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Alkynes From Furans: A General Fragmentation Method Applied to the Synthesis of the Proposed Structure of Aglatomin B

Jiachen Deng[†], Jingjing Wu[†], Hailong Tian, Jiajing Bao, Yong Shi, Weisheng Tian* and Jinghan Gui*

Abstract: Furans are versatile synthons in organic chemistry. Herein we present a general method that transforms furans into alkynes via dual C–C double bond cleavage. The reaction is proposed to proceed by sequential [4+2] cycloaddition between furan and singlet oxygen and a formal *retro*-(3+2) fragmentation of the endoperoxide intermediate. A wide array of furans, including those derived from sapogenins, are amenable to this reaction, providing the corresponding alkynoic acids in up to 88% yields. The synthetic utility was demonstrated through a 7-step synthesis of the proposed structure of pregnane natural product aglatomin B from a known intermediate.

Alkynes are one of the most important and versatile structural motifs in organic synthesis as they could function as both nucleophiles and electrophiles to engage in a plethora of C–C and C–heteroatom bond-forming reactions.[1] Consequently, the development of efficient and practical methods to synthesize alkynes has attracted considerable attention from the chemistry community. Among various methods for alkyne synthesis, the alkyne-forming fragmentations[2] play a unique role since they offer a straightforward means to the structural modification of complex molecules. The history of such reaction manifolds can be traced back to 1963 when Bodendorf reported the first example of alkyne-forming fragmentation of β-chloroacroleins (Figure 1A).[3] Shortly afterward, the venerable Eschenmoser-Tanabe fragmentation was invented to convert α,β-epoxy ketones to acetylenic ketones or aldehydes via the intermediacy of tosylhydrazones.[4] Subsequent variations of this classical method utilized reactions between β-halo,[5] β-phenylseleno,[6] or β-tosylhydrazino-α,β-unsaturated ketones[7] with an alkylithium or NaOMe to access alkynyl functionalities. More recently, the Dudley group further extended the reaction scope to versatile vinylogous acyl triflates wherein a variety of alkynyl ketones, alcohols and amides were afforded as products.[8] In a different approach, the Zard group described an iron-mediated decarboxylative ring cleavage of isoxazol-5-one, which provided an expedient synthesis of alkynes from β-keto-esters.[9] More recently, Brewer and his co-workers disclosed a Lewis acid mediated ring fragmentation of γ-oxy-β-hydroxy-α-diazo esters or ketones to yield carbonyl-tethered ynoates or ynones.[10] Despite these significant progress, the development of mild and green alkyne-forming fragmentations holds the potential to offer novel disconnection in retrosynthetic analysis, thus representing a worthwhile effort for synthetic chemists.

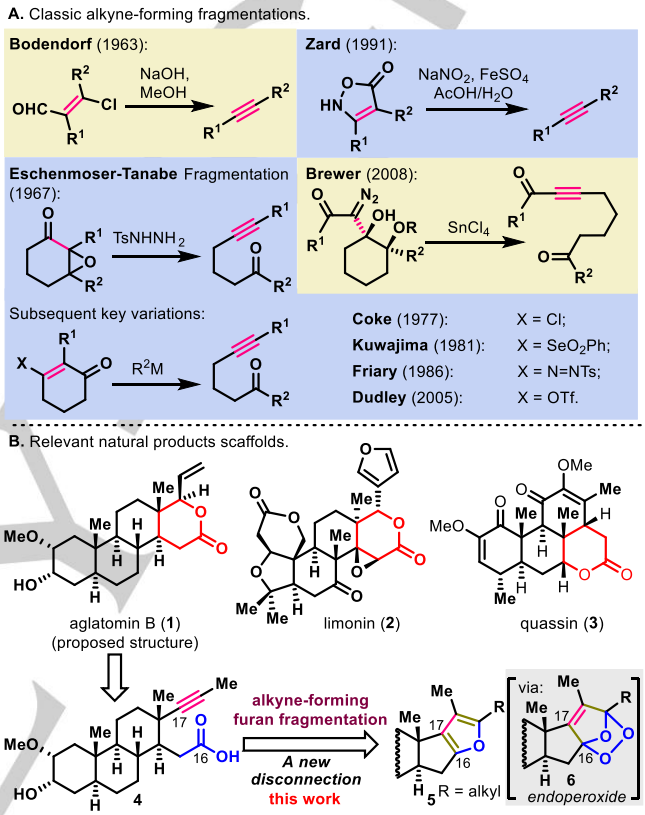

Figure 1. Alkyne-forming fragmentations: historical context and new development.

