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Preparation of Structurally Diverse Compounds from the Natural Product Lycorine

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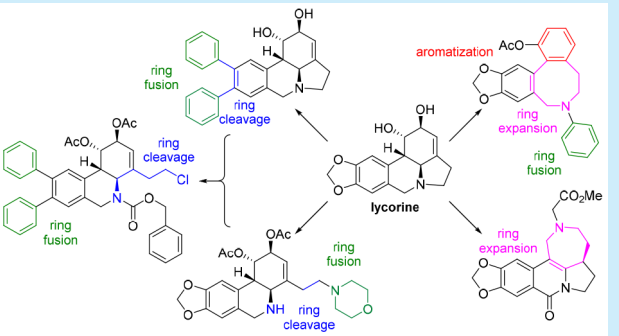
Supporting Information

ABSTRACT: The synthesis of a 52-member compound collection from the natural product lycorine is reported, highlighted by divergent cross-coupling and substitution strategies and an unusual ring rearrangement induced by reaction with aryne intermediates.



The success of high-throughput screening campaigns in drug discovery inherently relies on the content and quality of the small-molecule screening collections used. Typically, large compound libraries are dominated by members with a low percentage of sp^3-hybridized carbons and few, if any, stereogenic centers.[1] Such small molecules can be highly successful in targeting binding sites that favor relatively planar compounds (e.g., ATP binding site for kinase inhibition) but are less optimal for other biological targets, such as protein−protein interactions.[2] Several strategies have been utilized to increase the complexity of compounds in screening collections including diversity-oriented synthesis (DOS),[3] biology-oriented synthesis (BIOS),[4] and DNA-encoded library technology.[5]

Nature is not constrained by the factors that limit diversity of pharmaceutical libraries, such as ease of synthesis or a legacy of screening compounds previously prepared for existing biological targets. Natural products engage a broad range of biological molecules, and 50% of the small molecule anticancer drugs approved between 1981 and 2014 were natural products or contained a natural product core.[6] To take advantage of the distinctive features of natural products while leveraging the power of synthetic organic chemistry, we have reported a strategy termed complexity-to-diversity (CtD),[7] which uses ring system distortion and rearrangement reactions of natural products to rapidly generate collections of diverse compounds while maintaining desirable characteristics including a high fraction of sp^3-hybridized carbons (Fsp3), ring fusion density, number of stereogenic centers, and rigidity of ring systems. Using this approach, compound collections have been reported from gibberellic acid,[7a] adrenosterone,[7a] quinine,[7a] abietic acid,[8] sinomenine,[9] pleuromutilin,[10] yohimbine,[11] hemeanthamine,[12] ilimaquinone,[13] and others.[14] Structurally diverse, natural-product-like libraries have proven to be valuable tools in studying various biological processes.[11,15] For example, we recently reported the use of CtD compounds to assess the propensity of small molecules to accumulate in Gram-negative bacteria;[16] for this purpose, compounds with a low number of rotatable bonds, a high ring-fusion density, and the presence of ionizable nitrogens were crucial, thus leading us to choose lycorine (**1**) as a starting point for further CtD synthetic efforts (**2**−**14**, Scheme 1).

Lycorine (**1**) is an Amaryllidaceae alkaloid containing five rings with four contiguous stereogenic centers, a *trans*-diaxial diol, tertiary amine, and dioxolane.[17] Isolated from the bulbs and leaves of the plants of the Amaryllidaceae family such as amaryllis and daffodil, **1** is commercially available as the HCl salt. These plants have long been used in both Eastern and Western traditional medicine for their antitumor activity dating back to Herodotus.[18a] Lycorine was first isolated in 1877[19] and has demonstrated anticancer, antiangiogenesis, antiviral, antibacterial, antiparasitic, and anti-inflammatory activity but it is not a general toxin and is well tolerated in mammals.[18] The biological target(s) of lycorine is not well understood, though activity against topisomerase I, L-galactano-γ-lactone dehydrogenase, and acetylcholinersterase has been reported.[18b]

