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A pyrone remodeling strategy to access diverse heterocycles: application to the synthesis of fascaplysin natural products†

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The synthesis of diverse *N*-fused heterocycles, including the pyrido[1,2-*a*]indole scaffold, using an efficient pyrone remodeling strategy is described. The pyrido[1,2-*a*]indole core was demonstrated to be a versatile scaffold that can be site-selectively functionalized. The utility of this novel annulation strategy was showcased in a concise formal synthesis of three fascaplysin congeners.

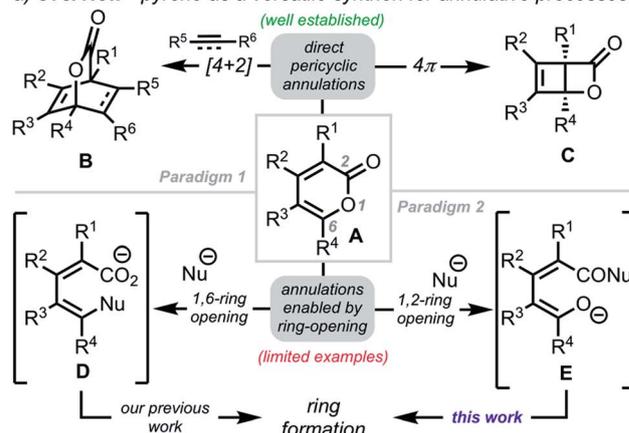
Introduction

The use of annulation reactions to construct complex structures remains a powerful strategy in chemical synthesis.¹ For almost a century, 2-pyrones (**A**, Scheme 1a) have served as valuable heterocycles for annulations due to their versatile reactivity, which can be broadly categorized into two main paradigms: (1) pericyclic annulative processes and (2) regioselective opening *via* nucleophilic addition to unveil reactive intermediates poised for subsequent annulation. With respect to the first paradigm, pericyclic reactions, such as [4+2]-cycloadditions² and 4π electrocyclizations,³ have been well documented to provide rapid access to bicycles such as **B** and **C**, which have been exploited in myriad ways.^{4,5} In contrast, there have been limited examples within the second paradigm. While nucleophilic 1,6-ring opening of 2-pyrones has proven to be a particularly effective strategy for orchestrating novel cyclization events *via* reactive intermediate **D**⁶ (our previous work^{6a,b}), leveraging the dienolate functionality (**E**) accessible through 1,2-ring opening in annulation reactions remains underexplored.⁷

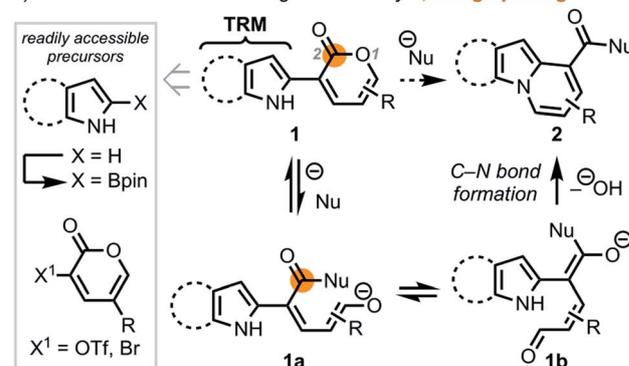
We envisioned a strategy to *N*-fused bicycles in which a tethered reactive moiety (TRM) on 2-pyrene would engage an *in situ* generated dienolate (such as **1b**) in an annulation reaction (Scheme 1b). The precursor *N*-heterocycle–pyrone adducts (e.g., **1**) were anticipated to arise modularly by coupling *N*-heterocycle boronate esters and pyrones (e.g., 3-OTf pyrone)⁸ *via* Suzuki coupling. The C2-borylated *N*-heterocycles were expected to arise directly from the precursor heterocycles by leveraging existing methods (e.g., C–H functionalization),⁹ thus enhancing the practicality of this approach. We

