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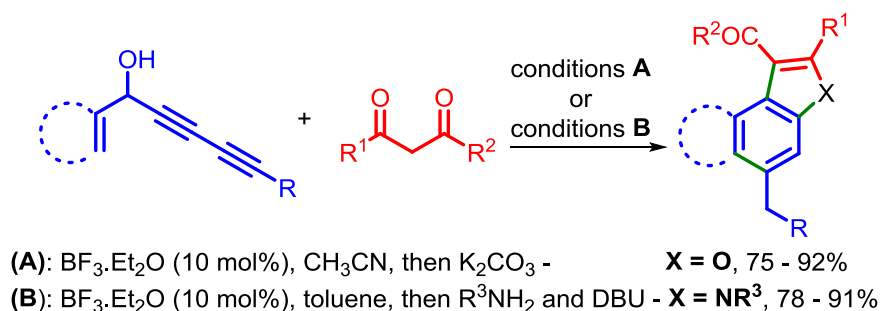
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Domino Reaction of 2,4-Diyn-1-ols with 1,3-Dicarbonyl Compounds: Direct access to Aryl/heteroaryl-Fused Benzofurans and Indoles

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Supporting Information Placeholder



ABSTRACT: A domino propargylation/furanylation (intramolecular *exo-dig*-cyclization)/benzannulation reaction of 2,4-diyn-1-ols with 1,3-dicarbonyl compounds has been developed for the first time. This provides a novel and effective method for the preparation of aryl/heteroaryl-fused benzofurans from easily accessible starting materials in a single step. The methodology was extended to pyrrolyl-benzannulation to obtain aryl/heteroaryl-fused indoles. Further, application of this approach in the synthesis of eustifoline D and dictyodendrin structural frameworks has been demonstrated.

Fused polycyclic heteroaromatics are privileged molecular scaffolds present in a range of bio-active molecules,¹ pharmaceuticals² and bioimaging probes,³ as well as in optoelectronic materials.⁴ Particularly, aryl/heteroaryl annulated-benzofurans are frequently used in organic light-emitting diodes (OLEDs) owing to their charge-transport properties and thermal stability.⁵ Further, π -expanded naphthalimides with fused furan ring were used as novel fluorescent probes and naphthofurans (R7000, **1A**) as mutagenic agents.⁶ Moreover, these scaffolds are found as core structure of natural products. For instance, the alkaloid eustifoline D (Figure 1, **1B**), isolated by Furukawa from the root bark of *Murraya euchrestifolia*, which has unique furo[2,3-*c*]carbazole framework, is used as an active constituent in some folk medicines in China.⁷ Likewise, aryl/heteroaryl annulated-indoles are the key motifs of various molecules having drawn attention of the pharmaceutical and material science communities. For example, dictyodendrin A and B, pyrrolo[2,3-*c*]carbazoles (Figure 1, **1C** and **1D**), are unusual natural alkaloids isolated from the Japanese marine sponge *Dictyodendrilla verongiformis* and known to possess telomerase inhibitory activity.⁸ Additionally, the 3*H*-benzo[*e*]indole skeleton has potential applications in molecular probes useful for optical imaging and photochromic materials.⁹ This tricyclic framework is also found in enzymes like indoleamine 2,3-dioxygenase (IDO, **1E**), fructose-2,6-

biphosphatase 3 (PFKFB3) inhibitors and drugs for treating Alzheimer's disease and other related conditions.¹⁰

