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Access to a Structurally Complex Compound Collection via Ring Distortion of the Alkaloid Sinomenine

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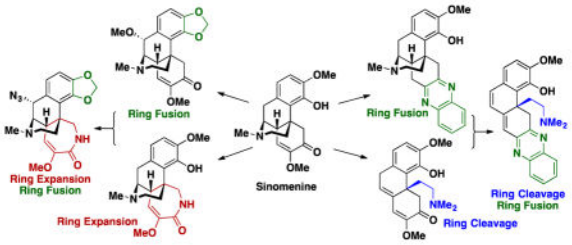
Abstract

Many compound collections used in high-throughput screening are composed of members whose structural complexity are considerably lower than natural products. We previously reported a strategy for the synthesis of complex and diverse small molecules from natural products using ring distortion reactions, called complexity-to-diversity (CtD), and herein CtD is applied in the synthesis of 16 diverse scaffolds and 65 total compounds from the alkaloid natural product sinomenine. Chemoinformatic analysis shows that these compounds possess complex ring systems and marked 3-dimensionality.

Graphical abstract



High-throughput screening (HTS) is a common method for identification of starting points for drug discovery projects, and 90% of first-in-class drugs from 1999 to 2008 originated from a screen.[1] As such, the compound collections utilized in HTS campaigns have been highly scrutinized, and it is now well appreciated that the typical large (>100,000 members) compound collection available from commercial sources is principally populated by small molecules considered to be structurally simple, with a high percentage of sp^2-hybridized carbons and few stereogenic centers.[2] For example, Tan and co-workers calculated an average fraction sp^3 (Fsp^3) of 0.37 for a collection representative of commercial screening collections, whereas natural product drugs have an average Fsp^3 of 0.68.[3] While structurally

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ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, NMR spectra, and graphs comparing complexity parameters (PDF)
X-ray data for **15** (CIF)
X-ray data for **20** (CIF)

simple compounds are valuable and have led to many drugs, especially for targets whose active sites favor the binding of flat molecules (e.g. kinases inhibitors[4] and certain tubulin binders[5,6]) there is a continual need for complementary sets of small molecules that have greater structural complexity; such compounds would be expected to hit different types of targets (e.g. protein-protein interactions).[7–10] Consequently, a priority for drug discovery is assembling compound collections populated by complex molecules.

Natural products are a major source of compounds with structural complexity, and many natural products or their derivatives are FDA approved drugs.[11] Inspired by the success of natural products in drug discovery, synthetic methods have been developed to rapidly generate complex compounds including diversity–oriented synthesis (DOS),[12–17] biology–oriented synthesis (BIOS),[18] and construction of natural product–inspired scaffolds.[19–23] We have previously reported the Complexity-to-Diversity (CtD) strategy in which the core ring systems of complex, readily available natural products are significantly altered using ring fusion, expansion, cleavage, and rearrangement reactions in the preparation of novel and structurally complex small molecules.[24–27] Herein we disclose the manipulation of the alkaloid sinomenine (**1**, Scheme 1) using the CtD approach to generate a collection of 65 compounds.

Sinomenine (**1**) is isolated from the roots and stems of the plant *Sinomenium acutum*, native to Japan and China.[28] It is used in Asia for the treatment of rheumatoid arthritis and possesses immunosuppressive and anti-inflammatory activities.[29,30] Structurally, sinomenine is composed of four fused rings and contains three contiguous stereogenic centers. The presence of an anisole, tertiary amine, enol ether, and ketone provides ready handles for alteration of three of the four rings and establishes sinomenine as an outstanding candidate for the CtD strategy. Furthermore, the hydrochloride salt of **1** is inexpensive and readily available in gram quantities.

In designing the CtD library, several known transformations of **1** were instructive for priming **1** for ring distortion reactions (Scheme 1). These reactions include hydrolysis of the enol ether on the C-ring of **1** to generate diketone **2**,[31] and oxidative dearomatization of the HCl salt of **1** to form quinone methide **3.**[32] Treatment of **2** with *o*-phenylenediamine produces quinoxaline **4**,[31] and reaction of **3** with nucleophiles yields various catechols (**5**) substituted at the benzylic position.[32] These known reactions, coupled with anticipated reactivity of the anisole, ketone, enol ether, and tertiary amine on the A, C, and D rings, provided strategic entry points into the core scaffold of **1**. An overview of routes to **6**–**22** from **1** is shown in Scheme 2 and is described in detail below.