hypothesized that opening **1** with a suitable nucleophile would first unveil dienolate **1a**, which upon equilibration to **1b**, would set the stage for annulation *via* direct capture of the aldehyde

a) overview - pyrone as a versatile synthon for annulative processes



b) this work - annulation design enabled by 1,2-ring opening

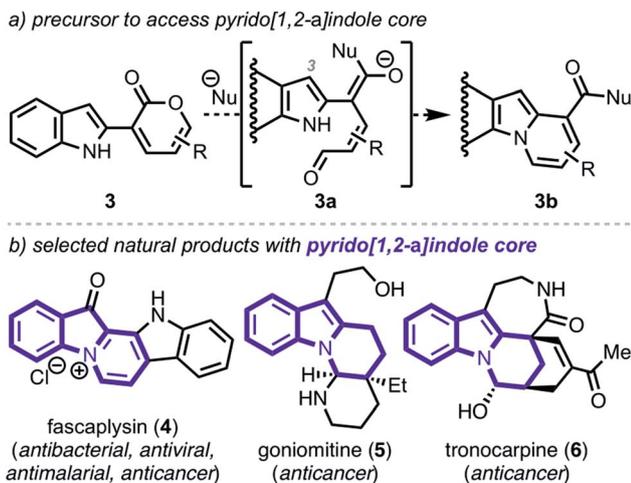


Scheme 1 Annulation strategies enabled by versatile reactivity of 2-pyrene derivatives.

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Scheme 2 Proposal to access pyrido[1,2-*a*]indole core.

group by the TRM to provide *N*-fused heterocycle 2. Notably, varying the TRM would provide a general platform for diverse heterocycle synthesis.

To demonstrate the viability of this strategy, we initially focused on converting indole–pyrone adduct **3** to the pyrido[1,2-*a*]indole scaffold (**3b**, Scheme 2a)—a key structural motif present in a number of biologically active natural products including faspaplysin (**4**, Scheme 2b),¹⁰ goniomitine (**5**),¹¹ and tronocarpine (**6**).¹² While there exists numerous methods to access this biologically relevant scaffold,^{13–17} many of these tactics rely on reaction precursors with highly specific substitution patterns and, therefore, are unfortunately not general or modular. Specifically, we recognized that while heterocyclic-dienolate adducts (such as C3-substituted intermediate **3a**) have proven to be effective precursors for benzannulation processes, strategies to install dienol/dienolate functionality at C2 of *1H*-indoles lacking C3-substitution have remained elusive due to regioselectivity challenges.^{13b,18,19} Overall, we envisioned that our approach to coupling pyrone—a masked dienolate—to the C2-position of *1H*-indole would provide a unique opportunity to address this longstanding regioselectivity challenge.

Results and discussion

We commenced our investigations with indole–pyrone **7a** (Table 1) and sodium methoxide as the nucleophile. Initially, we observed the formation of the desired pyrido[1,2-*a*]indole (**8a**) along with carbazole **9** and hemiaminal **10** as side products (entry 1). Changing the solvent from acetonitrile to 1,4-dioxane enhanced the formation of **9**, which was generally more pronounced in relatively non-polar solvents.²⁰ However, the use of polar solvents such as dimethylformamide resulted in complete decomposition of **7a** (entry 3). The formation of hemiaminal **10** corroborates the proposed reaction mechanism illustrated in Scheme 1b and led us to investigate the use of polar protic solvents, such as methanol, to favor the conversion of **10** to **8a**. We found, at this stage, that conducting the annulation in methanol furnished **8a** in 45% yield (entry 4). Further

Table 1 Reaction development and optimization

Entry	Solvent	NMR yield ^a (%) 8a : 9 : 10
1	CH ₃ CN	10 : 13 : 16
2	1,4-dioxane	0 : 15 : 21
3	DMF	decomp.
4	MeOH	45 : 0 : 0
5	THF/MeOH (1:1)	36 : 7 : 10
6	DCE/MeOH (1:1)	45 : 0 : 0
7	CH ₂ Cl ₂ /MeOH (1:1)	61 : 0 : 0
8 ^b	CH ₂ Cl ₂ /MeOH (1:1)	59 : 0 : 0
9 ^c	CH ₂ Cl ₂ /MeOH (1:1)	65 ^d : 0 : 0

