ARTICLE

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

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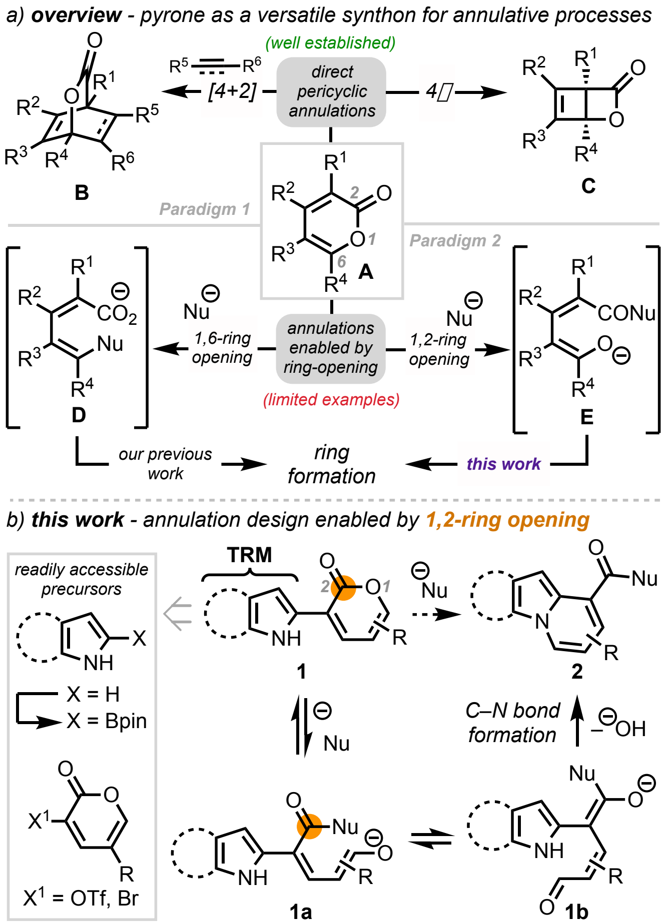
The synthesis of diverse *N*-fused heterocycles, including the pyrido[1,2-*a*]indole scaffold, using an efficient pyrone remodeling strategy is described. The pyrido[1,2-*a*]indole core was demonstrated to be a versatile scaffold that can be site-selectively functionalized. The utility of this novel 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] cycloadditions[2] 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-pyrone 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 the aldehyde group by the TRM to provide *N*-fused heterocycle **2**. Notably, varying the TRM would provide a general platform for diverse heterocycle synthesis.



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

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

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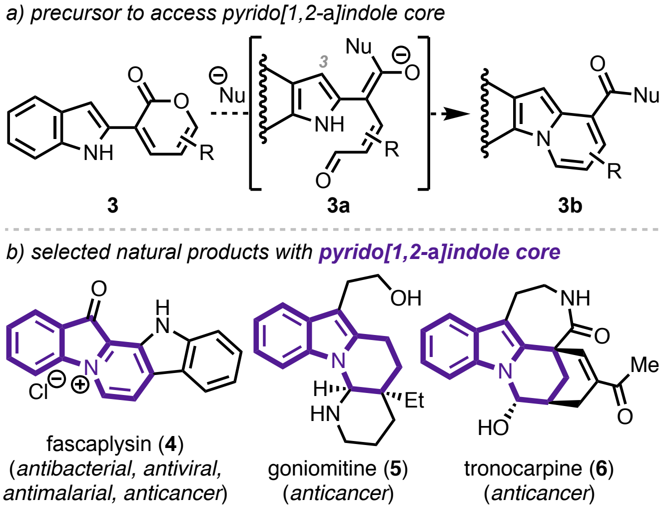
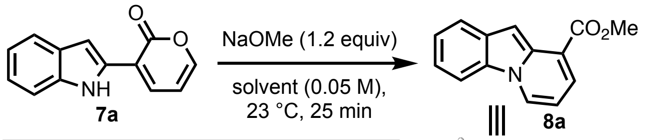
present in a number of biologically active natural products including fascaplysin (**4**, Scheme 2b),[10] goniomitine (**5**),[11] and tronocarpine (**6**).[12] While there exists numerous methods to access this biologically relevant scaffold,[13–17] many of these tactics rely on reaction precursors 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 1*H*-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 1*H*-indole would provide a unique opportunity to address this longstanding regioselectivity challenge.



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

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 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.



Entry	Solvent	NMR yield[a] (%) 8a : 9 : 10
1	CH_3CN	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_2Cl_2/MeOH (1:1)**	**61 : 0 : 0**
8[b]	**CH_2Cl_2/MeOH (1:1)**	**59 : 0 : 0**
9[c]	**CH_2Cl_2/MeOH (1:1)**	**65[d] : 0 : 0**

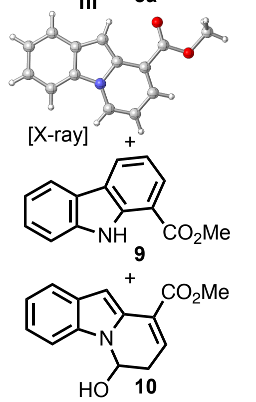


Table 1. Reaction development and optimization. [a]Determined by ^{1}H NMR analysis using 1,2,3-trimethoxybenzene as an internal standard. [b]Open flask set-up under non-anhydrous solvent conditions. [c]Reaction conducted on 1.3 g scale. [d]Isolated yield.