Aglatomin B (proposed structure, **1**) is a representative 16,17-*seco* pregnane natural product that was isolated from *A. Tomentosa* alongside the cytotoxic compound rocaglaol (Figure 1B).[11] From a structural perspective, aglatomin B possesses a δ-lactone ring which is prevalent in various natural products such as limonin (**2**)[12] and quassin (**3**)[13]. Retrosynthetic analysis of aglatomin B via disconnection at the lactone linkage led to alkynoic acid **4** as a potential precursor. Although alkynoic acids can be accessed through a number of synthetic methods,[14] preparation of **4** using existing technology conceivably necessitates lengthy functional group manipulations. Instead, it was surmised that the direct conversion of furan **5** into **4** offers an appealing strategic alternative, as **5** can be accessed from steroidal sapogenin in 2 steps. Herein we report the development of one such chemical transformation that converts furans into alkynes via the intermediacy of endoperoxides, which was successfully applied to the synthesis of the proposed structure of aglatomin B.

Furans are known to undergo Diel-Alder reaction with singlet oxygen to afford endoperoxides, which are versatile surrogates to

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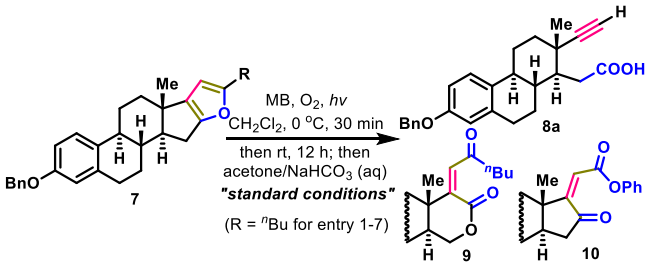
a number of valuable four-carbon building blocks, such as 1,4-dicarbonyl compounds, butenolides, etc.[15] Elegant work from the Vassilikogiannakis group highlights the simplifying power of this approach, culminating in the synthesis of polyoxygenated and alkaloid natural products.[16] However, the carbon framework of furans remains largely intact in these processes—furan fragmentation involving the cleavage of C-C bond is rare.[17]

Table 1. Effect of Reaction Parameters and Furan C2-substituent[a].



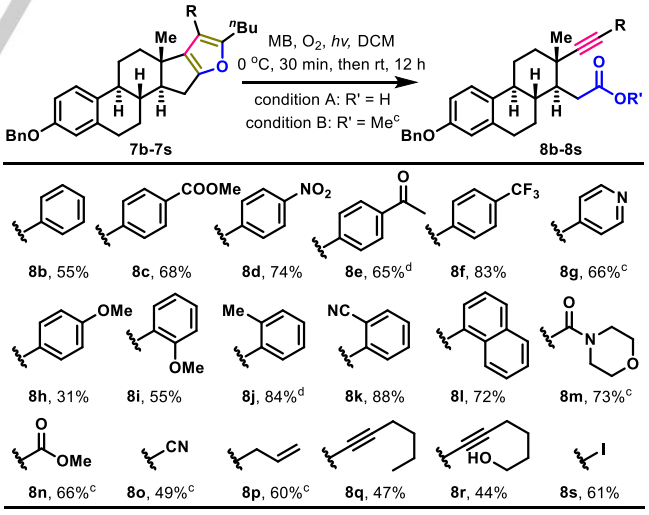
entry	variations from the "standard conditions"	**8a** (%)[b]	**9** (%)[b]	**10** (%)[b]
1	none (R = ^{n}Bu)	77	-	-
2	no MB	0	-	-
3	no light	0	-	-
4	without basic hydrolysis	10	-	-
5	TPP instead of MB	81	-	-
6	non-anhydrous DCM	70	-	-
7	MeOH instead of DCM	trace	30	-
8	R = Cy	78[c]	-	-
9	R = ^{t}Bu	77	-	-
10	R = Ph	-	-	74

[a] Standard conditions: **7** (50 mg), MB (1 mol %), O_2, *hv*, DCM, 0 °C, 30 min; then rt, 12 h; then acetone/sat. $NaHCO_3$ (aq.), rt, 12 h. [b] Isolated yield. [c] Hydrolyzed by 1M LiOH/THF(1/5), 4 h, rt.