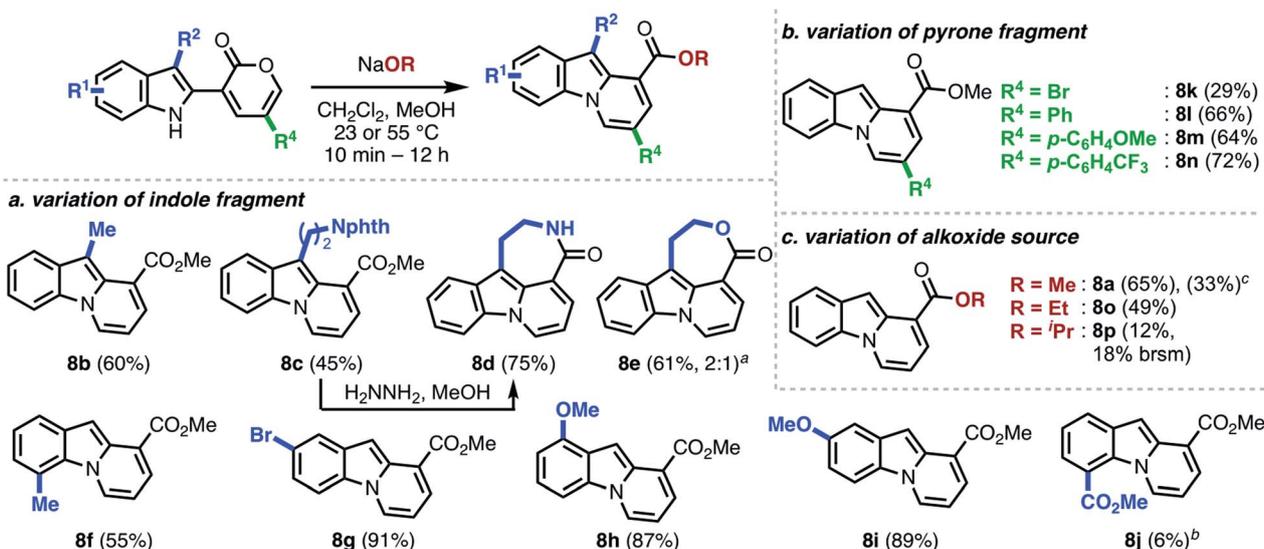
^a Determined by ¹H NMR analysis using 1,2,3-trimethoxybenzene as an internal standard. ^b Open flask set-up under non-anhydrous solvent conditions. ^c Reaction conducted on 1.3 g scale. ^d Isolated yield.

investigation using co-solvents (entries 5–7) led to the identification of a dichloromethane/methanol solvent mixture as optimal, furnishing **8a** in 61% yield (entry 7),²¹ presumably due to the increased solubility of **7a**. Gratifyingly, the yield remained unaffected when the annulation was conducted both under open-flask conditions (entry 8) and on 1.3 g scale (entry 9). The structure of **8a** was unambiguously confirmed by single-crystal X-ray analysis.

With optimized conditions in hand, we investigated the scope of this operationally simple pyrido[1,2-*a*]indole synthesis (Scheme 3). Indole–pyrone substrates with varied substitution patterns were readily synthesized through Suzuki coupling of indole boronate esters⁹ with either 3-bromo-^{8a} or 3-triflyloxy-2-pyrone.^{8b} Indole substitution at both C3 and C7 had minimal influence on the ring-opening/annulation process, and the corresponding pyrido[1,2-*a*]indoles were isolated in comparable yields (**8b–f**, Scheme 3a). Interestingly, tetracyclic scaffolds such as lactam **8d** and lactone **8e** were accessed from indole–pyrones derived from tryptamine and tryptophol, respectively. Notably, **8d** represents the core framework of tronocarpine (**6**). Next, we sought to investigate the tolerance of the overall transformation toward alterations of the electronics of the indole moiety. We observed that the presence of an electron-donating group, irrespective of the position, furnished the corresponding pyrido[1,2-*a*]indoles in high yields (**8g–8i**), whereas the product bearing an electron-withdrawing substituent (**8j**) was isolated in poor yield.²²