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 esters[9] with either 3-bromo-[8a] or 3-triflyloxy-2-pyrones.[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 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]

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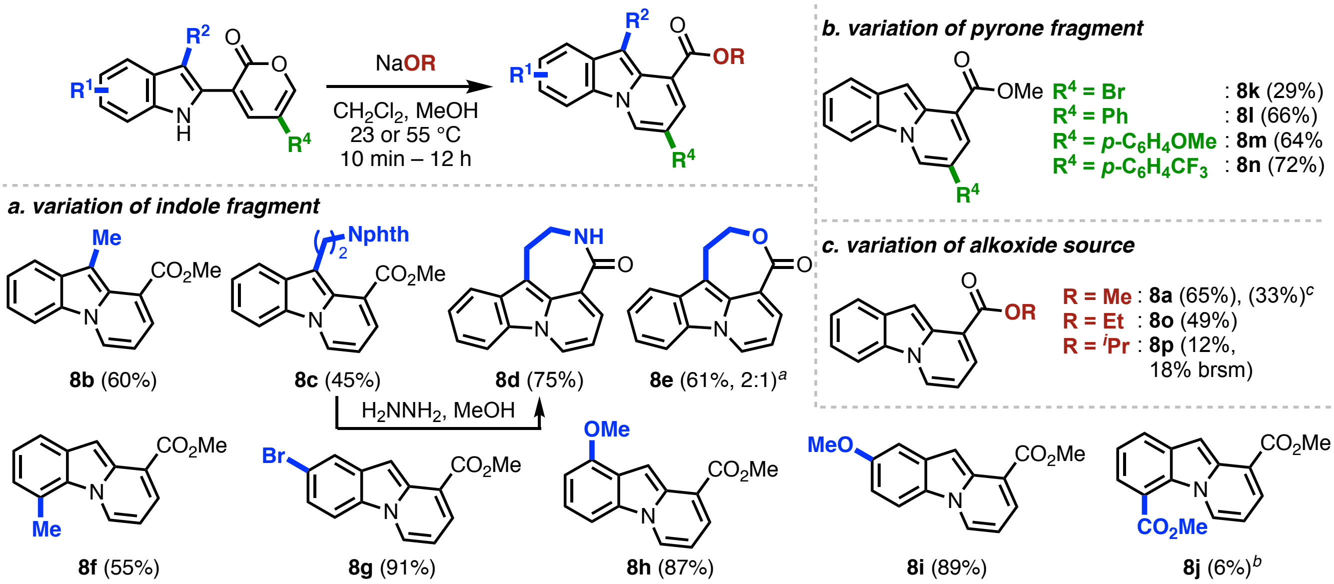
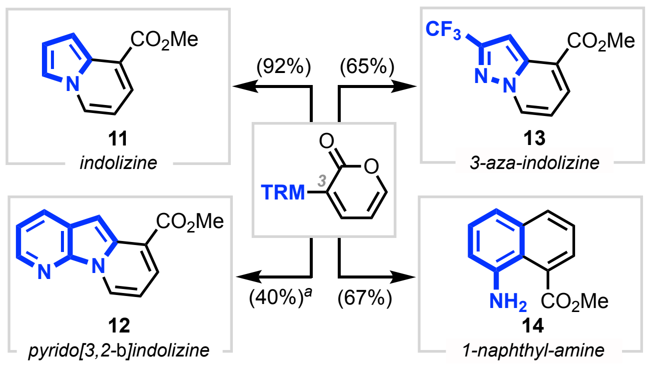


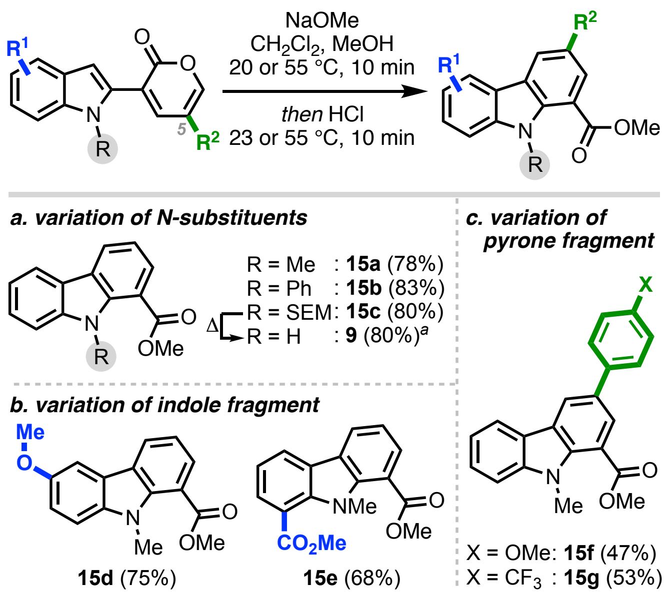
Scheme 3. Scope of modular pyrido[1,2-*a*]indole synthesis. [a]Isolated both lactone and alcohol-ester precursor in a ratio of 2:1. [b]Isolated **8j** along with the corresponding carbazole (29% yield). [c]One-pot procedure: Suzuki coupling + ring-opening/annulation.