Previous studies of lycorine have produced a number of derivatives to explore the relationship between its structure and biological activity.[20] These derivatives have been limited to appending various side chains to one or both alcohols,[21] or straightforward functional group manipulation (e.g., oxidation, reduction).[22] Two principal ring-cleavage strategies are also known (Scheme 2). Treatment of methylated[23] or diacetyla-

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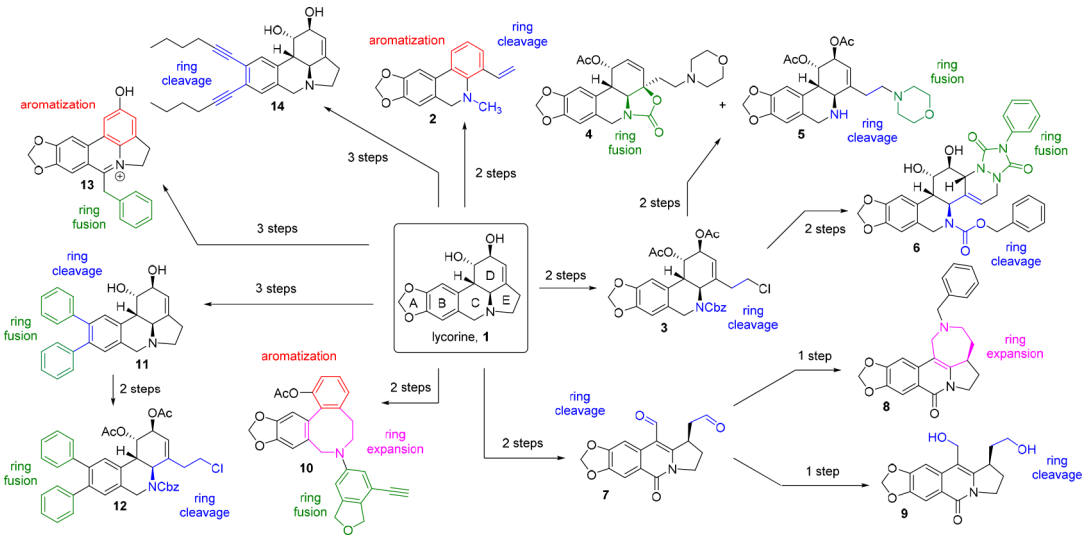
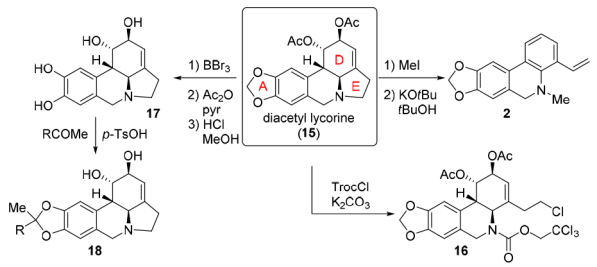
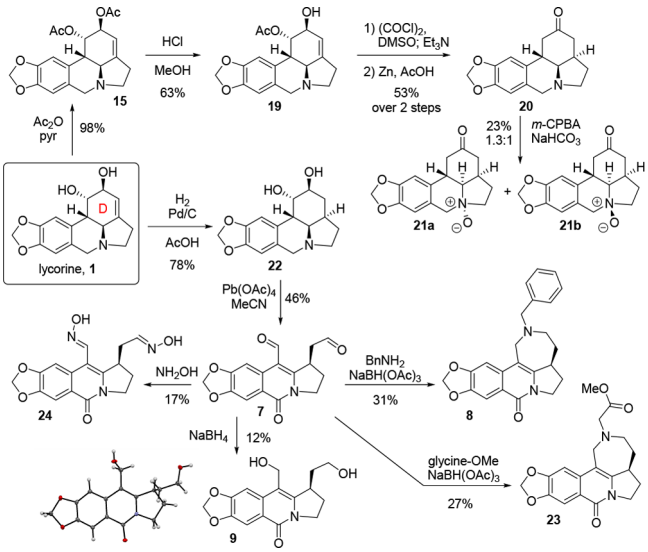
Scheme 1. Overview of Compounds Synthesized from Lycorine