As shown in Scheme 3b, the established reaction conditions were also applicable to the efficient preparation of pyrido[1,2-*a*]indoles **8k–n** bearing various substituents on the pyrone moiety. Unlike the electronic influence exerted by the substituents on the indole, C5-substitution on the pyrone moiety had little to no





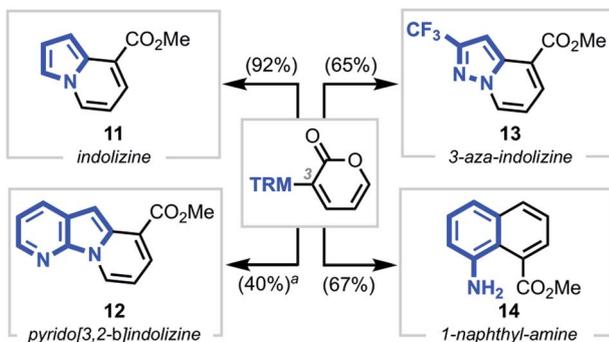
Scheme 3 Scope of modular pyrido[1,2-*a*]indole synthesis. ^aIsolated both lactone and alcohol-ester precursor in a ratio of 2 : 1. ^bIsolated **8j** along with the corresponding carbazole (29% yield). ^cOne-pot procedure: Suzuki coupling + ring-opening/annulation.

effect on the final reaction outcome with the sole exception being product **8k**, which was isolated in diminished yield. Additionally, we investigated the effect of other alkoxide nucleophiles (Scheme 3c). With increasing basicity and sterics of the alkoxide, more forcing conditions were generally required, and the yield of the final products (**8a**, **8o–p**) were also diminished.²²

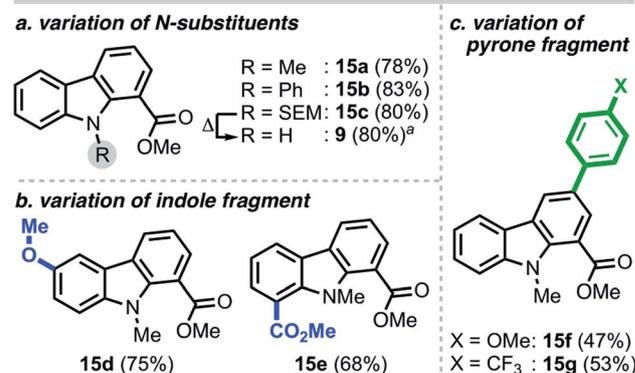
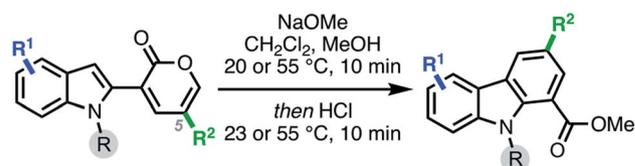
To further demonstrate the generality and versatility of our strategy, we next explored the synthesis of structurally diverse heterocyclic systems by subjecting various *N*-heterocyclic-pyrone adducts to the established reaction conditions (Scheme 4).²³ Gratifyingly, upon coupling various TRMs, such as pyrrole, 7-aza-indole, pyrazole, and aniline moieties, to the C3 position of 2-pyrone, heterocycles such as indolizine **11**, pyrido[3,2-*b*]indolizine **12**, 3-aza-indolizine **13**, and 1-naphthylamine **14** were isolated in moderate to high yields.