In investigating the hydrolysis of **1** it was discovered that treatment of **1** with hydrochloric acid and ammonium hydroxide resulted in isolation of keto–enamine **23.** Compound **23** (Scheme 3) was envisioned as a key intermediate and a lynchpin for the synthesis of new ring systems, through oxidative cleavage of the C ring, and through the condensation to quinoxaline **4**. Treatment of **23** with lead tetracetate resulted in a successful C-ring oxidative cleavage and a ring fusion to arrive at nitrile ester **6**; isolation of a single diastereomer of **6** suggests that ring fusion occurred before cleavage. Reduction of **6** afforded amino alcohol **24**, and exposure to triphosgene led to 9-membered carbamate **7**. Condensation of keto-

enamine **23** with *o*-phenylenediamine afforded **4**. Hofmann–type elimination was envisioned from **4** by sequential exposure to iodomethane and potassium carbonate. The elimination was carried out successfully to generate conjugated compound **8**, albeit in low yield, and the concomitant fusion of the anisole oxygen onto the C-ring to produce **9** was also observed.

Demethylated catechol **25**[32] (Scheme 4) was envisioned as an entry point for extensive modification of the A ring of sinomenine. Oxidation of the HCl salt of **1** with diacetoxyiodobenzene in water produced dearomatized compound **3**, and after dissolution in methanol catechol **25** was generated as a single diastereomer (Scheme 4) using the known protocol (albeit without purification of **3**).[32] Oxidative dearomatization of **25** with sodium periodate in methanol led to formation of *o*-quinone **26**, whose cleavage with lead tetracetate formed diester **10** and demethylated analog **27**. Catechols are known to undergo methylenation using methylene dihalides to form benzodioxoles.[33] Following this precedent, treatment of **25** with dibromomethane and potassium carbonate led to generation of benzodioxole **11** and an oxidized variant, ketone **12**. Exposure of **11** to Schmidt reaction conditions led to generation of ring–expanded **13**. These reaction conditions also induced stereoretentive displacement of the benzylic methoxy group in **11** with azide en route to **13** and to yield **28**. The azide approaches the substrate from the more accessible bottom face of the molecule. Methylation of benzodioxole **12** and subsequent treatment with potassium carbonate led to D-ring–opened **14**.

Further manipulation of the C and D-rings of **1** are shown in Scheme 5. Tosyl oxime **29** was synthesized from **1** in two steps. An attempted Beckmann rearrangement via subjection of **29** to 10% sodium hydroxide in dioxane led to unexpected ring fused compound **15**, which was characterized by X-ray crystallography. Formation of **15** likely occurs through an azirine intermediate as is observed in the Neber rearrangement.[34] Interestingly, **15** resembles the structure of (+)-morphine, and it is known that treatment of naturally occurring (−)-morphine with methanesulfonic acid yields apomorphine.[35] Therefore, similar reaction conditions were applied to **15**, resulting in a ring rearrangement involving aromatization of the C-ring, rearrangement of the D-ring, and addition and migration of a methoxy group to generate expected product **16** (the enantiomer of the apomorphine scaffold) as well as ring-contracted product **17**, which is likely formed through a benzilic acid-type rearrangement.

Finally, two of the transformations reported herein—Schmidt ring expansion of the C ring and Hofmann-type ring opening of the D ring—were applied to other complex scaffolds derived from **1**. In the presence of diacetoxyiodobenzene, **1** could be oxidized at the benzylic position to afford ketone **30** (Scheme 6).[32,36] The Schmidt reaction of **30** resulted in ring expansion (**18**), which could be followed by a Hofmann–type elimination to provide **19** (Scheme 6). Given the previous success of Hofmann–type eliminations, a direct ring cleavage of **1** was envisioned. Interestingly, treatment of sinomenine with iodomethane and subsequent elimination with potassium carbonate produced unexpected ring–cleaved, alkyl shifted **20**, characterized by X-ray crystallography (Scheme 6). *N*-oxidation followed by iron-mediated demethylation produced secondary amine **31**. Exposure of **31** to HCl induced another alkyl shift to arrive at the known natural product cepharatine A (**21**)[37] as well as **22**.

Previously, **21** had been enantioselectively synthesized in 10 steps,[38] making the work reported herein the shortest enantioselective synthesis to date (5 steps).

