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Diversity Oriented Synthesis: Concise Entry to Novel Derivatives of Yohimbine and Corynanthe Alkaloids

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Abstract

A novel MCAP-cycloaddition sequence has been applied to the facile synthesis of β-carboline intermediates to gain rapid access to novel derivatives of yohimbine-like and corynanthe-like compounds that may be easily diversified by cross-coupling reactions and *N*-derivatizations to generate small compound libraries.

Keywords

multicomponent assembly process; imine; dipolar cycloaddition; Suzuki reaction; *N*-Derivatization

The pentacyclic and tetracyclic ring systems characteristic of the *Yohimbine* and *Corynanthe* alkaloids, respectively, are exemplified in indole alkaloids such as yohimbine (**1**), tetrahydroalstonine (**2**) and geissoschizine (**3**), and alkaloids belonging to these families exhibit a remarkable range of biological activities.[1] For example, owing to their high affinity for α_1–adrenergic receptor, some of these alkaloids may be used to treat hypertension, depression and diabetes.[2] Accordingly, derivatives of these alkaloids are promising targets as bioactive compounds in drug discovery, and some analogs having substructures of these natural products have been found to exhibit useful biological activities.[3] In this context, it is significant that the synthesis of functionalized frameworks found in natural products has emerged as a useful strategy, which is known as biology oriented synthesis (BIOS),[4] for discovering biologically active compounds. We thus became interested in preparing **4** and **5**, as novel analogs of the *Yohimbine* and *Corynanthe* alkaloids.

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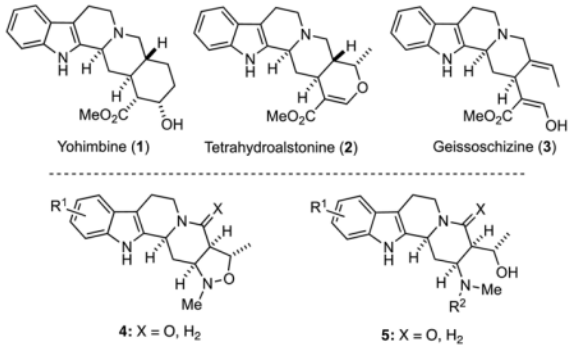
Supplementary Data

Supplementary data (representative experimental procedures and characterization data of compounds **14**, **16**, **20–23**, **24**, **26**, **27**, **33**, and **36**) can be found in the online version at doi:10.1016/j.tetlet.2011.xx.xxx.



We have recently been interested in the design and development of effective strategies for preparing functionalized heterocyclic scaffolds that can be easily diversified by cross-coupling and *N*-derivatization reactions.[5] Indeed, a three-component reaction of **6** to give **7**, a key step in our concise synthesis of tetrahydroalstonine (**2**) (Scheme 1),[6] served as the inspiration for a novel multicomponent assembly process (MCAP) that featured the use of Mannich-type reactions to give substituted aryl methylamine derivatives. These adducts can be subjected to various cyclization reactions that are enabled by selective functional group pairing to construct substituted heterocyclic ring systems.[7] We have demonstrated the utility of this general approach to diversity oriented synthesis (DOS) by applying it to preparation of small libraries of substituted benzodiazepines,[8] norbenzomorphans,[9] aryl piperidines,[10] tetrahydroisoquinolines,[11] as well as several conformationally-constrained benzoxazocines and benzazocines.[12] We now report the extension of this useful methodology to the facile preparation of compounds derived from the yohimbine and corynanthe scaffolds.