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-pyrones, 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.



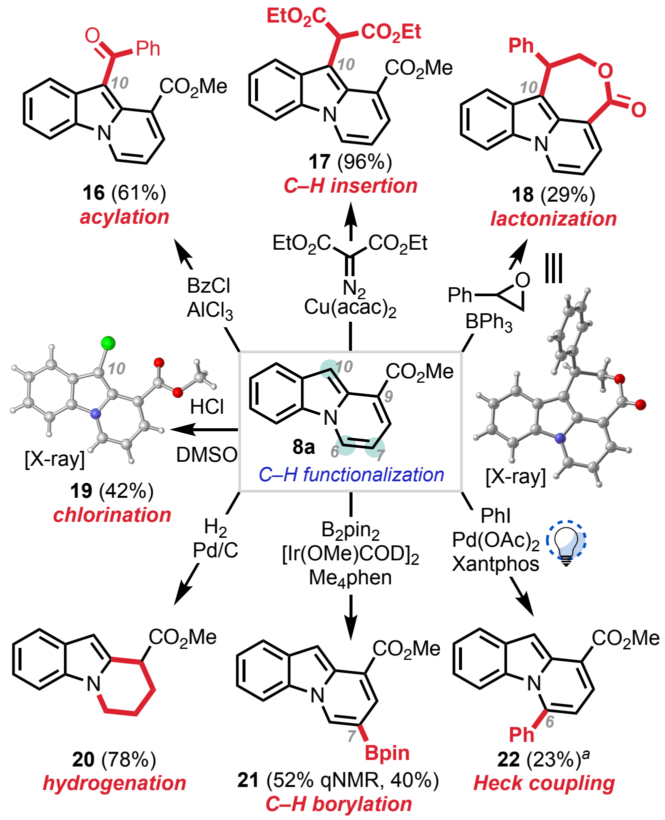
Scheme 4. Access to other novel heterocyclic cores. *Conditions*: NaOMe, CH_2Cl_2/MeOH, 23 or 55 °C, 10 min. [a]Yield over two steps starting from SEM-protected 7-azaindole–pyrone substrate.

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 formation[25] 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



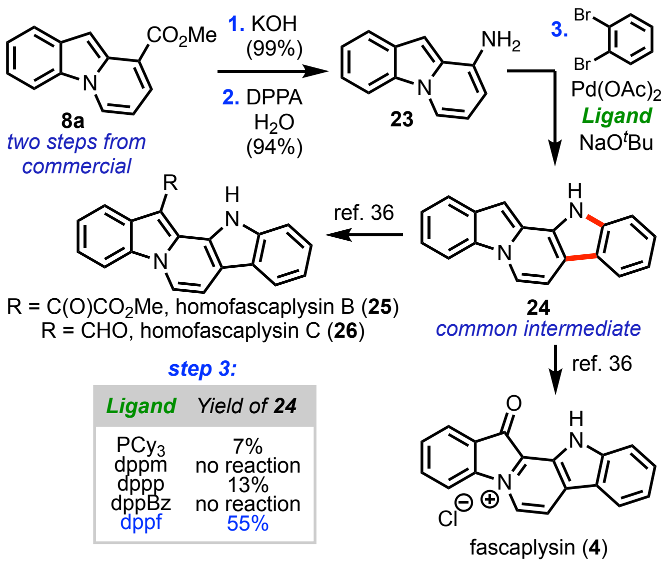
Scheme 5. Scope of modular carbazole synthesis. [a]SEM cleavage can also proceed in the same pot upon prolonged heating to furnish the free N–H carbazole **9**.

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 chlorination[30] 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[20,9] 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]



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

With the generality of this strategy successfully established, we next turned our attention toward applying our pyrone remodeling strategy to access the fascaplysin 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 rearrangement[33] to furnish amine **23** in high yield.



Scheme 7. Formal synthesis of fascaplysin congeners.

Taking inspiration from methodology developed by Ackermann and co-workers,[34] a palladium-catalyzed amination/C–H arylation domino coupling[35] was employed to couple **23** and 1,2-dibromobenze to furnish the pentacyclic core of the fascaplysin natural products (**24**), which possessed analytical data (^{1}H and ^{13}C NMR, HRMS, melting point, IR) in full agreement with those previously reported. The synthesis of **24** constitutes formal syntheses of fascaplysin (**1**) and homofascaplysins 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-pyrones, 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 fascaplysin 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.

Acknowledgements

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21 Alternatively, pyrido[1,2-*a*]indole core can also be accessed from the Boc protected indole–pyrone precursor albeit in poor yield. See the Supporting Information for detailed experimental results.

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.

26 As the precursors for carbazole synthesis lack a free N–H, the substituents on the indole fragment have little to no influence on the reaction outcome. This hypothesis supports the rationalization provided in ref. 22.

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