In summary, the natural product sinomenine was used as a starting point for the creation of a diverse collection of structurally complex compounds. The combination of ring distortion reactions, such as fusion, contraction, expansion, rearrangement, dearomatization, and aromatization were strategically combined to generate 16 scaffolds and 65 total compounds (all compounds are shown in Figure S1 of the Supporting Information). Of these compounds, 14 are known (**1**, **3, 4**, **21**, **25**, **30**, **49**–**52**, **55**–**57**, **60**), while the other 52 compounds are novel (full characterization data for all new compounds is in the Supporting information). In addition to the 28 compounds shown in the manuscript, another 37 compounds were synthesized from sinomenine. For these compounds (**32**–**68** in Figure S1) the synthetic routes are in Figure S2. Most of the 65 compounds were produced on a scale of 25 mg or greater. Chemoinformatic diversity analysis was used to compare this collection to a commercially available screening collection. The set of 66 compounds (including sinomenine) contains the following complexity parameters (average): Fsp^3 = 0.48, number of stereogenic centers = 3.1, ring fusion density[39] = 0.37, ring complexity index[39] = 1.40, and Glob[40] = 0.36, which are markedly higher in value compared to Chembridge compounds (combined Diverset™-CL and Diverset™-EXP) Fsp^3 = 0.38, number of stereogenic centers = 0.55, ring fusion density = 0.06, ring complexity index = 1.06, and Glob = 0.08. Please see Figure S3 for graphs comparing diversity parameters.

