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Facile syntheses of substituted, conformationally-constrained benzoxazocines and benzazocines via sequential multicomponent assembly and cyclization

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ABSTRACT

A multicomponent assembly process (MCAP) was utilized to prepare versatile intermediates that are suitably functionalized for subsequent cyclizations via Ullmann and Heck reactions to efficiently construct substituted 2,6-methanobenzo[*b*][1,5]oxazocines and 1,6-methanobenzo[*c*]azocines, respectively. The intramolecular Ullmann cyclization was conducted in tandem with an intermolecular arylation that enabled the rapid syntheses of a number of O-functionalized methanobenzoxazocines.

An effective approach for discovering new lead compounds for drug development programs and for identifying molecular probes to study biological systems involves screening of chemical libraries based upon privileged scaffolds.[1] By varying the nature of peripheral substituents on these molecular frameworks, it is often possible to obtain hits across a wide range of biological targets. Toward developing a general approach to the synthesis of heterocyclic scaffolds comprising privileged substructures, we designed a novel strategy for diversity-oriented synthesis (DOS) that featured a multicomponent assembly process (MCAP) involving Mannich-type reactions to give substituted aryl methylamine derivatives.[2–4] These adducts can be subjected to various cyclization reactions that are enabled by selective functional group pairing to construct substituted heterocyclic ring systems. We have demonstrated the utility of this approach by applying it to syntheses of small libraries of diversely substituted benzodiazepines,[5] norbenzomorphans,[6] aryl piperidines,[7] and tetrahydroisoquinolines.[8] We now report the extension of this useful methodology to the facile preparation of compounds having conformationally-constrained benzoxazocines **1** and benzazocines **2** as key structural subunits (Fig. 1).

Methylene-bridged benzoxazocines and benzazocines have received attention owing to their favorable biological profiles. For example, benzoxazocines related to **5**, which were prepared in five steps from 4-methylpyridine (**3**) (Eq. 1), exhibit analgesic, hypotensive, and CNS stimulating activities,[9] whereas benzazocines similar to **8**, which have been prepared in a six-step sequence from indene (**6**) (Eq. 2), have shown moderate antinociceptive activity

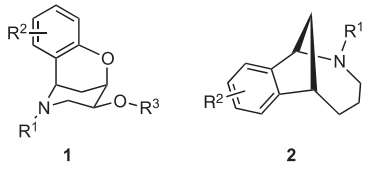

Figure 1. Generic structures of conformationally-constrained benzoxazocines **1** and benzazocines **2**.

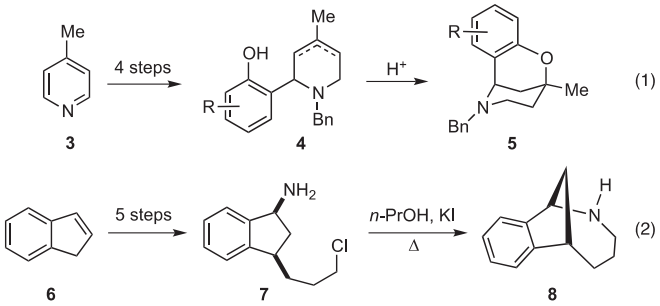

Figure 2. Previous syntheses of benzoxazocine **5** and benzazocine **8**.

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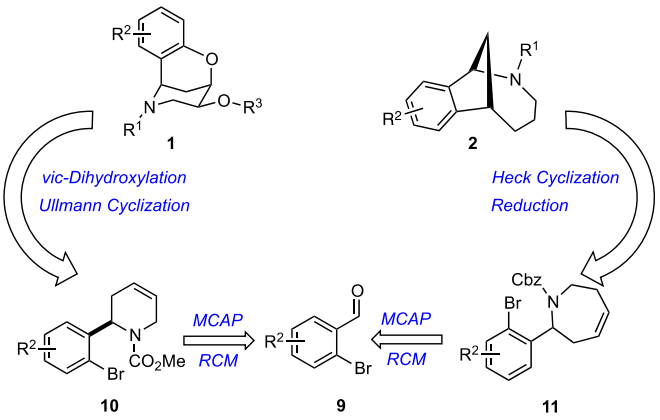


Scheme 1. General approaches to conformationally-constrained benzoxazocines **1** and benzazocines **2** from 2-bromobenzaldehydes **9**.

