforded an intermediate amide that underwent cyclization via an intramolecular 1,3-dipolar cycloaddition upon warming to room temperature to generate the novel benzodiazepine **43** in 63% yield. Further elaboration of **43** by cross-coupling reactions may also be readily envisioned.

BIOLOGICAL ACTIVITY

High throughput biological screening of the 180-member library of *Yohimbine* and *Corynanthe* alkaloid analogues through the NIH Molecular Library Probe Production Center Network (MLPCN) and the National Institute of Mental Health's (NIMH) Psychoactive Drug Screening Program (PDSP) is currently underway in hopes of identifying compounds with useful biological activities for further development. Notably, compound **17** was found to promote the differentiation of acute myeloid leukemia cells,[26] and is an agonist of mouse

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serotonin receptor 2A,[27] which may have implications in the treatment of schizophrenia, depression, and drug addiction.[28−30] Additionally compound **32**{1,22} is a human trace amine associated receptor 1 (hTAAR1) antagonist.[31]

SUMMARY

We have prepared a 180-member library of *Yohimbine* and *Corynanthe* alkaloid analogues utilizing a general sequence that features an MCAP followed by a 1,3-dipolar cycloaddition to generate functionalized scaffolds that were readily diversified using several well established reactions for refunctionalization and cross-coupling. An improved procedure for the generation of pyrimidinediones was developed, along with methods for formation of benzodiazepines and rutaecarpine derivatives. These compounds have been submitted to the NIH Molecular Libraries Small Molecule Repository (MLSMR) for distribution to HTS centers within the Molecular Libraries Probe Production Centers Network (MLPCN) and biological screening is currently underway. Further applications of novel MCAPs are in progress, and the results of these investigations 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 physiochemical properties for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: sfmartin@mail.utexas.edu.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Professor Robert Williams on the occasion of his 60th birthday.

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