Each of the pyrone–heterocycle substrates described to this point contain a free N–H group, thus enabling cyclization directly from nitrogen to form a new N–C bond, with the sole

exception being 1-naphthylamine **14**.²⁴ On the basis of the latter result and our initial hypothesis (Scheme 1b), we envisioned that employing *N*-protected substrates would direct the cyclization to the reactive carbon center, thus facilitating C–C bond formation²⁵ and carbazole synthesis (Scheme 5). Interestingly, we found the annulation to be tolerant of various indole *N*-substituents, providing carbazoles **15a–c** and **9** in high yields. Notably, unlike the pyrido[1,2-*a*]indole scope, the nature of the substituents—both on the indole and pyrone moieties—had little influence on the final reaction outcome, delivering the corresponding carbazoles (**15d–g**) in good yields.²⁶

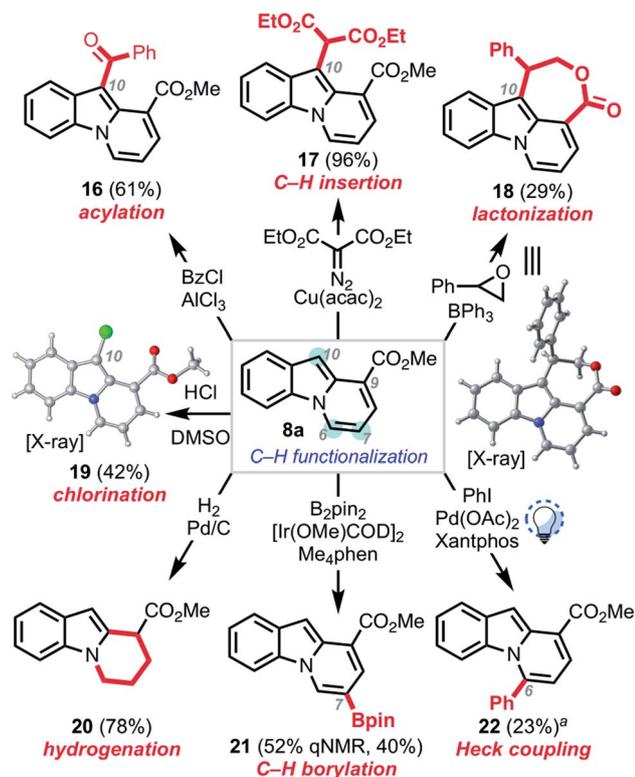


Scheme 4 Access to other novel heterocyclic cores. Conditions: NaOMe, CH₂Cl₂/MeOH, 23 or 55 °C, 10 min. ^aYield over two steps starting from SEM-protected 7-azaindole–pyrone substrate.



Scheme 5 Scope of modular carbazole synthesis. ^aSEM cleavage can also proceed in the same pot upon prolonged heating to furnish the free N–H carbazole **9**.



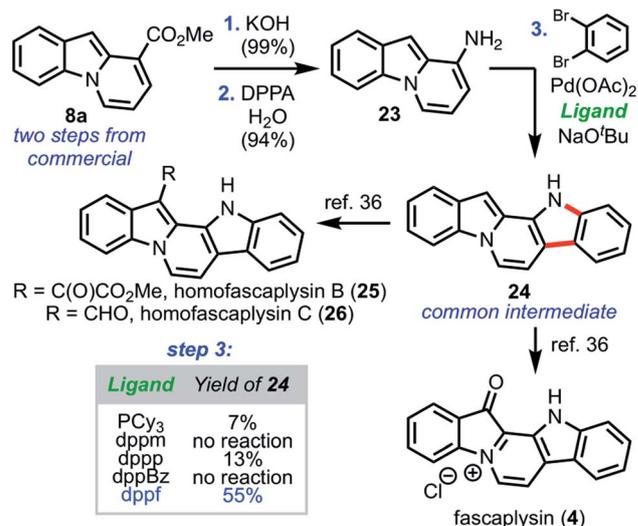


Scheme 6 Derivatizations of pyrido[1,2-*a*]indoles. ^aSignificant portion of **8a** (75%) remained unreacted.

