Cascade Reactions Hot Paper

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Total Synthesis of Camptothecin and Related Natural Products by a Flexible Strategy

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Abstract: *A flexible strategy for constructing natural products containing indolizinone or quinolizinone scaffolds and their analogues was developed, which was based on a cascade exo hydroamination followed by spontaneous lactamization. This method was applied in the total synthesis of camptothecin in nine steps in a new ring-forming approach. It was also used to efficiently prepare five biogenetically or structurally related natural alkaloids, including 22-hydroxyacuminatine, oxypalmatine, norketoyobyrine, naucleficine, and nauclefine, as well as 35 natural-product-like molecules. We believe that this method and the small-molecule library prepared with it can open new avenues for studying the bioactivity of camptothecin and Nauclea natural products.*

Camptothecin (CPT, **1**; Figure 1 a) was isolated by Wani and Wall in 1966[1] from the bark and stem of *Camptotheca acuminata* ("Xi Shu"), a plant native to China. This natural alkaloid potently inhibits tumor growth by binding to topoisomerase I, preventing DNA religation. The resulting DNA damage leads to cell apoptosis.[2] Both the academic community and the pharmaceutical industry have made significant efforts in chemical synthesis[3] as well as bioactivity and mechanistic studies[2,3au,4] of CPT for cancer chemotherapy. However, initial drug development studies with CPT failed because of its poor solubility and severe, unpredictable toxicity.[5] Subsequent structural modifications of CPT have led to the commercially available anticancer drugs topotecan (Hycamtin, **3**; Figure 1 a),[6] belotecan (**4**),[7] and irinotecan (Camptosar, **5**)[8] as well as several CPT analogues that are anticancer drug candidates.

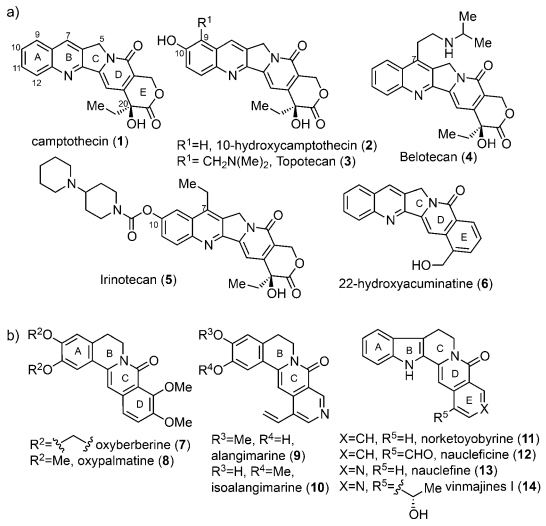

Figure 1. The camptothecin family and structurally related natural products.

We herein report the development of a flexible strategy for the efficient synthesis of CPT and biogenetically or structurally related natural products, including 22-hydroxyacuminatine (**6**),[9] oxypalmatine (**8**),[10] norketoyobyrine (**11**),[11] naucleficine (**12**),[12] and nauclefine (**13**).[13] This strategy is based on a cascade cyclization reaction for the construction of the indolizinone or quinolizinone scaffold (B/C or C/D rings). We thus generated a small library of natural-product-like molecules for future bioactivity studies.

CPT (**1**; Figure 1 a) contains a highly conjugated pentacyclic skeleton with quinoline (A/B rings), indolizinone (C/D rings), and α-hydroxylactone moieties (E ring).[14] 22-Hydroxyacuminatine (**6**) and CPT differ in the E ring, which is a substituted arene ring in **6**. We reasoned that taking the indolizinone scaffold (C/D rings) as a point cut and expanding the C ring by one carbon atom should lead to a large family of alkaloid-containing quinolizinones (Figure 1 b) differing primarily in the various fused aromatic or heteroaromatic rings connected to the quinolizinone moiety (**7**–**14**). Compounds **11**–**14** belong to a large family of indoloquinolizidine-type alkaloids isolated from *Nauclea latifolia* plants, which are traditionally used in ethnomedicine.[15] Extracts and compounds isolated from different parts of this plant, most likely indoloquinolizidine alkaloids,[13,16] exhibit a broad spectrum of bioactivities.