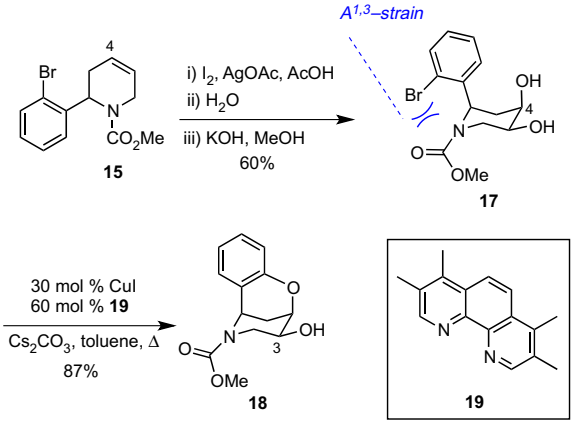
(Fig. 2).[10] Because routes to both of these scaffolds and their analogs are rare,[11] there is an unmet need for the development of flexible approaches for their synthesis that enable facile diversification for biological screening.

Although the routes depicted in Eqs. 1 and 2 do provide access to analogs of **1** and **2**, they are somewhat lengthy and not well suited for the facile syntheses of polysubstituted derivatives. Accordingly, we envisioned a unified approach to both scaffolds might be developed using an MCAP involving substituted bromobenzaldehydes **9** to assemble intermediates that could be readily transformed into substituted piperidines **10** and azepines **11** by a ring closing metathesis (RCM) (Scheme 1).[12,13] Stereoselective *vic*-dihydroxylation of **10** followed by an Ullmann cyclization would lead to compounds of the general structure **1**, whereas cyclization of **11** via a Heck reaction followed by reduction would afford methanobenzazocines **2**. Since a vast array of substituted bromobenzaldehydes is readily available, it is conceivable that a more diverse collection of compounds could be obtained. For example, we previously demonstrated that our MCAP/cyclization strategy may be applied to the preparation of scaffolds containing aryl chlorides, which can be easily derivatized through various cross-coupling reactions.[6] We now report the reduction of the plan adumbrated in Scheme 1 to practice as exemplified by the syntheses of derivatives of **1** and **2** that incorporate functional handles that may be exploited for further diversification reactions.

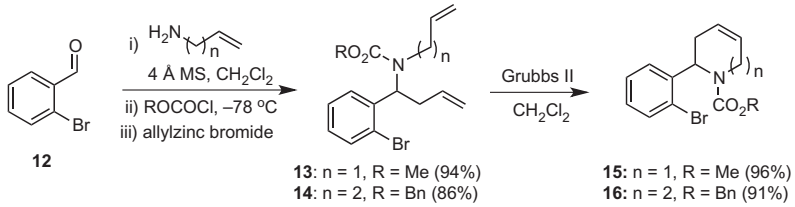
The first step toward implementing the plan outlined in Scheme 1 involved condensation of *o*-bromobenzaldehyde (**12**) with allylamine, followed by treatment with methyl chloroformate and allylzinc bromide to give **13** in 94% yield (Scheme 2). In a similar fashion, **12** was treated sequentially with 1-amino-3-butene, benzyl chloroformate, and allylzinc bromide to furnish **14** in 86% yield. Although the stated yields for carbamates **13** and **14** are for purified materials, it is important from a practical standpoint that they are of sufficient purity to use directly in the next step. When the dienes **13** and **14** were subjected to ring closing metathesis (RCM) using Grubbs 2nd generation catalyst, tetrahydropyridine **15** and tetrahydroazepine **16** were produced in excellent overall yields from **12**. Because these compounds serve as key intermediates, it is notable that they could be easily prepared on a multigram scale.

With **15** in hand, our next objective was to stereoselectively introduce a hydroxyl group at C(4) of **15** *cis* to the aryl moiety for the planned etherification reaction. Because hydroxyl groups may be further derivatized by a number of refunctionalizations, we elected to dihydroxylate **15** so that the product benzoxazocine would contain a free hydroxyl group. Accordingly, tetrahydropyridine **15** was subjected to Woodward's dihydroxylation conditions[14] to form the vicinal diol **17** as a single diastereomer (Scheme 3). The stereochemical outcome of this transformation was presumably dictated by the pseudoaxial orientation of the aryl group that results from $A^{1,3}$-strain[15] with the carbamate group. *Syn*-dihydroxylation from the more hindered face of the olefin, which is consistent with the mechanism of the Woodward dihydroxylation, then gave **17** in 60% yield. We envisioned that the cyclization of **17** by an intramolecular Ullmann reaction would also be facilitated by $A^{1,3}$-strain that would favorably position the aryl bromide proximal to the hydroxyl group at C(4). Indeed, when diol **17** was heated with CuI, 3,4,7,8-tetramethyl-1,10-phenanthroline (**19**), and Cs_2CO_3 in toluene according to the protocol of Buchwald,[16] benzoxazocine **18** was obtained in 87% yield. The intramolecular Ullmann cyclization of **17** represents a novel entry to this bridged tricyclic scaffold.