We envisioned that compounds generally related to **4** could be accessed by a sequential MCAP of a dihydro-β-carboline such as **6** followed by a dipolar cycloaddition of a nitrone derived from the adduct.[7] Toward this end, treatment of **6** with crotonyl chloride and *tert*-butyldimethyl(vinyloxy)silane in CH_2Cl_2 afforded the amide **8** in 85% yield. Heating **8** with *N*-methylhydroxylamine hydrochloride and triethylamine in refluxing toluene then provided an intermediate nitrone that underwent a spontaneous [3+2] dipolar cycloaddition to give **9** as a single diastereoisomer. When **9** was treated with $LiAlH_4$, the amine **10** was obtained in nearly quantitative yield. Subsequent reductive scission of the *N*–*O* bond in **10** using Ni_2B, which was generated *in situ*,[13] delivered the amino alcohol **11** in 64% yield. The amino group in **11** could then be derivatized by a number of selective *N*-functionalizations. For example, *N*-acylation provides amides such as **12**, whereas reaction with isocyanates gives ureas like **13**.

In order to establish the versatility of our approach to yohimbine analogs as **9** and **10** and corynanthe-like compounds like **11**–**13**, we queried whether representative bromo substituted carbolines might be employed as starting materials. We reasoned that a bromo group would be a convenient functional handle for performing a variety of cross-coupling reactions to introduce other substituents.

Accordingly, the known 5-bromo-β-carboline (**14**),[14] which was prepared in four steps from 4-bromoindole was treated with *tert*-butyldimethyl(vinyloxy)silane and crotonyl chloride to provide an intermediate adduct that was then heated with *N*-methylhydroxylamine to afford the isoxazolidine **15** in 43% overall yield (Scheme 3). The intramolecular dipolar cycloaddition reaction was highly stereoselective as **15** was the only isomer detected. After exploring a number of conditions for performing a Suzuki cross-coupling reaction, we found the best yield of **16** was obtained by heating phenylboronic acid and **15** in the presence of 5 mol % [$Pd(dppf)Cl_2$] CH_2Cl_2 and Cs_2CO_3 in refluxing toluene for 17 h. Use of other catalysts including $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(t\text{-}Bu_3P)_2$ gave lower yields. We performed

exploratory experiments to use **15** as a reaction partner in Buchwald-Hartwig type cross-couplings with secondary amines, but these preliminary reactions were low yielding. Reduction of the lactam moiety in **16** with alane gave the amine **17** in 85% yield. Subsequent reductive cleavage of the *N,O*–bond in **17** using nickel boride as before produced the desired amino alcohol **18** in excellent yield. Selective *N*-functionalization of **18** was then achieved in several ways. For example, reductive amination of **18** with cyclohexanecarboxaldehyde, which proceeded via a relatively stable intermediate *N,O*-acetal, using $NaCNBH_3$ under mildly acidic conditions to furnish **19** in 53% yield. Similarly, the cycloadduct **15** was converted into the amino alcohol **22** in good overall yield via sequential Suzuki cross-coupling, lactam reduction, and, *N–O* bond scission. Reaction of the secondary amine in **22** with ethylisocyanate gave the urea **23** in 72% yield.

We then extended this chemistry in a straightforward fashion to the syntheses of 8-substituted analogs as outlined in Scheme 4. In the event the known 8-bromocarboline **24**,[14] which was prepared in four steps from 7-bromoindole, *tert*-butyldimethyl(vinyloxy)silane, and crotonyl chloride were combined in a multicomponent assembly process to provide an intermediate adduct, heating of which with *N*-methylhydroxylamine generated the isoxazolidine **25** in 50% yield. When **25** was subjected to cross-coupling reactions with aryl boronic acids in the presence of 5 mol % $[Pd(dppf)Cl_2]$ CH_2Cl_2 and Cs_2CO_3 in refluxing toluene, **26** and **30** were obtained in 68% and 86% yields, respectively. The products of these Suzuki cross-couplings were invariably contaminated with about 10% of the debrominated material **9**. Although we conducted several exploratory experiments we were unable to identify conditions under which debromination did not occur. Fortunately, compound **9** could be largely removed from the coupled product by exploiting the lower solubility of **9** in ethyl acetate or by column chromatography. Reduction of the lactam moiety of **26** and **30** with $LiAlH_4$, followed by cleavage of the *N–O* bond with nickel boride provided the amino alcohols **28** and **32;** alane could also be used to reduce the lactam. The amino alcohol **28** was then converted into the urea **29** upon reaction with phenylisocyanate, whereas **32** was transformed into the amide **33** with *p*-toluoyl chloride.