We reasoned that both indolizinone (5/6-membered ring system, **I**) and quinolizinone (6/6-membered ring system, **II**) scaffolds could be effectively constructed from substrate **III** by cascade cyclization (Scheme 1). This process would involve a key hydroamination (C–N bond formation) followed by lactamization. We envisioned that C–N bond formation could be achieved by two pathways: 1) alkyne group activation with π-Lewis acids or 2) alkyne group polarization by introduction of conjugated electron-withdrawing groups. We predicted that this cascade reaction would present two major challenges: 1) controlling the *endo*/*exo* regioselectivity of the cyclization and 2) controlling the geometry of the cyclized product to ensure subsequent lactamization. We aimed to use a convergent approach in which **III** would be prepared from the coupling components **IV** and **V** and ethynylsilane in

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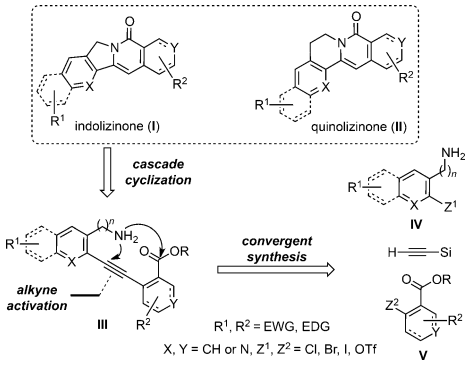


Scheme 1. Synthetic plan. EDG = electron-donating group, EWG = electron-withdrawing group.

Sonogashira coupling reactions. We predicted that changing the coupling components **IV** and **V** would allow for the facile preparation of various polycyclic rings, making this synthetic strategy quite flexible.

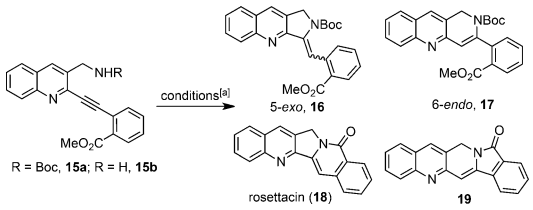
With these considerations in mind, we began by investigating the key cyclization reaction using **15a** and **15b** as model substrates. These substrates were efficiently prepared in four steps (see the Supporting Information). We initially focused on pathway 1 by taking advantage of previous reports on gold-catalyzed carbon–heteroatom bond-forming reactions.[17] As soft and carbophilic Lewis acids, Au complexes have emerged as some of the strongest activators of C–C triple bonds; they effectively coordinate to various C–C π-bonds, facilitating nucleophilic attack by diverse functional groups.[18] We first screened various cationic gold(I) complexes with different phosphine ligands and anions for their ability to promote the intramolecular hydroamination of **15a**. PPh_3AuNTf_2 (generated in situ from PPh_3AuCl and $AgNTf_2$) gave the best result, furnishing a mixture of regioisomers **16** (5-*exo*-cyclized product) and **17** (6-*endo*-cyclized product) in respective yields of 12% and 8% (Table 1, entry 1; see the Supporting Information for more screening results). We investigated various transition-metal-based catalysts in the hydroamination reaction, including $AgNTf_2$, $[RhCl(cod)]_2$, $Pt(NTf_2)_2$, and $Cu(OTf)_2$ (entries 2–5).[19] The results were similar to those obtained with gold catalysts.

Based on these results, we postulated that the low reaction conversion may be due to the Boc protecting group decreasing the nucleophilicity of the primary amine, and that the low regioselectivity of the cyclization might be due to the interaction of the metal catalyst with the nitrogen atom of the quinoline moiety. Interestingly, treatment of **15a** with $InBr_3$ in DCE at 80°C yielded the desired cyclized product rosettacin (**18**)[20] in 27% yield (entry 6), together with the 6-*endo*-cyclized products **17** (8% yield) and **19** (7% yield). We realized that deprotection and lactamization occurred spontaneously after poorly regioselective hydroamination. We concluded that substrate **15b** (R = H) might be more suitable than **15a** for the formation of indolizinones. The *ortho* electron-withdrawing ester in **15b** may polarize the alkyne group through a conjugative effect, facilitating the desired 5-*exo* hydroamination.