Scheme 2. Known Cleavage Reactions of A and E Rings



Scheme 3. Functionalization of the D-Ring of Lycorine



ted[22a] lycorine (**15**) with a strong base results in Hofmann elimination to open ring E and aromatization of ring D (**2**). Cleavage of the E-ring can be accomplished without concomitant aromatization by formation of the carbamate, with in situ nucleophilic attack by chloride (**16**).[22a] The dioxolane ring A can also be opened to yield catechol **17** and re-formed to produce a variety of ketal derivatives (**18**).[22c]

We sought to construct a complex and diverse set of compounds from lycorine using the CtD strategy; an overview of these efforts is provided in Scheme 1. Several challenges presented themselves in the course of this work, including the difficulty in altering the thermodynamically stable, contiguous arrangement of rings (in contrast to the facile ring rearrangements observed for the overlapping ring systems of pleuromutilin[10] and gibberellic acid[7a]), avoiding aromatization of the D-ring (primed by the diaxial orientation of oxygen leaving groups) and the low solubility of lycorine and many of its derivatives.

Lycorine's highly functional group rich D-ring provides numerous opportunities for diversification (Scheme 3). Lycorine is highly insoluble in most organic solvents, so conversion to known diacetyl lycorine (**15**)[22a] provided a more tractable intermediate. Selective deprotection of the allylic alcohol (**19**) was followed by oxidation to the α,β-unsaturated ketone, then reductive deoxygenation with zinc in acetic acid,[24] to provide D-ring ketone **20** as a single isomer. Oxidation of **20** with 3-chloroperbenzoic acid provided diastereomeric *N*-oxides **21a** and **21b**.

The D-ring diol of lycorine also provides an opportunity for direct ring cleavage. The *trans*-diaxial diol does not permit cleavage by periodate, but lead(IV) acetate is known to cleave *trans*-diols.[25] Attempts to cleave the diol of lycorine itself resulted in aromatization of ring D and an intractable mixture of decomposition products. However, reduction to dihydrolycorine resulted in a single diastereomer (**22**) that was susceptible to cleavage to dialdehyde **7** (Scheme 3). Under these conditions, the C-ring was also oxidized to the pyridone, which was confirmed by X-ray crystallography of reduced diol derivative **9**. Dialdehyde **7** was condensed with amines to give azepene derivatives **8** and **23**, as well as dioxime **24**.

Hofmann elimination to open ring E also resulted in aromatization of ring D, as previously reported.[22a] With the goal of retaining the native stereogenic centers and high Fsp3 of lycorine, we pursued a carbamate-opening strategy similar to that shown in Scheme 2, although with benzyl chloroformate due to ease of selective carboxybenzyl removal. The resulting carbamate (**3**, Scheme 4) contained an alkyl halide that was then substituted with amine nucleophiles to form **25** and **26**. Reaction with sodium azide to give primary alkyl azide **27** provided an additional diversification point via subsequent copper-catalyzed azide−alkyne coupling reactions (**28**−**30**).