In summary, we have extended our general approach for diversity oriented synthesis[7] and applied a MCAP/cyclization sequence to various dihydro-β-carbolines to gain facile access to novel compounds having scaffolds related to the *Yohimbine* and *Corynanthe* alkaloids. Intermediates are functionalized to enable a number of different derivatization reactions, including Suzuki cross-coupling reactions and *N*-functionalization by reductive alkylation, acylation, urea and thiourea formation, and sulfonylation. The application of this general plan for DOS to the synthesis of small libraries of biaryl compounds for biological screening is in progress, and the results of these and related investigations will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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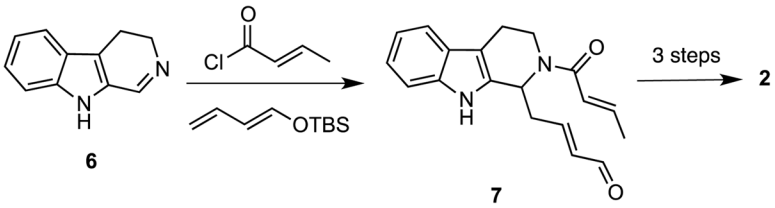
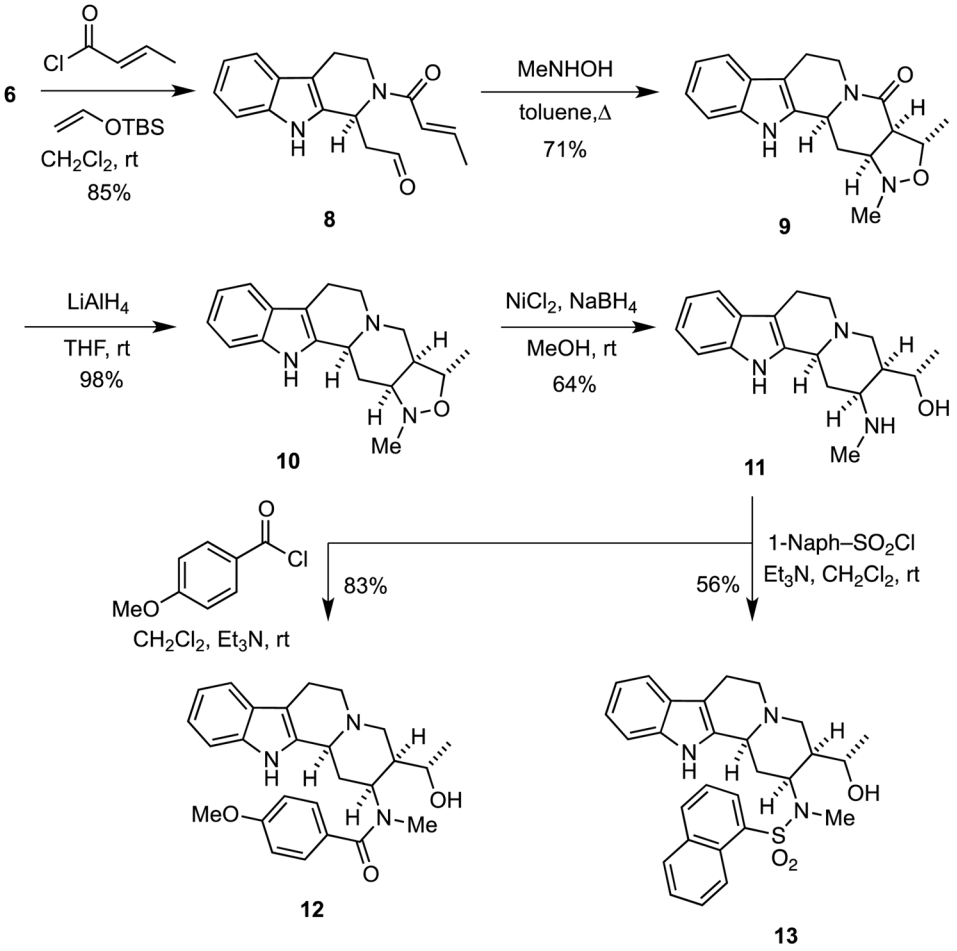
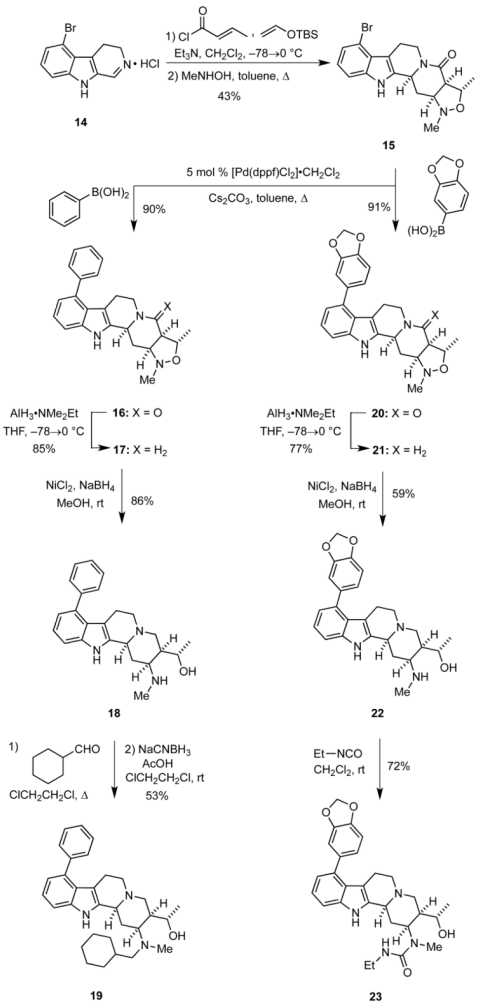