To test this hypothesis, we treated **15a** with TFA in DCM at 0°C, which afforded the primary amine trifluoroacetate. This salt was dissolved in DCE, and K_2CO_3 (3 equiv) was added to neutralize the excess TFA. Gold(I) catalysis using PPh_3AuNTf_2 led to full consumption of the substrate but low yields of the cyclized products rosettacin (**18**) and **19** (entry 7). In the absence of gold catalyst, cyclization products were not detected, even after 18 h (entry 8). In strong contrast, treating the trifluoroacetate salt **15b** with K_2CO_3 in methanol at 40°C generated rosettacin (**18**) in 74% yield (entry 9). The cyclization proceeded with good regioselectivity; the 6-*endo*-cyclized product was not detected. We further optimized the reaction conditions by screening different bases and solvents. Using the weaker base Na_2CO_3 or the stronger base DBU reduced the yield (entries 10 and 11; see the Supporting Information for more screening results). In the end, we selected Cs_2CO_3 as the base for the cyclization because of its better solubility in methanol (entry 12).

We then explored the scope and generality of the reaction under the optimized conditions to obtain a library of polycyclic indolizinones, including related natural products such as **6** and their derivatives. We focused on the functional-group tolerance and the properties of the two fragments (A and B) that are connected to the alkyne. With a quinoline ring

Table 1: Optimization of the reaction conditions.[a]



Entry	Substrate	Catalyst	Base	Solvent	*t* [h]	Conv. [%][b]	Yield [%][b]
1	**15a**	PPh_3AuNTf_2	–	DCE	18	20	**16** (12), **17** (8)
2	**15a**	$AgNTf_2$	–	DCE	18	8	**16** (4), **17** (4)
3	**15a**	$[RhCl(cod)]_2$	–	DCE	20	32	**16** (7)
4	**15a**	$Pt(NTf_2)_2$	–	DCE	18	53	**16** (3), **17** (47)
5	**15a**	$Cu(OTf)_2$	–	toluene	6	100	**16** (22), **17** (27)
6	**15a**	$InBr_3$	–	DCE	6	100	**17** (8), **18** (27), **19** (7)
7[c,d]	**15b**	PPh_3AuNTf_2	K_2CO_3	DCE	2	100	**18** (6), **19** (3)
8[c,d]	**15b**	–	K_2CO_3	DCE	18	100	ND
9[d]	**15b**	–	K_2CO_3	MeOH	18	100	**18** (74)
10[d]	**15b**	–	Na_2CO_3	MeOH	18	100	**18** (43)
11[d]	**15b**	–	DBU	MeOH	18	100	**18** (10)
12[d]	**15b**	–	Cs_2CO_3	MeOH	18	100	**18** (77)

[a] Conditions: Starting material (0.05 mmol, $c = 0.05$ mol L^{-1}), 40°C. [b] Determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] With EtOH (5 equiv). [d] Conditions: 1) **15a**, TFA, DCM, 0°C, 2 h; 2) base, solvent, 40°C. Boc = *tert*-butoxycarbonyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, DCM = dichloromethane, Tf = trifluoromethanesulfonyl.

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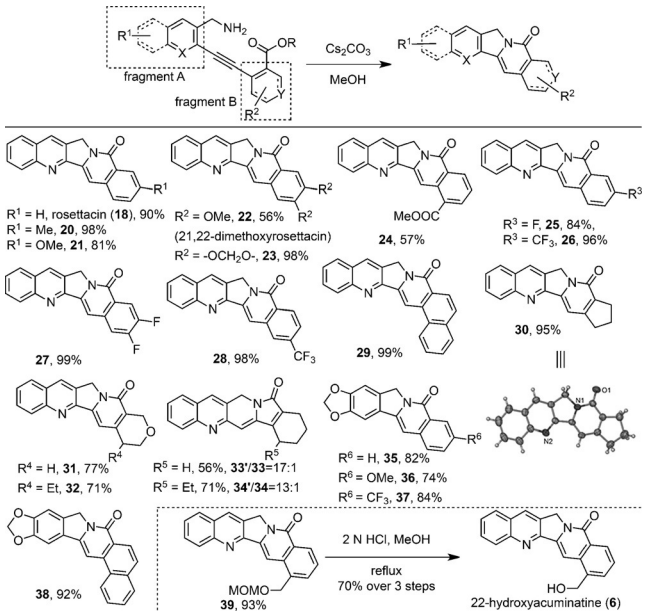
as fragment A and an arene ring as fragment B, we first tested the effect of the electron density of fragment B on the reaction. The reaction was not affected by electron-donating substituents (-OMe, -Me, -OCH_2O-) and electron-withdrawing substituents (-CO_2Me, -F, -CF_3) on the aryl ring (**20**–**28**, Scheme 2). The desired cyclized products were obtained in