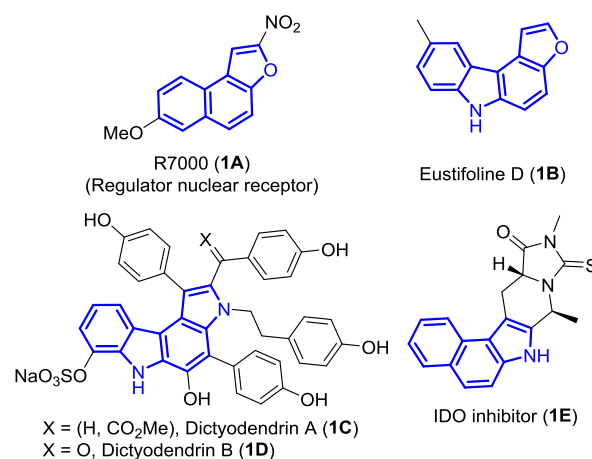
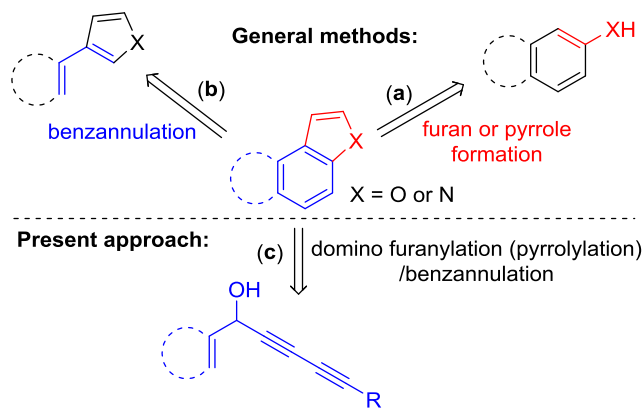


Figure 1. Selected molecules having aryl/heteroaryl-fused benzofurans and indoles

Due to their pharmacological importance and unique electronic properties, the development of synthetic methods for the construction of aryl/heteroaryl-fused benzofurans and indoles has attracted substantial attention in medicinal, as well as in

materials chemistry.¹¹⁻¹³ Typically, these methods proceed either through the construction of furan or pyrrole rings on aryl/heteroaryl-annulated benzenes (Scheme 1a)¹¹ or *via* the formation of benzene rings on substituted furans or pyrroles, (Scheme 1b).¹² However, one-pot assembly of aryl/heteroaryl-annulated benzofuran or indoles from acyclic precursors are uncommon¹³ and still remains challenge. Hence, development of such new methods enabling the direct access to diversely functionalized (hetero)aryl-fused benzofurans and indoles from readily accessible acyclic compounds is highly desirable. In this direction, domino reaction is one of the effective strategies for the construction of functionalized heterocycles with molecular diversity and atom- as well as pot-economy by avoiding separation of the intermediates.¹⁴

Scheme 1. Approaches to the synthesis of aryl/heteroaryl-fused benzofurans and indoles

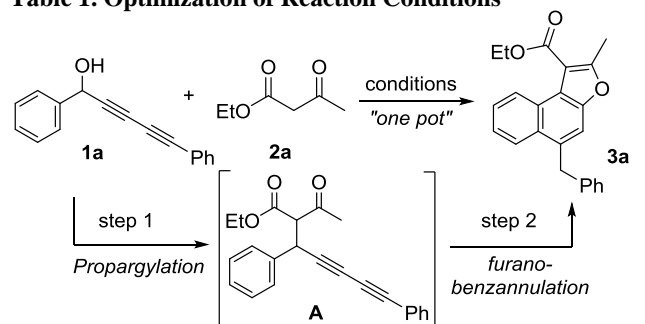


On the other hand, 1-aryl/heteroaryl propargyl alcohols have emerged as adaptable precursors to yield various hetero/carbocycles through nucleophilic substitution followed by alkyne-assisted annulation.¹⁵ However, their analogues with extended alkyne conjugation, 1-aryl-2,4-diyne-1-ols, are under-explored.¹⁶ These 2,4-diyne-1-ols offer an important avenue to undergo additional cyclization in a cascade manner. Our research interests in exploring 2,4-diyne-1-ols,¹⁷ led us to examine the possibility of cycloisomerizations for the synthesis of aryl/heteroaryl-annulated benzofurans and indoles. Herein, we describe a novel domino propargylation/furanylation (pyrrolylation)/benzannulation reactions of 2,4-diyne-1-ols with 1,3-dicarbonyl compounds to access the corresponding aryl/heteroaryl-fused benzofurans/indoles in one-pot (Scheme 1c). To our knowledge, an approach to benzofuran or indole by the sequential construction of the furan or pyrrole and benzene ring from the annulation of diyne-1-ols has not been described to date.