We envisioned that fusion with cycloalkanes may impart sufficient strain[18] in the furan ring wherein the corresponding endoperoxide intermediate **6** (Figure 1B) may be poised to undergo a formal *retro*-(3+2) fragmentation, thereby affording alkynoic acid products after hydrolysis of the resulting anhydrides. In addition, in light of the documented dependence of furan oxidation product on its substitution pattern,[15a] judicious selection of the furan C2-substituent (R group in **6**) should also play a crucial role to further facilitate this distinctive fragmentation of endoperoxide **6**. Gratifyingly, after some initial forays, it was found that the oxidation of estrone-derived furan **7** by singlet oxygen, followed by basic hydrolysis, afforded the desired alkynoic acid **8a** in 77% yield (entry 1, Table 1). No desired product was obtained in the absence of singlet oxygen (entry 2, 3), and omission of the basic hydrolysis step led to products in much lower yields owing to the presence of anhydride (structure not shown, see **22** in Scheme 2) (entry 4). Although *meso*-tetraphenylporphyrin (TPP) and methylene blue (MB) gave similar efficiency, the latter was chosen for the ease of product purification (entry 5). The use of non-anhydrous dichloromethane led to a slightly diminished yield (entry 6). Meanwhile, Baeyer-Villiger type product γ-ketoester **9** was predominantly afforded in protic solvents with trace amount of the desired product detected (entry 7). Further screening of some non-protic solvents (such as THF, cyclohexane, toluene or Et_2O) didn't show great difference (62-75% yield) despite the documented solvent effect on the nature of the products[17b] (see SI for details). Whereas the use of secondary or tertiary alkyl substituents at C2 had no noticeable impact on the reaction outcome (entry 8, 9), C2-phenyl substituted furan afforded the γ-ketoester **10** exclusively (entry 10).

With the standard conditions in hand, the scope of this furan fragmentation was investigated next. As shown in Table 2, furans with electron-deficient aryl substituents gave the corresponding products **8c**–**8f** in moderate to good yields. Notably, pyridine-substituted furan **7g** was also amenable to this reaction. In contrast, furan with electron-rich aryl substituent **7h** led to multiple unidentified side products, possibly attributable to the increased electron density of the furan nucleus. Thus, it was reasoned that if the electron-donating property of the aryl group was attenuated with an *ortho*-substituent, some side reactions might be suppressed. Indeed, furan with an *ortho*-methoxy substituted aryl group **8i** gave an improved yield compared to that of **8h**. Similarly, other furans with *ortho*-substituted aryl or 1-naphthyl groups **7j**–**7l** proved to be viable substrates, furnishing products **8j**–**8l** in good to excellent yields. Direct attachment of electron-withdrawing groups to furan generally led to moderate to good yields as in the case of amide (**8m**), ester (**8n**), and nitrile (**8o**). Substituents such as allyl and alkynyl groups were compatible with the reaction conditions, affording the corresponding skipped enyne (**8p**) and diyne products (**8q**, **8r**) respectively. Notably, 3-iodofuran **7s** was also a viable substrate for this reaction, which allowed for further downstream functionalizations of the resulting iodoalkynes via homo/cross-coupling reactions.[19]

Table 2. Substrate scope of substituted furans[a,b].



[a] Condition A: acetone/sat.$NaHCO_3$ (aq.), rt, 12 h; Conditions B: $TMSCHN_2$, toluene/MeOH, rt, 0.5 h. [b] Isolated yield. [c] For ease of purification, these products were derivatized as methyl esters. [d] Hydrolyzed by 1M LiOH/THF(1/5), rt, 4 h.

The degradation of steroidal sapogenins has been widely used since 1940s for the industrial production of valuable steroid drugs and hormones, such as progesterone, cortisone,