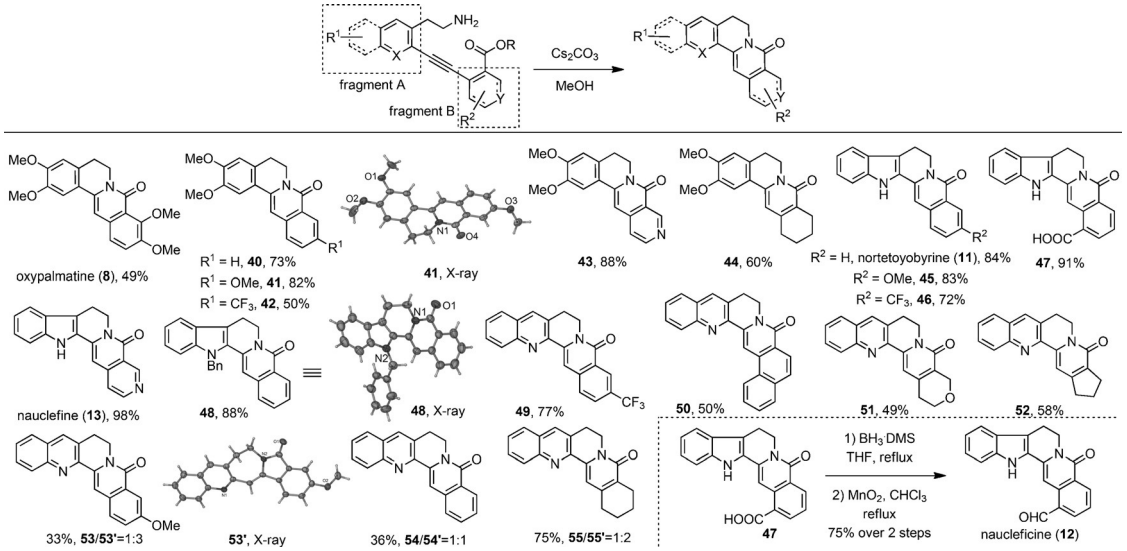


Scheme 2. Scope of the cascade cyclization for the preparation of polycyclic indolizinones. MOM = methoxymethyl.

good yields as single regioisomers. A naphthyl-substituted substrate also reacted smoothly to give the desired product **29** in excellent yield. We then changed fragment B to a cyclopentene or dihydropyran ring, and obtained the desired products **30**–**32** in acceptable yields. The structure of **30** was confirmed by X-ray analysis. The cyclized product **32** is of particular interest because it contains the basic skeleton of CPT at a lower oxidation state, making it potentially useful as a synthetic precursor. When fragment B was a cyclohexene ring, the regioselectivity of the cyclization changed, generating **33′** and **34′** as the major products by 6-*endo* cyclization. When both fragments A and B were arene rings, substrates bearing electron-donating or -withdrawing substituents worked well in the cascade cyclization, yielding the corresponding annulated products **35**–**38** in yields of 74–92%. It is noteworthy that 22-hydroxyacuminatine (**6**) could be prepared in a one-pot operation from its alkyne precursor through the key cascade cyclization and deprotection in 70% yield over three steps.