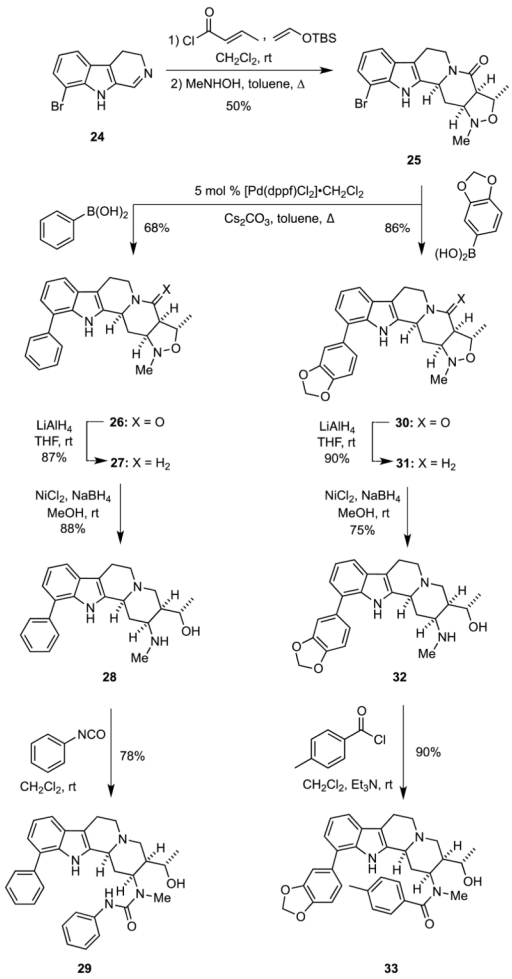
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.