To examine the proposed plan, the reaction between 1-phenyl-2,4-diyne-1-ol (**1a**) and ethyl acetoacetate (**2a**) was employed as a model reaction. Firstly, the propargylation reaction was tested in the presence of different acid-catalysts to form the intermediate **A** and found that $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol% in acetonitrile) was the best choice among the tested acid catalysts such as *p*TSA, $\text{Sc}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$, $\text{In}(\text{OTf})_3$ and FeCl_3 (entries 1 to 6, Table 1). Then, the conversion of **A** to the benzofuran **3a** was verified in the presence of a base through furan formation, followed by a benzannulation reaction. To our delight, treatment of **A** with K_2CO_3 in acetonitrile at 80 °C provided the target **3a** in 97% yield (entry 7, Table 1). Other bases, such as DBU or NaHCO_3 , were found to be less effective in yielding

3a (entries 8 and 9, Table 1) even after prolonged reaction time. With these conditions, next we performed both the reactions in a one-pot manner eluding the isolation of intermediate **A** to get **3a** in 92% yield (entry 10, Table 1).

Table 1. Optimization of Reaction Conditions^a



entry	propargylation [acid (10 mol %)]	furano-benzannulation (base, temp, time)	product	yield (%) ^b
1	<i>p</i> TSA, 1 h	---	A	72
2	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, 0.5 h	---	A	95
3	$\text{Sc}(\text{OTf})_3$, 1.5 h	---	A	70
4	$\text{Cu}(\text{OTf})_2$, 2 h	---	A	76
5	FeCl_3 , 1 h	---	A	65
6	$\text{In}(\text{OTf})_3$, 2 h	---	A	85
7	---	K_2CO_3 , 80 °C, 7 h	3a	97
8	---	DBU, 80 °C, 12 h	3a	20
9	---	NaHCO_3 , 80 °C, 12 h	3a	10
10 ^c	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, 0.5 h	K_2CO_3 , 80 °C, 7 h	3a	92

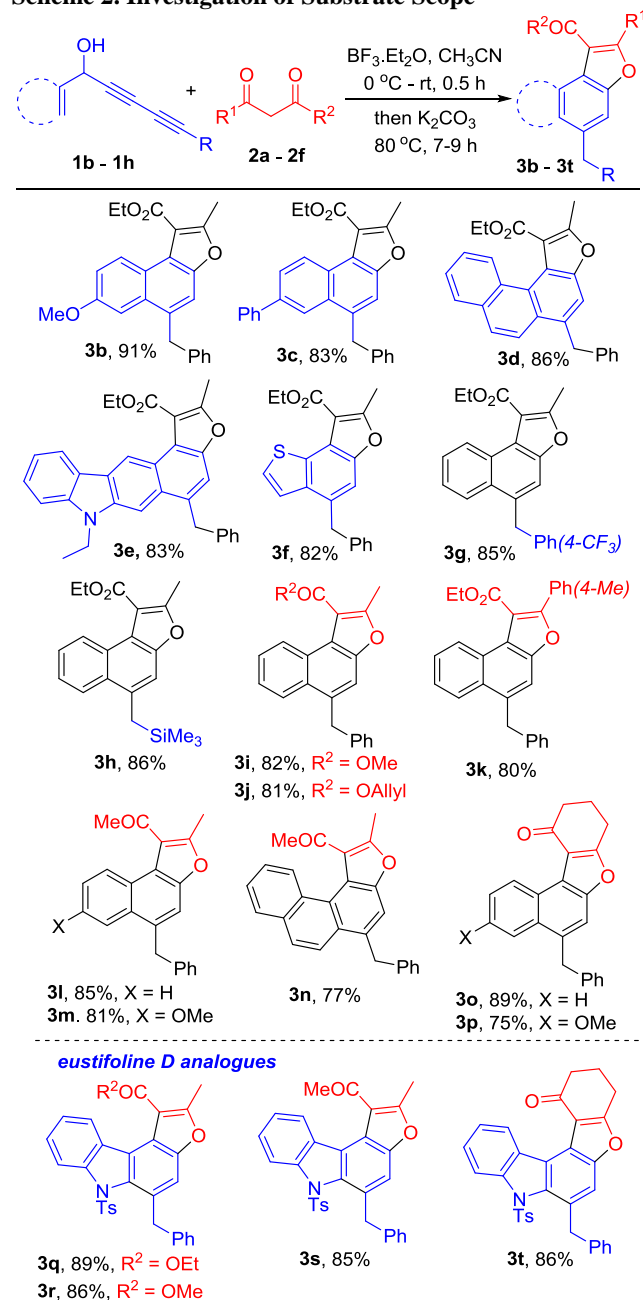
^a(entries 1 to 6): Reactions were performed using 0.5 mmol of **1a** with 0.35 mmol of **2a** in 3 mL of CH_3CN and acid at 0 °C to rt; (entries 7 to 9): Reaction of **A** with 1.25 mmol of base in CH_3CN at 80 °C; ^bIsolated yield; ^cOne-pot reaction