Next, we turned our attention to constructing natural products with a quinolizinone scaffold, as well as analogues of such molecules (Scheme 3). Cascade cyclization by 6-*exo* hydroamination followed by spontaneous lactamization usually furnished the desired products smoothly in yields of 49–98% under the optimized conditions. Oxypalmatine (**8**) was efficiently prepared in a four-step sequence, and some analogues with various substituents (**40**–**44**) were also produced. When fragment A was an indole, norketoyobyrine (**11**), naucleficine (**13**), and related structures (**45**–**48**) were generated in excellent yields through the same one-pot cyclization. The cyclized product **47** could be transformed into naucleficine (**12**) in 75% yield over two steps.[21] The structures of these analogues were confirmed by X-ray diffraction analysis of single crystals of **41** and **48**. We also tested reaction compatibility with substrates bearing quinoline rings that are one-carbon homologues of the substrates shown in Scheme 2. The corresponding cyclized products **49**–**52** were obtained in acceptable yields. In a few cases, cyclization proceeded mainly through the 7-*endo* pathway, generating unusual 7-5 fused skeletons (**53′**–**55′**). The structures of these compounds were confirmed by X-ray analysis of single crystals of **53′**.[22]

Studies of the generality of the cascade cyclization showed that in all cases, lactamization occurred spontaneously after



Scheme 3. Scope of the cascade cyclization for the preparation of polycyclic quinolizinones. DMS = dimethyl sulfide.

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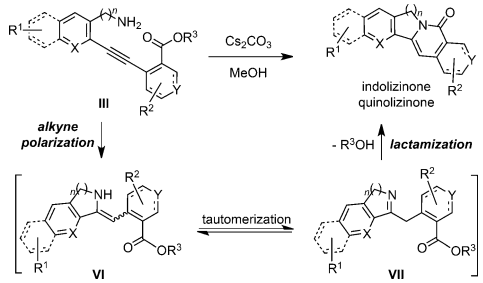
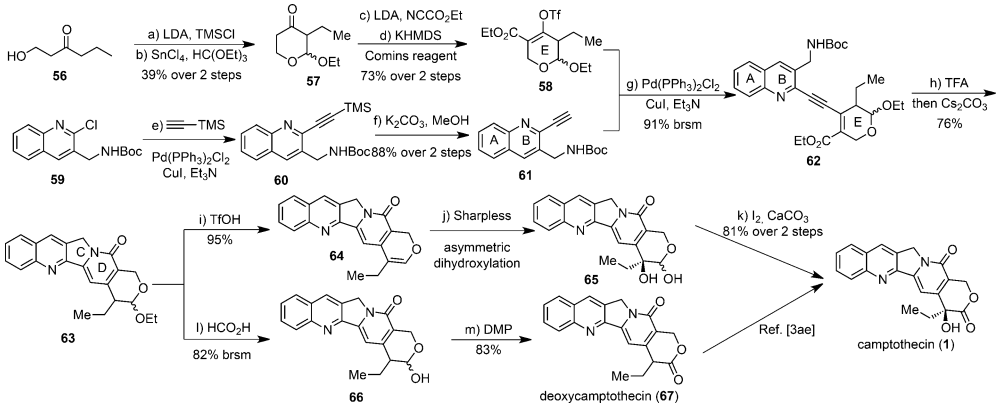
intramolecular hydroamination. The regioselectivity of the cyclization in most cases reflected the 5- or 6-*exo* pathway. Based on these results, we postulate a mechanism for the reaction (Scheme 4). The alkyne group is effectively polarized by the *ortho* electron-withdrawing ester group, facilitating C–N bond formation through primary amine addition under basic conditions. The resulting enamine adduct **VI** can theoretically form with *Z* or *E* geometry. We speculate that the *Z* olefin easily cyclizes to afford the desired indolizinone or quinolizinone while the enamine with *E* geometry may undergo lactamization through *E*/*Z* isomerization to form the final products via imine intermediate **VII**.



Scheme 4. Proposed reaction process.