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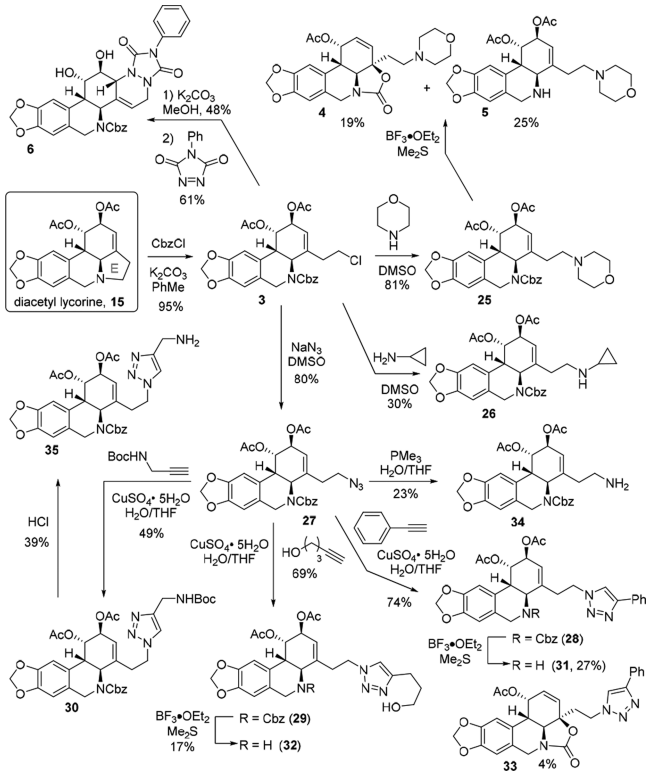
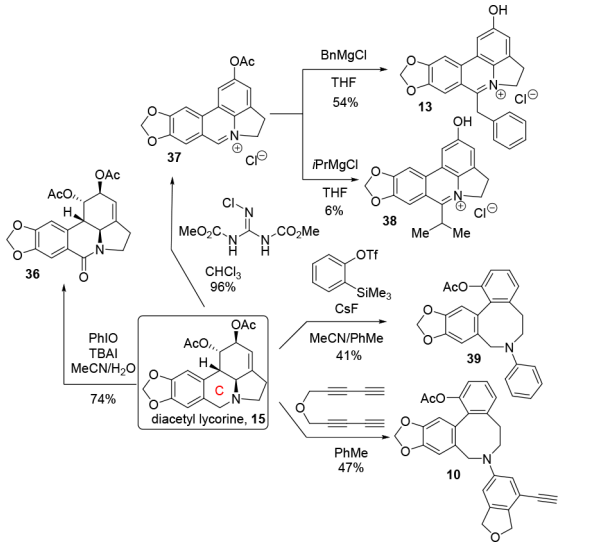
Scheme 4. Functionalization of the Cleaved E-Ring



Scheme 5. Functionalization of the C-Ring



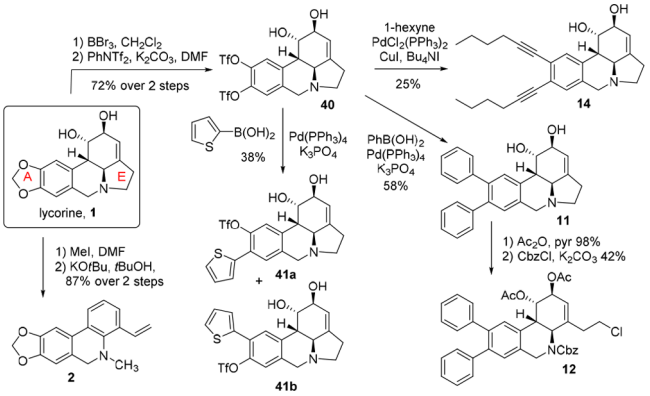
Removal of the Cbz protecting group under nucleophilic conditions[26] afforded expected secondary amine products **5**, **31**, and **32**. In addition, the intermediate carbamic acid underwent S_N2' displacement of the allylic acetate to provide ring fused carbamates **4**, **33**, (Scheme 4), and **42** (Supporting Information). Unhindered primary amines[16] **34** and **35** were also synthesized by azide reduction and Boc deprotection, respectively. Chloride **3** could also undergo elimination, resulting in diene **43** (SI), which is poised for an intermolecular Diels–Alder annulation to give novel ring system **6** (Scheme 4).