Having established the optimal reaction conditions, the scope with respect to 2,4-diyne-1-ols, as well as 1,3-dicarbonyl compounds, was next examined (Scheme 2). A variety of 1-aryl/heteroaryl 2,4-diyne-1-ols (*see the supporting information for structure of 2,4-diyne-1-ols*) were well tolerated in this domino furanylation/benzannulation with ethyl acetoacetate (**2a**) to give the corresponding aryl/heteroaryl-fused benzofurans **3** in good to high yields. 1,5-Diphenylpenta-2,4-diyne-1-ol (**1a**) having substitutions such as 4-OMe and 4-Ph groups on 1-phenyl ring reacted easily, affording the desired naphtho[2,1-*b*]furans **3b** (91%) and **3c** (83%), respectively. In addition, 2,4-diyne-1-ol bearing 1-naphthyl group at C1 position was also viable substrate, furnishing the corresponding phenanthro[3,4-*b*]furan **3d** in 86% yield. Remarkably, the present domino-annulation has a good tolerance of 1-heteroaryl groups such as 3-carbazolyl and 2-thiophenyl on diyne-1-ols, providing the 7*H*-benzofuro[5,4-*b*]carbazole **3e** and thieno[2,3-*e*]benzofuran **3f** in good yields. Further study revealed that the tested diyne-1-ols, either with 4- CF_3 -phenyl group or trimethyl silyl (TMS) at C5 position (alkyne carbon), underwent furanyl-benzannulation to furnish the expected naphtho[2,1-*b*]furans **3g** (85%) and **3h** (86%), respectively. Subsequently, diverse 1,3-dicarbonyl compounds were investigated in their reactions with **1a** under the optimal conditions. The alkyl acetoacetate possessing either methyl or allyl group

endured this reaction to afford naphtho-furans **3i** (82%) and **3j** (81%). The reaction of ethyl 3-oxo-3-(*p*-tolyl)propanoate (**2d**) with **1a** worked well to afford **3k** in 80% yield. Similarly, diketo-compound, pentane-2,4-dione (**2e**) was also indicated to be suitable in this domino-annulation with different diyn-1-ols to deliver the matching naphtho[2,1-*b*]furans **3l**, **3m** and phenanthro[3,4-*b*]furan **3n** in good yield. Notably, 1,3-cyclohexadione (**2f**, cyclic diketo compound) also smoothly participated to produce 9,10-dihydronaphtho[2,1-*b*]benzofuran-11(*8H*)-ones **3o** (89%) and **3p** (75%).

Next, we endeavored to construct the furo[2,3-*c*]carbazole, a unique framework embedded in eustifoline D natural product.⁷ Pleasingly, the reaction of suitable 2,4-diyne-1-ol **1i**, derived from indole-3-carboxaldehyde, with **2a** under optimal conditions, offered the furo[2,3-*c*]carbazole **3q** in 89% yield (Scheme 2). Additionally, few more 1,3-dicarbonyls including