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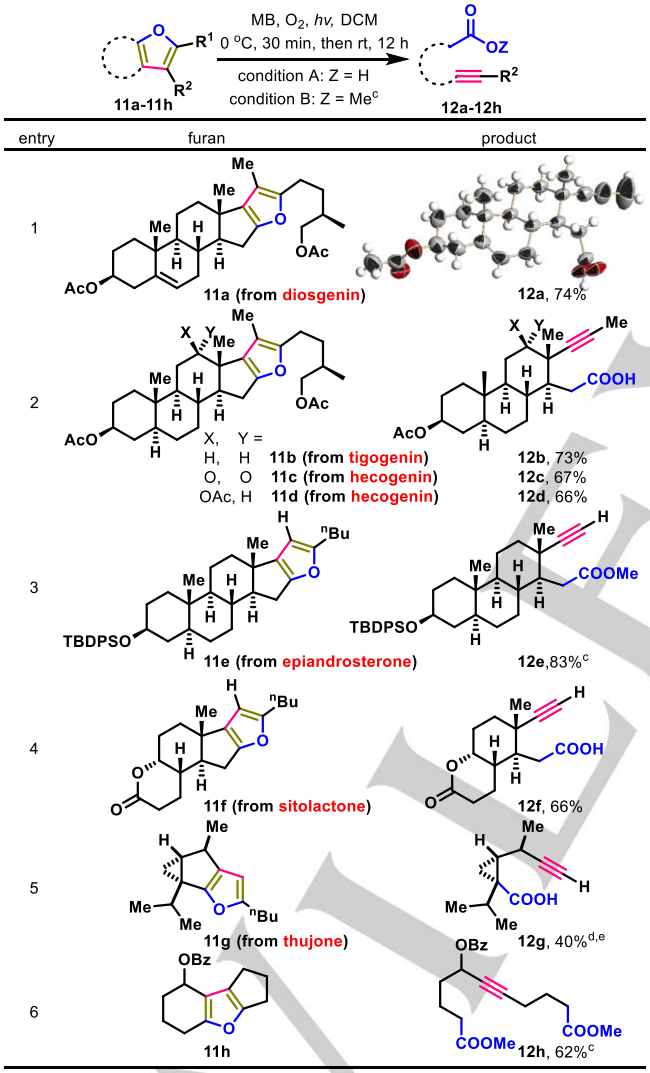
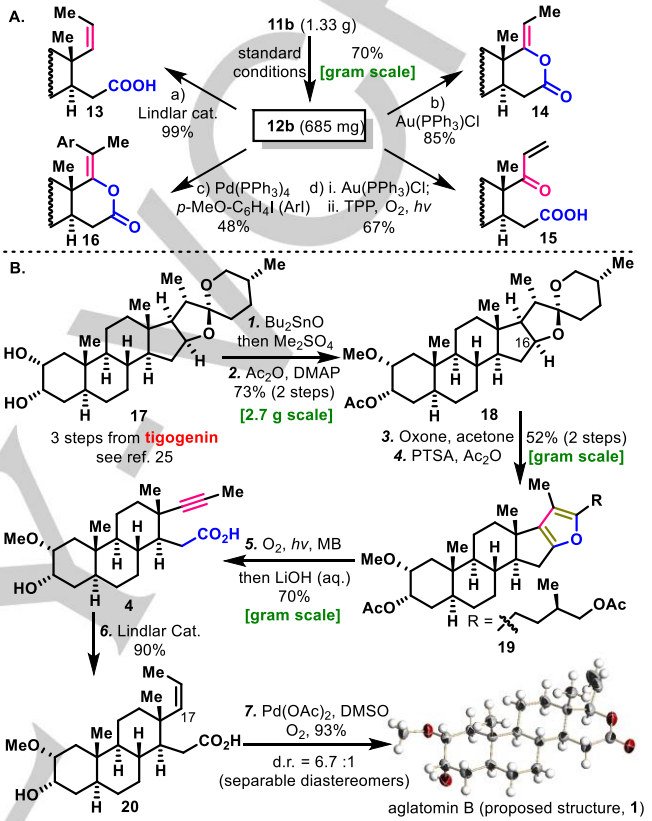
prednisone, and estradiol. Previously, this transformation was accomplished by Marker's CrO_3-based method[20] or more recently, Tian's H_2O_2-based technology.[21] Steroidal furans **11a**–**11d** derived conveniently from diosgenin, tigogenin and hecogenin were found to react smoothly under the optimized conditions (Table 3), giving rise to alkynoic acids **12a**–**12d**, thus offering a complimentary and efficient method for sapogenin degradation. Additionally, furans derived from epiandrosterone, sitolactone and thujone **11e**–**11g** were all found to be competent substrates, generating alkynoic acids **12e**–**12g** that might be otherwise difficult to access. Other non-steroid furan substrate (**11h**) also reacted smoothly, furnishing long-chain alkynoic ester **12h** as product.

Table 3. Substrate scope of annulated furans[a,b]..



[a] Condition A: acetone/sat.$NaHCO_3$ (aq.), rt, 12 h; Conditions B: $TMSCHN_2$, toluene/MeOH, rt, 0.5 h. [b] Isolated yield. [c] For ease of purification, these products were derivatized as methyl esters. [d] Hydrolyzed by 1M LiOH/THF(1/5), rt, 4 h. [e] DCE, 40 °C, *hv*, 20 min.