Although the C(3) hydroxyl group of **18** might be employed in bimolecular Ullmann coupling reactions, we were intrigued by the more attractive possibility of accessing 3-O-arylated benzoxazocines directly from diol **17**. Specifically, we queried whether it might be feasible to develop a one-pot transformation that would feature both intra- and intermolecular Ullmann reactions. Indeed, we discovered that when **18** was heated with an aryl iodide, base, CuI, and **19** in toluene (method A), a tandem double Ullmann reaction ensued to give aryl ethers **20** and **21** in 52% and 48% yields, respectively (Table 1, entries 1 and 2). This procedure was

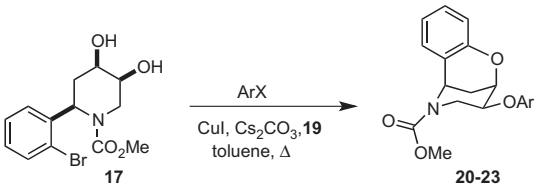


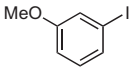
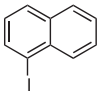
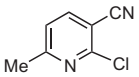
Scheme 3. Synthesis of benzoxazocine **18** via Ullmann reaction.



Scheme 2. Multicomponent assembly processes followed by RCM reactions.

Table 1
One-pot synthesis of *O*-arylated benzoxazocines from diol **17.**



Entry	ArX	Method	Compound	Yield (%)
1		a	**20**	52
2		a	**21**	48
3		b	**22**	53
4		b	**23**	54

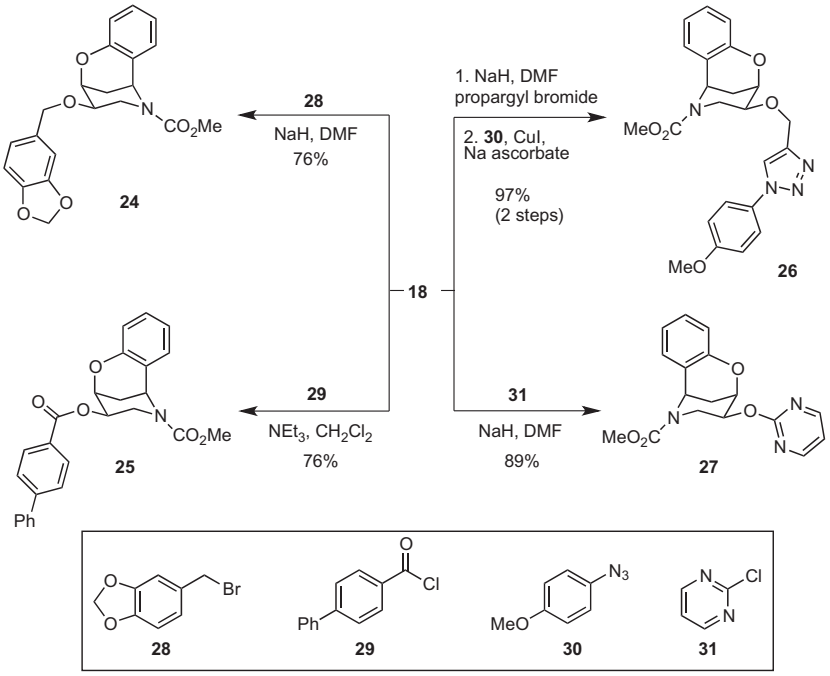
efficacious for aryl iodide coupling partners, but we found that such reactions with halopyridines proceeded to give **22** and **23** in only about 30% yields. This decrease in yield is attributed to competitive intermolecular bis-arylation of diol **17**, a process that was observed to a much lesser extent with aryl iodide coupling partners. We soon discovered that the undesired bis-arylation could be avoided if the halopyridine component was introduced after the initial cyclization was complete. Accordingly, diol **17**, CuI, **19** and base were heated in toluene until **17** had been consumed (TLC), whereupon the appropriate halopyridine was added (method B). In this manner **22** and **23** were obtained in 53% and 54% yields, respectively (entries 3 and 4).