Complex molecules are different from and complementary to compounds in standard screening collections. As we have demonstrated previously with gibberellic acid[24], adrenosterone[24], quinine[24], abietic acid[25], pleuromutilin[26], and now here with sinomenine, natural products are an outstanding starting point for the construction of complex and diverse small molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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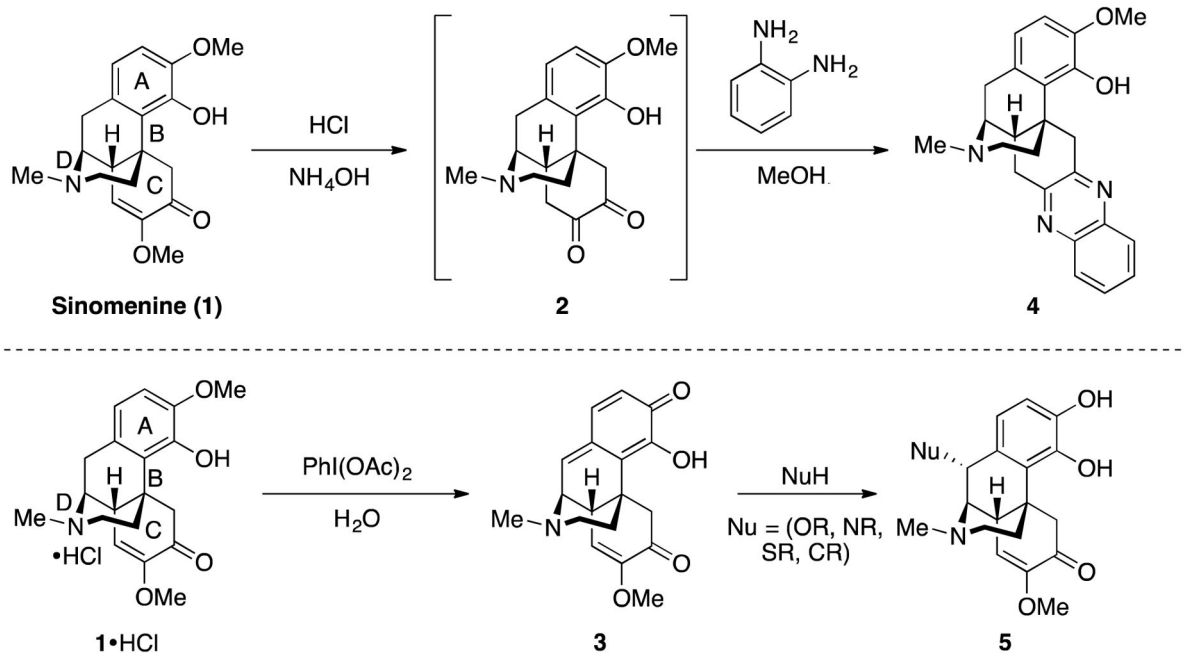
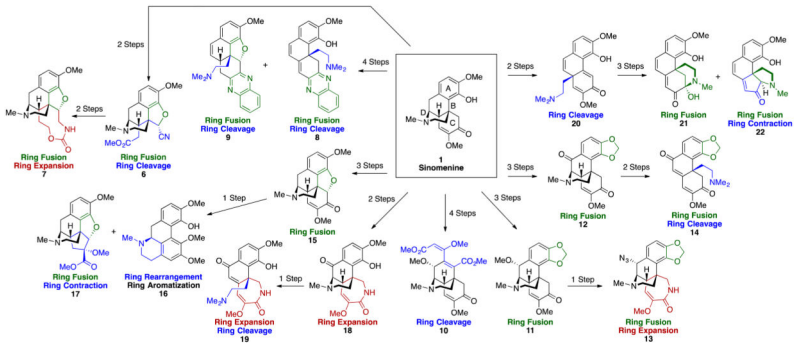
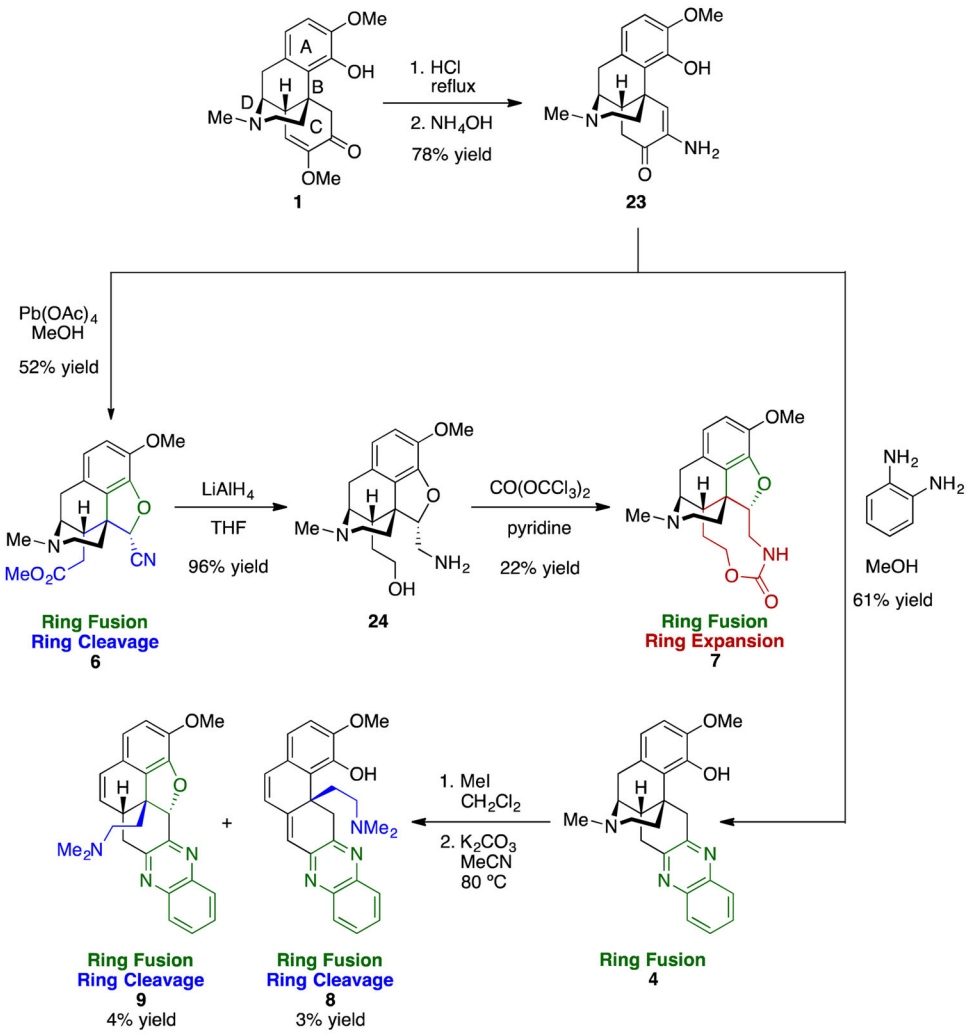