The practicality and scalability of this technology is readily evident from the preparation of alkynoic acid **12b** in gram scale. Subsequently, this ability to procure ample amounts of **12b** allowed its diversification through different transformations (Scheme 1A). Partial reduction with Lindlar catalyst gave *cis*-alkene **13** in quantitative yield. Cyclization under gold catalysis[22] afforded the enol acetate **14**, which could be further oxidized with singlet oxygen to furnish enone **15**. The alkynoic acid cyclization could also be effected in tandem with palladium-catalyzed cross-coupling,[23] delivering arylated enol acetate **16** in 48% yield.



Scheme 1. Synthetic transformations of alkynoic acids (A) and synthesis of the proposed structure of aglatomin B (B).

This reaction offers a distinct strategy for the synthesis of steroid natural products, exemplified by aglatomin B as shown in Scheme 1B. The synthesis commenced with known diol intermediate **17**, which was readily prepared in 3 steps from tigogenin.[24] After regioselective methylation of a hydroxyl group with Bu_2SnO/Me_2SO_4[25] followed by acetylation, **17** was transformed into intermediate **18** in 73% yield over 2 steps. Regioselective oxidation of **18** at the C16-position by DMDO,[26] followed by treatment with Ac_2O and PTSA, afforded furan **19** as the precursor of the key fragmentation reaction. Under standard conditions and using aqueous LiOH for hydrolysis, alkynoic acid **4** was obtained in 70% yield on gram-scale, with the concomitant removal of the C3-acetoxy group. Subsequent lactone installation in the desired C17 stereochemistry proved especially challenging (see SI for details). Eventually, it was found that partial reduction of alkyne with Lindlar catalyst followed by palladium-catalyzed oxidative cyclization[27] could deliver aglatomin B (**1**) with good levels of diastereoselectivity. Barring some discrepancies between the NMR data of the synthetic sample and the natural

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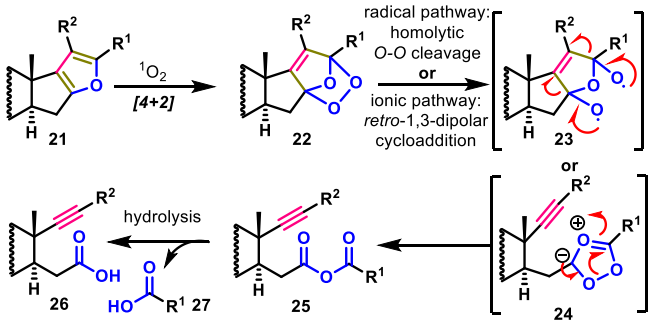
isolate[11] (see SI), the synthetic sample was ambiguously shown to possess the proposed structure of aglatomin B via X-ray crystallography[28].

Two distinct mechanistic pathways have been proposed for this reaction (scheme 2). Furan first engages singlet oxygen to afford Diels-Alder adduct **22**, which could undergo either homolytic *O-O* cleavage[29] (radical pathway) or *retro*-1,3-dipolar cycloaddition (ionic pathway) to furnish anhydride **25** (see page S10 of SI for a more detailed analysis).[30] Hydrolysis of the anhydride then yields alkynoic acid **26** and carboxylic acid **27**.



Scheme 2. Mechanistic Hypothesis.

In summary, through a unique mode of endoperoxide fragmentation, a simple means to convert furans into alkynoic acids has been enabled. This mild reaction exhibited operational simplicity, chemoselectivity, and good scalability.[31] A series of furans, especially those with electron-withdrawing groups or bulky substituents, were found to be viable substrates. Notably, this fragmentation has demonstrated potential utility in the degradation of steroidal sapogenins, thus providing a complimentary approach to current technology. This versatile reaction has also allowed for the diverse transformations of alkynoic acids and a concise synthesis of the proposed structure of aglatomin B. The extension of this fragmentation to other non-cycloalkane fused furans and detailed studies of the reaction mechanism are currently under investigation.

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Keywords: alkynes • furans • fragmentation • natural product synthesis • singlet oxygen

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[28] Due to the substantive spectral differences between synthetic and naturally occurring aglatomin B, it is possible that the structure of isolated aglatomin B differs from that reported in ref 11.

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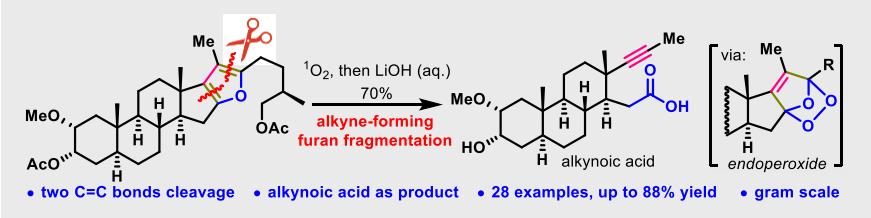

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