Scheme 2. Investigation of Substrate Scope^a

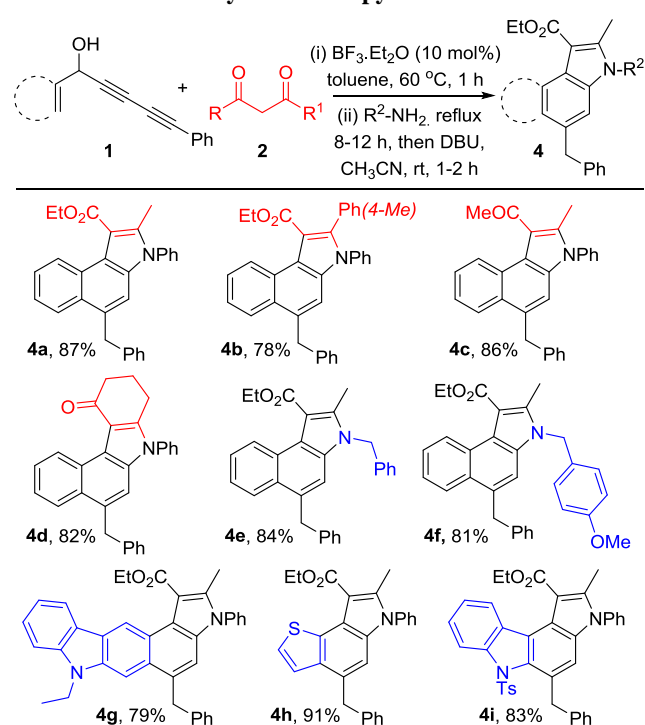


^aAll reactions were performed using 0.5 mmol of **1** with 0.35 mmol of **2** in 3 mL of CH_3CN and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol %). After stirring at rt for 30 min, K_2CO_3 (1.25 mmol) was added and stirred at 80°C .

1,3-cyclohexanedione were examined with 2,4-diyne-1-ol **1i**, to get the corresponding furo[2,3-*c*]carbazole products **3r**, **3s** and **3t** (eustifoline D analogues) in good yields (Scheme 2).

Next, we wondered if the annulated-indole products **4** could be formed also in the presence of an amine using the present approach *via* domino pyrrolylation/benzannulation reactions. The reaction of **1a** with **2a** in the presence of aniline was carried out under the conditions used for furano-benzannulation. As predicted, the construction of **4a** is challenged by the catalytic activity of acid in the presence of aniline (base) and only a low yield of the product formation was observed, which forced us to further optimize the reaction conditions (*for details see supporting information Table S1*). Gratifyingly, the desired benzo[e]indole **4a** was isolated in 87% yield by heating in toluene at 60°C in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol %) for 1 h followed by addition of amine and reflux for 8 h, then removal of toluene, addition of DBU in CH_3CN and stirred at room temperature for 1 h. These optimized conditions were subsequently employed to examine the generality of this method (Scheme 3). Initially, diverse 1,3-dicarbonyl compounds **2d** to **2f** were treated with **1a** in the presence of aniline and the reaction proceeded smoothly, affording the desired benzo[e]indoles **4b** to **4d** in 78–86% yields. Different amines such as benzyl amine and 4-methoxy benzylamine were also studied in the reaction of **1a** with **2a** to obtain the expected *N*-benzyl products **4e** (84%) and **4f** (81%), respectively. To our delight, annulation of 1-heteroaryl 2,4-diyne-1-ols **1e** and **1f** with **2a** in the presence of aniline, led to the formation of 3,7-dihydroindolo[5,4-*b*]carbazole **4g** (79%) and 6*H*-thieno[3,2-*e*]indole **4h** (91%), respectively. Notably, the developed method was found to be suitable for the synthesis of pyrrolo[2,3-*c*]carbazole **4i**, from the reaction of 1-(3-indolyl)-2,4-diyne-1-ol **1i** with **2a** in 83% yield (Scheme 3). This molecule has the structural motif of dictyodendrin A and B.⁸

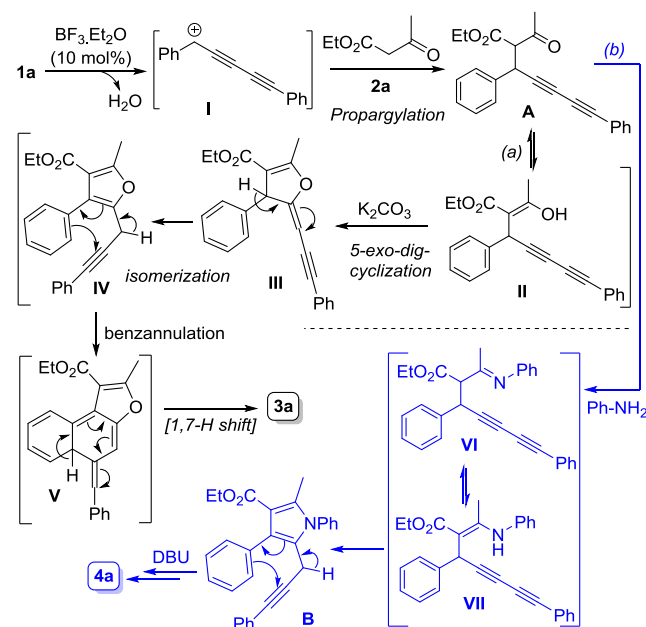
Scheme 3. Generality of domino pyrrolo-benzannulation^{a,b}