To further demonstrate the synthetic potential of this method, we used this cascade cyclization as a key ring-forming step in the total synthesis of CPT (**1**). The synthesis commenced with the preparation of the coupling fragments, vinyl triflate **58** and quinoline **61** (Scheme 5). Treatment of the known β-hydroxyketone **56** with LDA and TMSCl followed by $SnCl_4$-promoted cyclization with triethyl orthoformate gave rise to acetal **57** in 39% yield over two steps.[23] The resulting acetal **57** was treated with LDA and Mander's reagent ($NCCO_2Et$) to afford the β-keto ester intermediate, which was efficiently transformed into enol triflate **58** in 73% yield over two steps. Sonogashira coupling[24] between 2-chloroquinoline **59** and (trimethylsilyl)acetylene followed by removal of the TMS group afforded terminal alkyne **61** in 88% over two steps. A second Sonogashira reaction was used to couple fragments **58** and **61**, which furnished the densely functionalized alkyne **62** on large scale and in good yield. Then the key cascade cyclization was tested to build the basic skeleton of CPT. Treatment of compound **62** with trifluoroacetic acid in dichloromethane for 4 h yielded the Boc-deprotected product. After azeotropic dehydration with toluene, the free primary amine was dissolved in anhydrous methanol and treated with cesium carbonate in the dark, affording the desired pentacyclic structure **63** as a single regioisomer in 76% yield. Compound **63** was transformed into CPT through two pathways. Treatment of **63** with trifluoromethanesulfonic acid (TfOH) in acetonitrile at room temperature resulted in the formation of the known advanced intermediate **64** in 95% yield. **64** was efficiently converted into (+)-**1** by Sharpless asymmetric dihydroxylation using $(DHQD)_2PYR$ as the ligand, followed by I_2/$CaCO_3$-based hemiacetal oxidation, which was developed by Chavan[3al] and Yao.[3ap] In the second pathway, acetal **63** was hydrolyzed to semiacetal **66** under weakly acidic conditions at 40 °C, and **66** was easily obtained by Dess–Martin periodinane oxidation to generate deoxycamptothecin (**67**) in 83% yield. **67** can be easily converted into (+)-**1** by asymmetric α-hydroxylation of the lactone as previously reported.[3ae]

In summary, we have developed a flexible strategy for constructing indolizinone- or quinolizinone-containing skeletons. These intramolecular cyclizations involve a cascade *exo*-type hydroamination followed by spontaneous lactamization. This rationally designed cascade reaction occurs under extremely mild conditions in the absence of transition metals, and it provides good regioselectivity. The reaction precursors can be efficiently prepared from easily available building blocks through a convergent approach, enabling the divergent synthesis of various substrates simply by changing the coupling fragments. This method also provides a reliable, unified approach for synthesizing CPT and *Nauclea* natural alkaloids, as shown by the synthesis of six natural products and 35 analogues. Using this method, we achieved the total synthesis of CPT (**1**) in nine steps in a novel ring-forming approach. We believe that this approach, together with the small-molecule library



Scheme 5. Total synthesis of camptothecin. a) LDA, TMSCl, THF, −78 °C to 25 °C; b) $HC(OEt)_3$, $SnCl_4$, CH_2Cl_2, −78 °C, 39% over 2 steps; c) LDA, $NCCO_2Et$, THF, −78 °C; d) KHMDS, THF, Comins reagent, −78 °C to 25 °C, 73% over 2 steps; e) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, toluene, 25 °C; f) K_2CO_3, MeOH, 0 °C, 88% over 2 steps; g) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, toluene, 60 °C, 91% brsm; h) TFA, CH_2Cl_2, 0 °C; then Cs_2CO_3, MeOH, 25 °C, 76%; i) TfOH, MeCN, 25 °C, 95%; j) $K_2OsO_2(OH)_4$, $(DHQD)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 0 °C; k) I_2, $CaCO_3$, MeOH, H_2O, 40 °C, 81% over 2 steps; l) HCO_2H, H_2O, 40 °C, 82% brsm; m) DMP, CH_2Cl_2, 25 °C, 83%. brsm = based on recovered starting material, DMP = Dess–Martin periodinane, KHMDS = potassium bis(trimethylsilyl)amide, LDA = lithium diisopropylamide, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

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that it created, may open the door to novel bioactivity studies of both types of natural products. Currently, we are using this strategy to synthesize more challenging natural alkaloids; these studies will be reported in due course.

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