We next sought to explore the subsequent reactivity of the C7-ester functionalized pyrido[1,2-*a*]indole products (Scheme 6). Friedel–Crafts acylation,²⁷ copper-catalyzed carbenoid C–H insertion,²⁸ Lewis acid-mediated epoxide opening/attendant lactonization,²⁹ and chlorination³⁰ all proceeded to provide the corresponding C10-functionalized pyrido[1,2-*a*]indoles **16**–**19**. The structure of **18** and **19** were unambiguously confirmed by single-crystal X-ray analysis. Hydrogenation proceeded smoothly to furnish tetrahydro pyrido[1,2-*a*]indole **20**. Treating **8a** under Hartwig borylation conditions^{9,20} yielded boronate ester **21**, resulting from borylation at the C7 position. Photo-mediated Heck coupling^{20,31} of **8a** with iodobenzene gave biaryl compound **22**, thus providing a platform to functionalize the C6 position as well, albeit at low conversion.³²

With the generality of this strategy successfully established, we next turned our attention toward applying our pyrone remodeling strategy to access the faspaplysin family of natural products. As illustrated in Scheme 7, we began by hydrolyzing ester **8a** to afford the intermediate carboxylic acid, which smoothly underwent Curtius rearrangement³³ to furnish amine **23** in high yield.

Taking inspiration from methodology developed by Ackermann and co-workers,³⁴ a palladium-catalyzed amination/C–H arylation domino coupling³⁵ was employed to couple **23** and 1,2-dibromobenzene to furnish the pentacyclic core of the faspaplysin natural products (**24**), which possessed analytical data (¹H and ¹³C NMR, HRMS, melting point, IR) in full agreement with those previously reported. The synthesis of **24** constitutes



Scheme 7 Formal synthesis of faspaplysin congeners.

formal syntheses of faspaplysin (**1**) and homofaspaplysin B and C (**25** and **26**), which can all be accessed independently in a single step from **24**.³⁶

Conclusions

In summary, we have developed a general, novel pyrone remodeling strategy, which capitalizes on the 1,2-ring opening of 2-pyrone, to construct diverse heterocyclic scaffolds. This transformation, which was initially validated through pyrido[1,2-*a*]indole synthesis, features a diverse substrate scope, with varied substitution patterns on both the indole and pyrone moieties. The scope was additionally extended to access carbazole cores and other *N*-fused heterocycles, thus, showcasing the generality of this strategy. The unusual reactivity of the pyrido[1,2-*a*]indole core was explored in several synthetic transformations, which enabled selective functionalization of three distinct carbon positions. Finally, the utility of this strategy was further demonstrated in a concise formal synthesis of three faspaplysin congeners. Studies to further expand the non-intuitive potential of 2-pyrone and its derivatives in the total synthesis of complex natural products are the focus of our current efforts.

Conflicts of interest

There are no conflicts to declare.

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- 22 Mechanistically, having an electron-withdrawing substituent on the indole moiety renders the free N–H of the precursor indole-pyrone more acidic, which upon exposure to sodium methoxide results in undesired deprotonation to yield the corresponding indole-1-ide, which is resistant toward the desired ring-opening/annulative process. For the same reason, increasing the basicity of the alkoxide source also has a negative effect on this overall transformation.
- 23 In general, *N*-heterocyclic-pyrone adducts with enhanced N–H acidity were more resistant toward the desired ring-opening/annulative process as mentioned in ref. 24. For instance, both the 7-aza-indole and pyrazole substrate required more forcing conditions to effect the desired transformation.
- 24 For the aniline substrate, the cyclization did not occur from the nitrogen center to provide the corresponding benzazepine core.
- 25 For the carbazole formation, addition of HCl was crucial to effect the C-addition to the unveiled aldehyde group.
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