Scheme 1.
Key transformations known for sinomenine



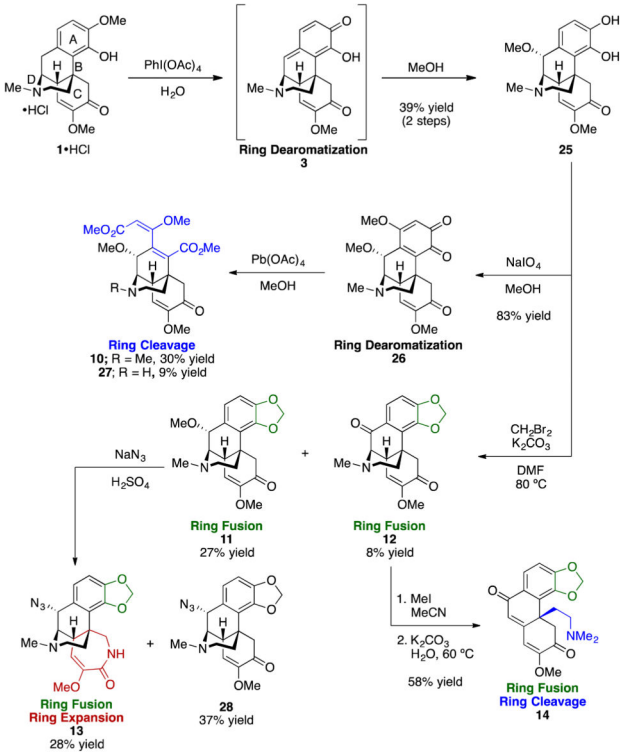
Scheme 2.

Overview of scaffolds generated from the alkaloid sinomenine

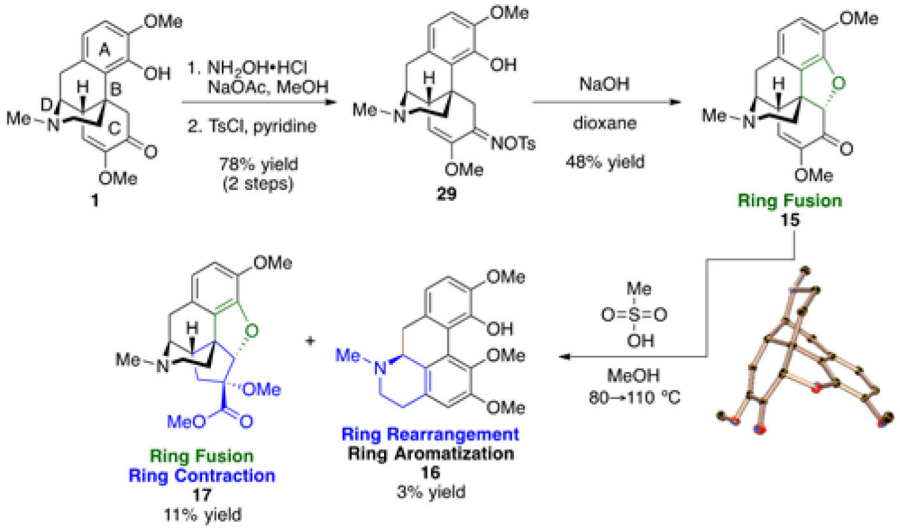


Scheme 3.

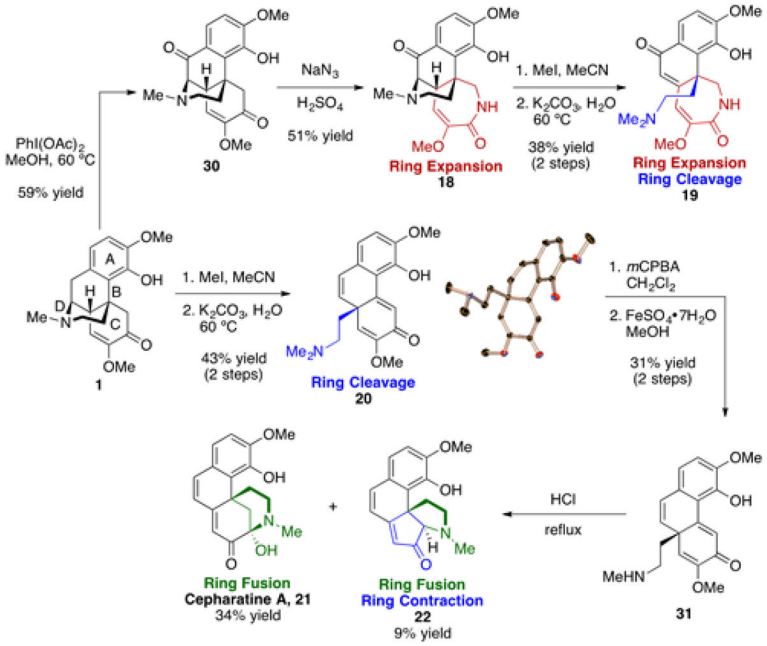
New scaffolds through intermediate **23**



Scheme 4.
New scaffolds through intermediate **25**



Scheme 5.
Distortion of C and D ring systems



Scheme 6.

Synthesis of **19** and cepharatine A