Functionalization of the C-ring of lycorine proved more challenging (Scheme 5). Benzylic oxidation of diacetyl lycorine proceeded smoothly as previously described (**36**),[27] but attempts to open the resulting lactam were unsuccessful. C-ring oxidation to iminium ion **37** with concomitant D-ring aromatization was observed upon treatment with electrophilic chlorinating reagent Palau'Chlor,[28] rather than the expected arene chlorination. In fact, **37** is the acylated form of the Amaryllidaceae alkaloid lycobetaine (also known as ungeremine), a potent topoisomerase IIβ poison.[29] Facile access to this intermediate provided the opportunity to synthesize analogues of lycobetaine via an organomagnesium addition to the iminium ion (**13**, **38**), a strategy used on the alkaloid berberine.[30]

As a more global strategy for ring rearrangement, Hoye and co-workers recently reported diverse reactivities of benzyne intermediates with several natural product classes.[31] Indeed, treatment of diacetyl lycorine (**15**) with traditional benzyne precursor *o*-(trimethylsilyl)phenyl triflate[32] afforded eight-membered C-ring-expanded product **39**. The nucleophilic attack of the tertiary amine to the benzyne formed in situ might be expected (forming the N–aryl bond found in **39**), but an unexpected 1,2-alkyl shift followed by D-ring aromatization also occurred (see the SI for a proposed mechanism). The more mild hexa-dehydro-Diels–Alder reaction to form benzyne intermediates, pioneered by Hoye,[31] did not inhibit aromatization and produced an analogous product (**10**).

Finally, cleavage of the A-ring of lycorine using a reported strategy provided known catechol **17**,[22c] which was converted to the novel ditriflate **40** (Scheme 6). Subsequent Suzuki and

Scheme 6. A-Ring Opening and Cross-Coupling



Sonogashira reactions appended different functional groups to the aromatic ring, forming **11**, **14**, **41a**, and **41b**. Hofmann elimination/aromatization generated **2**. Combining A- and E-ring opening with Suzuki product **11** resulted in **12**, thus modifying multiple rings of lycorine.

In total, 52 compounds were synthesized in five or fewer steps from lycorine using the CtD approach of ring system distortion, including ring cleavage and ring expansion. Of these compounds, eight (**2**, **15**, **17**, **19**, **22**, **36**, and SI compounds **44** and **45**) have been previously reported, and the remainder are novel. A full list compounds and corresponding synthetic schemes can be found in Figures S1 and S2. The resultant collection displayed physicochemical properties more similar to natural products than compounds in existing screening libraries (see Figure S3), such as the commercial ChemBridge Microformat Library [figures for the latter shown in brackets]: Fsp3 = 0.42 [0.23], ring fusion density = 0.37 [0.06], number

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of stereogenic centers = 3.6 [0.25], AlogP = 2.76 [3.99], Glob = 0.14 [0.08].[33] To quantify the structural diversity of the compound set, a Tanimoto similarity matrix was also generated for all compounds (Figure S4), with a small average Tanimoto coefficient of 0.19 (with 1.00 indicating identical structures).[34] In addition, ≥25 mg were synthesized for most derivatives, and compounds were produced at ≥95% purity. Collections of compounds derived from natural products, such as those disclosed herein, are structurally distinct from, but complementary to, existing screening libraries and will be useful for a variety of biological investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02562.

Experimental procedures, NMR spectra, and graphs of physicochemical properties of all products (PDF)

Accession Codes

CCDC 1853000 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): The University of Illinois has filed patents on some of this work.

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(33) Abbreviations used: Fsp3 = fraction of sp^3-hybridized carbon atoms, AlogP = atomic partition coefficient, Glob = globularity (smallest eigenvalue divided by the largest eigenvalue of the covariance matrix of atomic coordinates, a measure of sphericity).
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