^aReactions performed using 0.5 mmol of **1** and 0.6 mmol of **2** and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol %) in toluene (3 mL) at 60°C for 1 h, then addition of $\text{R}^2\text{-NH}_2$ (0.6 mmol) and reflux for 8-12 h. Removal of toluene and addition of DBU in CH_3CN (0.5 mmol) stirred at rt. ^bIsolated yields

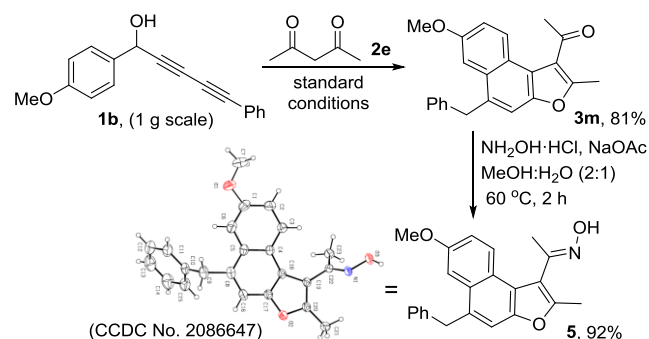
On the basis of our experimental results and the literature reports,¹⁷⁻¹⁸ plausible reaction mechanism is depicted in Scheme 4. Initially, the propargylation (involving nucleophilic substitution *via* a carbocation **I**) occurred to generate the intermediate **A** (isolated and fully characterized) from **1a** and propargylic alcohol **2a** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Next, base-mediated intramolecular 5-*exo-dig*-cyclization of enol **II** and subsequent isomerization of **III** would provide the propargyl-furan **IV**. Later, intermediate undergoes further cycloisomerization through **V** (1,7-hydrogen shift driven aromatization) to result in the benzannulated product, fused-benzofuran **3a**. For the formation of benzo-annulated indole (Scheme 4, route b), it is considered that the intermediate **A** reacts with aniline to give the corresponding imines **VI** which tautomerize to the corresponding conjugated enamines **VII**. From these derivatives, similar sequence of cyclization-isomerization-benzannulation-aromatization should occur to afford the target **4a** *via* pyrrole **B** (isolated and fully characterized).

Scheme 4. Proposed Mechanism



To establish the reaction scalability of this method, a gram scale preparation of **3m** (81%) was attained by the reaction of **1b** with **2e**. Additionally, the practicality of functional groups on the furan ring is shown through further derivatization towards expanding the structural diversity. To our delight, the treatment of **3m** with $\text{NH}_2\text{OH} \cdot \text{HCl}/\text{NaOAc}$ in $\text{MeOH}:\text{H}_2\text{O}$ (2:1) provided the ketoxime **5** in 92% yield (Scheme 5). The structure of **5** was confirmed by a single crystal X-ray method.

Scheme 5. Gram-Scale Synthesis of **3m** and derivatization



In summary, this study presents a handy reaction of 2,4-diyne-1-ols with 1,3-dicarbonyl compounds as a novel method for the synthesis of distinctly functionalized aryl/heteroaryl-annulated benzofurans and indoles. Remarkably, the reaction allows the assembly of two C-C and one C-O (two C-N) bonds by the cleavage of one C-O in a one-pot operation *via* a domino acid-catalyzed propargylation of 1,3-dicarbonyls followed by base-mediated furanylation or pyrrolylation (intramolecular *exo-dig*-cyclization)/benzannulation sequence. This protocol enables accessing eustifoline D analogues as well as the structural framework of dictyodendrins in good to excellent yields. The developed approach is noteworthy for its wide scope, good yields and a mild, operationally simple strategy.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization details and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions.

Notes

The authors declare no competing financial interest.

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