The benzoxazocine scaffold **18** was an excellent embarkation point for other O-derivatization processes as is exemplified by the syntheses of **24**–**27** (Scheme 4). For example, benzylation and acylation of the free OH group in **18** with **28** and **29**, respectively, afforded the corresponding ether **24** and ester **25**. Propargylation of **18** followed by a Huisgen [3+2] cycloaddition with the aryl azide **30** delivered triazole **26** in 97% overall yield from **18**. Finally, a SN_{Ar} reaction between **18** and 2-chloropyrimidine (**31**) provided the O-arylated benzoxazocine **27**.

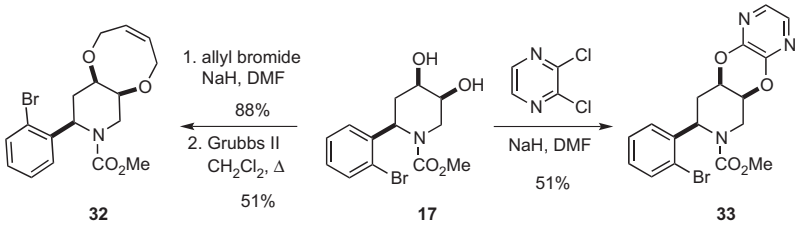
The relative orientation of the substituents on **17** is well suited to the purpose of appending additional fused rings as illustrated by the use of **17** in two different ring forming reactions to deliver novel heterocyclic scaffolds. Bis-O-allylation of **17** gave a diene intermediate that underwent a RCM reaction in the presence of Grubbs 2nd generation catalyst to form the piperidino-1,4-dioxocine **32** (Scheme 5). Alternatively, when a mixture of **17** and 2,3-dichloropyrazine was treated with NaH in DMF, the fused tricycle **33** was obtained via a double SN_{Ar} reaction in 51% yield.

Having developed a facile entry to several bridged benzoxazocines, we turned our attention to the preparation of the bridged benzazocine **36**. Toward this goal, **16** was subjected to an intramolecular Heck cyclization in the presence of Bu_4NCl[4a,17] to provide a readily separable mixture (1.3:1.0) of benzazocine isomers **34** and **35** in 79% yield. Although attempts to isomerize **35** to the thermodynamic enecarbamate product **34** were unsuccessful,[18,6] the isomers were successfully converged to **36** via complementary reducing conditions. Namely, ionic reduction[19] of **34** employing Et_3SiH and TFA and catalytic hydrogenation of **35** with Adam's catalyst gave **36** in 59% and 96% yields, respectively (Scheme 6). Constrained benzazocine **36** is well suited for analog synthesis via N-derivatization. Moreover, we have shown that the use of chlorinated bromobenzaldehyde inputs in the MCAP leads to benzoxazocines possessing aromatic functional handles, thereby enabling a broad range of diversification reactions.[6]

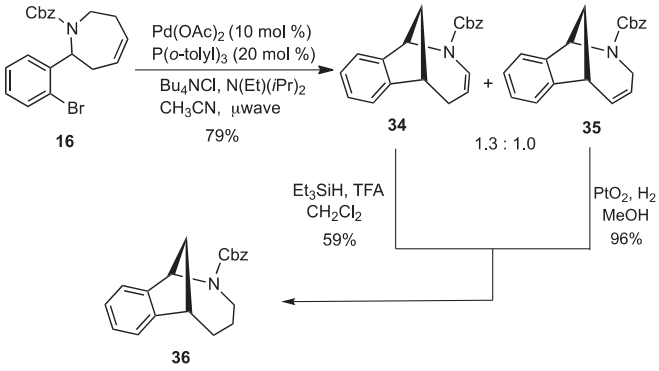
In summary, we have extended our original MCAP/cyclization strategy to generate intermediates that can be quickly elaborated into conformationally constrained benzoxazocines and benzazocines. Our approach to O-arylated benzoxazocines was improved through the development of a one-pot double Ullmann reaction, in which functionalized benzoxazocines were obtained in only four steps from commercially available starting materials. Furthermore,



Scheme 4. Syntheses of benzoxazocine derivatives **24**–**27**.



Scheme 5. Fused scaffolds from diol **17**.



Scheme 6. Bridged benzazocine **36** from an intramolecular Heck reaction.

diol **17** proved to be a versatile intermediate that could be diverted toward novel, fused heterocyclic ring systems. Further applications of this and related approaches to the syntheses of unique compound libraries are in progress, and the results of these investigations will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures and characterization data of compounds **14**, **16**, **20**–**23**, **24**, **26**, **27**, **33**, and **36**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.022.

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